Blood Conservation in Arthroplasty

A dissertation submitted to the University of Oxford in partial fulfilment of the requirements for the degree of

Doctor of Philosophy in Musculoskeletal Sciences



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Abstract

Hip and knee arthroplasty are associated with significant blood loss which can exceed two litres, and 90% of patients are anaemic following arthroplasty surgery. Perioperative anaemia and allogeneic blood transfusion are associated with adverse outcomes. The aim of this thesis is to investigate strategies to minimise blood loss and perioperative anaemia in patients undergoing lower limb arthroplasty, offering improved patient outcomes and reduced healthcare costs.

The first study in this thesis explores the effect of perioperative anaemia on the risk of major adverse cardiac events (MACE) within 90 days of surgery. The results suggest that a lower preoperative haemoglobin, postoperative haemoglobin and nadir haemoglobin increased the risk of MACE by approximately 2% for every 1g/L decrease in haemoglobin. The odds ratio for all three haemoglobin models (preoperative Hb, postoperative Hb and nadir Hb) were found to be similar and the confidence intervals overlapped suggesting no difference between preoperative Hb, postoperative Hb and nadir Hb in terms of MACE risk.

It is often during the postoperative period when adverse events manifest, possibly as a result of reduced tissue oxygenation. The adoption of restrictive transfusion thresholds of 70g/L, in recognition of the adverse outcomes associated with blood transfusion, has meant that patients are being discharged with more severe anaemia. The second study of this thesis was to develop a prediction model to identify patients who are at

risk of prolonged postoperative anaemia, and who do not recover their postoperative haemoglobin (Hb) levels within six weeks of arthroplasty surgery. A significant proportion of patients failed to recover their Hb levels to within 10g/L of preoperative Hb levels (41%; n=98). The developed model is based on readily available measures, including age, sex, ASA, preoperative transferrin saturation level, preoperative folate level, discharge Hb, the presence or absence of preoperative anaemia, procedure type (TKA or THA) and whether the surgery was a primary or revision procedure. Following internal validation via bootstrapping, the model showed good predictive ability with a useful R^2 value of greater than 60%. The developed model will enable patients to be better counselled regarding their risk of prolonged anaemia and will identify individuals suitable for clinical trials investigating the optimal treatment for prolonged postoperative anaemia.

Finally, it has never been clearer to prevent bleeding and anaemia from the outset. Reducing blood loss during surgery offers the opportunity to reduce the risk of allogenic blood transfusion, reduce cost and improve patients' outcomes following surgery. There are many licenced drugs to prevent bleeding, including antifibrinolytics (Tranexamic acid, Aprotinin and Epsilon-aminocaproic acid), Desmopressin, Recombinant factor VIIa and factor XIII, Fibrinogen, Fibrin sealants and non-fibrin sealants, however it is uncertain which of these drugs is most effective at preventing bleeding, along with their optimal timing of administration, dose and route. The final study in this thesis aimed to determine the relative effectiveness of pharmacological interventions for preventing

blood loss, and identify the optimal timing, dose and route of administration of pharmacological interventions. Tranexamic acid was found to be the most effective drug for reducing bleeding in hip and knee arthroplasty patients. Tranexamic acid consistently ranked higher than other treatments such as Aprotinin, EACA and topical fibrin sealants compared with placebo. Mixed routes of administration (oral and intra-articular, intravenous and intra-articular) appeared to be more effective than single routes of administration along with higher doses of tranexamic acid. This thesis recommends the use of tranexamic acid in all lower limb arthroplasty procedures.

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Abbreviations

AIC	Akaike’s Information Criteria
AI	Artificial Intelligence
ASA	American Society of Anesthesiologists
BMI	Body Mass Index
BT	Allogenic blood transfusion
CI	Confidence Interval
CNB	Central neuraxial block
CRP	C-reactive Protein
COPD	Chronic Obstructive Pulmonary Disease
EACA	Epsilon-Aminocaproic Acid
eGFR	Estimated Glomerular Filtration Rate
FBC	Full Blood Count
GA	General Anaesthetic
Hb	Haemoglobin
IA	Intraarticular
IV	Intravenous
JLA	James Lind Alliance
LASSO	Least Absolute Shrinkage and Selection Operator
LOHS	Length of hospital stay
MACE	Major adverse cardiovascular events
MNTE	Mean number of transfusion episodes

NICE	National Institute for Health and Care Excellence
NMA	Network meta-analysis
OR	Odds Ratio
PAROS	Postoperative Anaemia Recovery Observational Study
PBM	Patient blood management
POAC	Preoperative assessment clinic
PPI	Patient and Public Involvement
PROMS	Patient Reported Outcome Measures
RCT	Randomised Controlled Trial
RR	Risk Ratio
SD	Standard Deviation
THA	Total hip arthroplasty
TKA	Total knee arthroplasty
TXA	Tranexamic Acid
UME	Unrelated mean effect
xFXIII	Recombinant factor XIII

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Chapter 1 Introduction

1.1 **Clinical challenges**

Musculoskeletal conditions such as osteoarthritis represent a major international public health challenge[1]. Osteoarthritis affecting the hip or knee is the eleventh highest contributor to global disability in the Global Burden of Disease Study[2]. Hip and knee arthroplasty are well-established means of improving quality of life, offering restoration of function and effective pain relief for patients suffering from osteoarthritis. The majority of patients report feeling “much better” following their surgery (85.6% of patients following hip arthroplasty[3] and 70.8% of patients following knee arthroplasty[4]).

Internationally, the number of arthroplasty procedures is increasing. In a study across 20 OECD (Organisation for Economic Co-operation and Development) countries, the annual growth rate of total hip arthroplasty is projected to rise from 1.8 million per year in 2015 to 2.8 million per year in the year 2050[5]. The incidence of hip arthroplasty is expected to increase from a mean of 184 per 100,000 population to 275 per 100,000 population[5]. For knee arthroplasty, the mean incidence was 150 per 100,000 population in 2015 and this figure is likely to increase four-fold by the year 2030[6].

However, while most patients have excellent improvement in their quality of life, surgery is associated with complications including death. In the UK, mortality from primary hip and knee arthroplasty within 90 days of surgery ranges from 0.2% in younger people (younger than 55 years), to 3.1% in older people (over 85 years)[7]. The risk of death within 90 days of surgery increases with revision procedures (1.96%; CI: 1.87 to 2.06%, in hip revision arthroplasty patients, median age 74 and 1.05%; CI: 0.94 to 1.16%, in knee revision arthroplasty, median age 68).

Significant blood loss of more than two litres (~40% of circulating volume) can result from arthroplasty surgery and up to 90% of patients are anaemic following arthroplasty[8,9]. For revision surgery, the prevalence of preoperative anaemia and the average blood loss may be even greater[9,10]. The increased prevalence of preoperative anaemia amongst people undergoing revision surgery is likely due to the patient population being older, more comorbid and malnourished, which are all factors that contribute to anaemia.

Preoperative anaemia and the need for allogeneic blood transfusion due to blood loss from surgery has been associated with worse outcomes including increased postoperative mortality[11], thromboembolic events[12] and infection[13]. Unsafe and unnecessary transfusion practice exposes patients to the risk of serious adverse events and reduces availability of blood products for patients that really need transfusion[14]. Evidence-based strategies to conserve blood and thus reduce allogeneic

transfusions are needed to improve patient outcomes and reduce healthcare costs. Key goals to deliver an optimal patient pathway involve embracing the pillars of “patient blood management”. The concept of patient blood management (PBM) is defined as “the timely application of evidence-based medical and surgical concepts designed to manage anaemia, optimise haemostasis and minimise blood loss in order to improve patient outcomes after surgery”[15]. These include approaches to identify and treat preoperative anaemia, reduce intraoperative blood loss, and address postoperative anaemia in arthroplasty patients.

1.2 **Preoperative anaemia and outcome**

Studies have demonstrated up to a 42% increased risk of mortality in patients who are anaemic prior to surgery[16,17]. Preoperative anaemia has been found to increase the risk blood transfusion, complications and longer hospital length of stay in patients undergoing major elective surgery (defined as surgery lasting longer than 1 hour)[18]. The commonest cause of anaemia is iron deficiency anaemia. Iron deficiency anaemia may be due to either nutritional deficiencies or blood loss resulting in low iron stores and absolute iron deficiency. Patients undergoing surgery often have chronic diseases or inflammation which can disrupt the normal iron pathway and iron metabolism. Hepcidin is the key regulator of iron homeostasis in the body. Hepcidin becomes elevated with inflammation which inhibits iron

transport out of cells. This process prevents dietary iron absorption and causes iron to become sequestered into macrophages which leads to functional iron deficiency and anaemia of chronic disease[19,20].

However, evidence on the associations between preoperative anaemia and adverse outcomes remains unclear for orthopaedic patients. There are published studies of orthopaedic patients which have failed to reproduce the association between preoperative anaemia and mortality[21]. It therefore remains unclear whether preoperative anaemia is an independent risk factor for adverse outcomes, or a surrogate marker of comorbidity.

1.3 **Postoperative anaemia and outcome**

Postoperative anaemia has been associated with adverse events such as infections, longer hospital length of stay and death[22]. Postoperative anaemia is also thought to impact recovery, rehabilitation, hospital readmissions and reoperations[23]. Studies exploring the relationship between postoperative anaemia and patient fatigue have proved inconclusive to date[24,25]. The benefits of enhancing the recovery of postoperative Hb may include a reduced risk of adverse events as well as an improved patient-reported quality of life through minimising anaemia-associated fatigue. Fatigue itself may reduce mobility and increase the risk of postoperative complications.

Historically, treatment for post-operative anaemia has been primarily through blood transfusions. However, blood transfusions are associated with a number of complications and poor medical and surgical outcomes, including allergic reaction, postoperative infections and venous thromboembolism[26]. As a consequence, clinicians now often adopt a restrictive transfusion threshold and patients are being discharged with lower Hb than ever before.

Few studies explore the consequence of postoperative anaemia in the recovery phase and fewer still on the effects of prolonged anaemia on outcome. However, the studies exploring postoperative anaemia report prolonged recovery, increased mortality, myocardial infarction and readmission[27-29]. It is important that clinicians where possible, aim to reduce intraoperative bleeding and optimise preoperative anaemia to prevent the knock-on effect of postoperative anaemia. However, the challenge to the research community is if postoperative anaemia is unavoidable, determining the most effective method for treating postoperative anaemia and the time at which to intervene.

1.1 **Pharmacological treatments to prevent bleeding**

Preoperative anaemia, intraoperative bleeding and a liberal transfusion threshold are the main risk factors for receiving a blood transfusion[30]. When blood loss from surgery results in a Hb below a certain threshold with associated symptoms, a blood transfusion may be administered

despite blood transfusion being associated with risk. The clinical and economic disadvantages of receiving a blood transfusion have led towards the use of drugs to prevent bleeding. Drugs which may reduce the risk the bleeding may offer a lower risk profile, be more cost effective (administering blood currently costs GBP 153.30[31]) and help to preserve a limited resource. However, the current challenges are establishing which pharmacological interventions are most effective at preventing bleeding, at what dose, route and time, and to establish whether there are any adverse events associated with their use.

There are several drugs licensed for use to prevent bleeding in surgery. The mechanism of action, along with any potential risks of drugs available are described below:

1.1.1 Antifibrinolytics

Surgery activates the clotting cascade, which results in the formation of a clot. As part of the process, there are mechanisms in place to break clots down (fibrinolysis). Antifibrinolytic drugs act to prevent the process of fibrinolysis which increases the strength of the clot and stability, in order to prevent more bleeding[32]. Tranexamic acid and EACA are synthetic derivatives of the amino acid lysine, and Aprotinin, derived from bovine lung, is a non-specific serine protease inhibitor. In the UK, Tranexamic acid is used in 42% of elective surgical cases[33]. Antifibrinolytic drugs can be given orally, intravenously or topically[34]. They have few reported side effects, however there is a theoretical

increased risk of thromboembolism, which may prevent the use of antifibrinolytics, particularly in those patients considered at higher risk.

1.1.2 Desmopressin

Desmopressin is a vasopressin analogue which results in increased levels of factor VIII and von Willebrand factor, and also acts directly on platelets to decrease bleeding time[35]. It acts to enable platelets to adhere to wound sites and form clots to prevent bleeding. The drug can be administered intravenously, subcutaneously or intranasally[34]. It is predominantly used in cardiac surgery and results in fewer blood transfusions.[36] Potential reported side effects include facial flushing and with repeated use, may lead to hyponatremia (low sodium levels)[36].

1.1.3 Recombinant factor VIIa and factor XIII

Recombinant factor VIIa (rFVIIa) is a drug licensed for use in haemophilia patients, patients with congenital factor VII deficiency and inhibitory alloantibodies. However, it has also been used off-license to prevent bleeding in surgery, particularly where blood loss is expected to be high and to prevent bleeding that is difficult to control through other means[37]. However, it is unclear how much the drug prevents bleeding in patients with haemophilia. Factor XIII shields a developing clot from fibrinolysis and improves the strength of a clot. Recombinant factor XIII (rFXIII) is dose-dependent and improves clot formation. It is thought higher levels of rFXIII in circulating blood may prevent bleeding[38].

1.1.4 Fibrinogen

Fibrinogen concentrate is a haemostatic protein used for the treatment of acute bleeding episodes. It is derived from blood and is administered intravenously. Fibrinogen forms a critical component of the clotting cascade and is converted to fibrin by thrombin, forming the basis of a clot. As fibrinogen concentrate is derived from blood, there is a small risk of viral infection with its use, however, it is carefully manufactured and therefore is unlikely to result in infection[39].

1.1.5 Fibrin sealants

Fibrin sealants are derived from blood plasma and consist of fibrinogen, thrombin, factor XIII, an antifibrinolytic agent and calcium chloride. Fibrin sealants are usually applied to an actively bleeding wound or bony surfaces. Fibrin sealants come in a variety of forms and some do not contain antifibrinolytics[40]. Side effects can include allergy although this is rare[41]. As with fibrinogen, fibrin sealants also contain blood products although due to processing the risk of transmitting infections is lower than allogeneic blood transfusions[42].

1.1.6 Non-fibrin sealants

Non-fibrin sealants tend to be in liquid form, and is applied topically. It polymerises to form a film where platelet aggregation and activation can occur. Non-fibrin sealants rely on the individual's fibrin to create the blood clot. They may also be manufactured in the form of dressings,

powders and bandages and may form an alternative to the use of a tourniquet where its use may be impractical. They generally function through mechanical compression of the tissues when they expand. As a consequence, adverse events are generally associated with expansion of the sealant such as nerve compression[43].

1.1 Scope of Thesis

This thesis focuses on addressing questions arising in the blood management of lower limb arthroplasty patients preoperatively, intraoperatively and postoperatively which remain under-determined. It also aims to address several important James Lind Alliance research priorities across blood transfusion, orthopaedics and anaesthetics.

1.2 Thesis Aims and Objectives

This thesis aims to explore the effect of anaemia on outcome, identify patients at greatest risk of prolonged anaemia and those most likely to benefit from intervention and explore pharmacological strategies to prevent bleeding. The thesis will be divided across three key areas of enquiry:

1) **Which is more strongly associated with outcome following hip or knee arthroplasty: preoperative haemoglobin, nadir haemoglobin or postoperative haemoglobin?**

Aim: Investigate whether preoperative Hb, nadir Hb or postoperative Hb is more strongly associated with post-operative adverse outcomes.

This study aims to address two James Lind Alliance top ten priority questions, the first in identification of factors which can be modified to influence outcome following hip and knee arthroplasty[44] and the second is exploring the effect of postoperative anaemia and patient outcomes.[45] A cohort study of patients undergoing hip or knee arthroplasty using unadjusted and adjusted logistic regression was used to explore the association between preoperative, nadir and postoperative Hb and the risk of MACE (major adverse cardiac events) within 90 days of surgery. With the adoption of restrictive transfusion thresholds, patients are being discharged with more severe and prolonged anaemia. Therefore, the second question of this thesis is:

2) **How do we identify which patients are most likely to benefit from intervention to prevent postoperative anaemia? Are we able to predict who will recover their haemoglobin concentration by six weeks following surgery?**

Chapter 3:

Aim: To develop and internally validate, a prediction model to identify patients who do not recover their haemoglobin concentration (Hb) to within 10g/l of preoperative levels six weeks.

Postoperative anaemia recovery was identified as a research priority in a consensus status statement published in 2018[46] and 'how can we improve patient recovery from surgery' is another James Lind Alliance priority question in Anaesthesia and Perioperative Care[47]. A prospective cohort study was conducted to develop and internally validate via bootstrapping, a prediction model to predict patients who did and did not recover their haemoglobin concentration to preoperative levels following hip and knee arthroplasty. The results of this study will help to identify those patients most likely to benefit from an intervention and help future studies target the patient population at greatest risk of prolonged anaemia.

3) **What is the most effective drug for preventing bleeding intraoperatively and what is the optimal route, dose and timing of administration of that drug in arthroplasty patients?**

Chapter 4:

Aim: Determine the relative effectiveness of drugs for preventing blood loss in lower limb arthroplasty, and to identify the optimal dose, timing and route of the drug.

This project addresses a blood transfusion top ten James Lind Alliance priority question 'what are the best drug alternatives to blood transfusion to reduce and prevent bleeding.'[48] As it would be impossible to compare all drugs, routes and timing of administration of drugs in

one randomised controlled trial, a network meta-analysis of RCTs was conducted. This method enables data from direct comparisons to indirectly estimate treatment effects of missing comparisons to produce treatment estimates[49]. The results of this study will provide a treatment hierarchy for healthcare workers and may influence guidelines and future practice.

Chapter 2 Identifying patients with perioperative anaemia who are at greatest risk of adverse outcomes after hip and knee arthroplasty

2.1 **Abstract**

Introduction

Identification of factors which can be modified to influence outcome following hip and knee arthroplasty is a top ten James Lind Alliance (JLA) research priority question. A third of patients are anaemic prior to hip or knee arthroplasty and up to 90% of patients postoperatively are anaemic. It remains unclear whether preoperative anaemia is an independent risk factor for adverse outcomes, or a surrogate marker of comorbidity. Preoperative and postoperative anaemia have been associated with increased risk of adverse outcomes including mortality. Studies show up to a 42% increased risk of mortality in patients who are anaemic prior to surgery. However, evidence on the associations between perioperative anaemia and adverse outcomes remain unclear for orthopaedic patients. The nadir Hb (lowest recorded Hb) during an inpatient episode, may be more informative than preoperative or postoperative anaemia. Nadir Hb has been found to be a more influential predictor of outcome than preoperative or postoperative Hb in patients suffering from head trauma[50]. However, little has been published on nadir Hb and outcome for orthopaedic patients.

Aims

To investigate whether preoperative Hb (within 7 days prior to surgery), nadir Hb (the lowest Hb recorded for a patient), or postoperative Hb (day following surgery Hb) is more strongly associated with post-operative adverse outcomes following primary and revision hip or knee arthroplasty surgery. Secondary aims include whether blood transfusion given in the intraoperative and postoperative period is associated with adverse outcomes.

Methods

A cohort study using data from a single centre including primary and revision hip or knee arthroplasty (THA and TKA) patients from 2011 to 2018 from Geneva University Hospitals was conducted. This dataset was used as it has been validated in a community where follow-up is almost exclusively at the same institution and where postoperative blood tests were taken routinely at 7 days postoperatively. Inclusion criteria: primary or revision THA or TKA. Exclusion criteria: unicompartmental knee arthroplasty, haematological disorders or surgery for malignancy. Variables for collection included patient demographics, patient comorbidities (including ASA), surgery type and duration, blood tests (including iron studies) preoperatively and lowest haemoglobin results, length of hospital stay, ischemic-specific complications (stroke, myocardial infarction, cardiac failure requiring admission) and mortality. The primary outcome measure was MACE

(Major adverse cardiovascular events) within 90 days of surgery. The composite MACE included all-cause mortality, myocardial infarction, cerebrovascular event and cardiac failure requiring readmission. Overall baseline characteristics were described along with MACE for both primary and revision THA and TKAs. Unadjusted and adjusted logistic regression was used to explore the relationship between age, ASA, sex, BMI, preoperative Hb, postoperative Hb (defined as day one following surgery Hb), nadir Hb, preoperative co-morbidities, duration of surgery, procedure type, blood transfusion and MACE at 90 days.

Results

5378 patients met the inclusion criteria. 40.4 %(n =2175) were male and the mean age of the cohort was 69 years (SD 12.3, range 16-100). The 90-day MACE rate was more common with revision procedures (6.3%; n = 36 for revision THA and 3.5%; n = 9 for revision TKA) compared with primary procedures (1.2%; n =31 for primary THA and 0.7%; n=14 for primary TKA). In the adjusted analysis, a lower Hb was associated with an increased risk of MACE in all haemoglobin models (postoperative Hb (OR; 0.98; CI 0.97 to 0.99) , preoperative Hb (OR; 0.98; CI 0.97 to 0.99) and nadir Hb (OR; 0.98; CI 0.97 to 0.99). Red blood cell transfusion increased the risk of MACE by over two-fold (OR; 2.34 CI; 1.37 to 3.99). BMI, procedure type, operative time and the number of comorbidities a patient had were not found to be risk factors for MACE within 90 days.

Conclusion

This study found that a lower Hb is a risk factor MACE within 90 days of surgery. All three anaemia models (preoperative Hb, postoperative Hb and nadir Hb) were similar in terms of the risk of MACE at 90 days with the risk of MACE increasing by approximately 2% for every 1g/L decrease in Hb. The odds ratio for all three anaemia models were similar with overlapping confidence intervals. Allogeneic blood transfusion also increases the risk of adverse outcomes. Healthcare workers should consider optimising and preventing anaemia along the pre, intra and post-operative pathway, and adopting blood conservations measures to reduce the need for blood transfusion to reduce the risk the of MACE at 90 days.

2.1 Introduction

This cohort study was conducted according to a protocol approved by the University of Oxford Clinical Trials and Research Governance. The data was obtained through a collaboration between Oxford University and the Geneva National Joint Registry. The registry data collection was approved by the local ethics committee (CCER Geneva, no. PB_2017-00164, Switzerland). I was responsible for study concept and design, data cleaning and translation, statistical analysis and written manuscript (submission pending).

2.2 **Background**

Each year over three million hip and knee arthroplasties are performed worldwide, with a further 25% increase projected over the next 20 years[51]. Hip and knee arthroplasty are highly successful in most cases with significant improvements in patient reported quality of life. However, it is not without potential complications.

Hip and knee arthroplasty represent major surgery and total blood loss can exceed 2000ml, when considering visible and hidden losses[9], and more than 90% of patients are anaemic postoperatively[8]. Furthermore, patients often have multiple preoperative co-morbidities and at least a third are anaemic prior to surgery[52]. Cohort studies of over 500,000 patients demonstrate an independent association between preoperative anaemia and 30-day morbidity (odds ratio (OR) 1.41, 95% CI 1.30 to 1.40) and mortality (OR 1.42; 95% CI 1.31 to 1.54)[16,17].

Mortality rates within 90 days of primary hip and knee replacement range from 0.2% in patients aged under 55 years to 2.9% in patients aged over 85 years[7], with even higher rates of mortality after revision surgery. The leading cause of death is ischaemic heart disease[53]. Other salient medical complications include cardiovascular and cerebrovascular events, venous thromboembolic disease, urinary tract infection, and lower respiratory tract infection. Periprosthetic infection affects approximately 1% patients, although in some units may affect up to 5% patients[54]. Infected prosthetic joints frequently require

multiple revision operations with further elevated risks of medical and surgical complications, and an average cost of £100,000 per patient[54].

Preoperative anaemia is associated with an increased risk of adverse outcomes from joint replacement[16,17] including surgical site infection[55] and mortality[21,56,57]. The largest studies are retrospective cohorts of over 10,000 patients and demonstrate an association between preoperative anaemia and increased mortality rates in patients undergoing non-cardiac surgery[16,17]. A meta-analysis conducted by Fowler et al, which included some orthopaedic patients also concluded an association with preoperative anaemia and increased mortality postoperatively[58].

However, many of the larger published cohort studies do not include specific analyses for orthopaedic patients and findings from patients with conditions such as malignancy may not be generalisable to patients receiving a joint replacement. It remains unclear whether anaemia is an independent risk factor for adverse outcomes for orthopaedic patients. Interventions which treat preoperative anaemia demonstrate reduced rates of transfusion, readmission, and length of stay[59,60], however, they have not demonstrated a clear reduction in postoperative complication rates or improved functional outcomes following surgery[59,61].

The effect of anaemia following surgery has been less well studied, with little evidence published on the impact of postoperative anaemia and patient outcome. Postoperative anaemia may help to predict patient

outcomes more accurately than preoperative anaemia. Exploring the effect of postoperative anaemia and patient outcomes has been identified as one of the top ten research priority questions by the James Lind Alliance[48].

Nadir Hb (the lowest recorded Hb, during an inpatient episode) may be more informative than preoperative or postoperative Hb[50]. Nadir Hb has been found to be a more powerful predictor of outcome than preoperative or postoperative Hb levels in patients suffering from head trauma. However, little has been published on nadir Hb and outcome for orthopaedic patients.

Finally, it is not clear whether allogeneic blood transfusion is a risk factor for adverse events in patients undergoing elective hip or knee arthroplasty. Transfusion has been shown to increase the risk of infection following surgery[62], however it is unclear whether transfusion independently increases the risk of mortality or ischaemic events.

Over two thirds of cases of preoperative anaemia are secondary to iron deficiency[63,64] and preoperative iron supplementation in these patients has shown to improve postoperative morbidity and mortality[59]. This suggests that preoperative anaemia is a modifiable risk factor for morbidity and mortality rather than purely a marker of comorbidity.

2.3 Objectives

The primary objective of this study is to investigate whether preoperative Hb (within 7 days prior to surgery), nadir Hb (the lowest Hb recorded for a patient), or postoperative Hb (day following surgery Hb) is more strongly associated with post-operative adverse outcomes following primary and revision hip or knee arthroplasty surgery. The secondary objective is to investigate whether blood transfusion given in the intraoperative and postoperative period is associated with adverse outcomes.

2.4 Methodology

2.4.1 Study Procedures

A prospective registry-based cohort study was conducted. Consecutive patients undergoing primary and revision total hip arthroplasty (THA) and total knee arthroplasty (TKA) were recruited into the database from a single institution (Geneva University Hospitals) between 01/01/2011 to 31/12/2018 and data collected prospectively. The minimum follow-up was 12 months. The local ethics committee approved the registry. At the time of primary surgery, information on baseline characteristics and surgery details are entered into the registry.

Variables for collection included patient demographics (age, sex, BMI), number of patient comorbidities (including a history of diabetes, heart

murmur or rheumatic fever, angina or chest pain, heart attack, history of heart failure, pacemaker, hypertension, pulmonary embolism, deep vein thrombosis, recurrent urinary tract infections, liver disease, bowel disease, renal disease, chronic obstructive pulmonary disease (COPD), cerebrovascular event (CVA), asthma, peripheral arterial disease and high cholesterol), American Society of Anesthesiologists (ASA), procedure, duration of surgery, length of hospital stay, haemoglobin levels (7 day preoperative Hb, day one following surgery, and 7 day post-operative Hb) mortality at 90 days, blood transfusion and rehospitalisation within 90 days.

The age of the patient and operation details were documented in the registry by the operating surgeon on a prespecified data collection form at the time of surgery. Information on comorbidities, including ASA and BMI were collected from the anaesthesiology report and discharge summary. The sample size was dictated by the number of cases undertaken and coded during the study period. For the purposes of this study, strongly associated was defined as an increase in the risk of MACE by 1% for every unit decrease in Hb.

2.4.2 Inclusion/exclusion criteria

Patients undergoing primary or revision knee or hip arthroplasty (excluding unicompartmental knee replacement) were included. Procedure codes included were primary or revision THA/TKA. Patients with known haematological conditions and procedures performed for

malignancy were excluded. Patients were included if they had a haemoglobin measurement within 7 days prior to surgery and within one week postoperatively.

2.4.3 Outcome measures

The primary outcome measure used was the validated composite score MACE (Major adverse cardiovascular events)[65] within 90 days. MACE consists of all-cause mortality, myocardial infarction, cerebrovascular event and cardiac failure requiring readmission. MACE is commonly used in elective orthopaedic studies to assess outcome[66,67]. The contribution of each component of MACE was described for primary and revision THA and TKA. Where multiple occurrences of MACE occurred, only the first was counted[68].

2.4.4 Statistical analyses

Descriptive statistics were used to report patient demographics and outcome measures for primary and revision THA and TKAs. Means with standard deviations (SDs) and ranges were used to describe continuous data, and medians with interquartile ranges were used if the continuous data was not normally distributed. Numbers and percentages were used to describe categorical data.

Unadjusted logistic regression was used to explore the relationship between age, ASA, sex, BMI, preoperative Hb, postoperative Hb (defined as day one following surgery Hb), nadir Hb, preoperative co-morbidities,

duration of surgery, procedure type, blood transfusion and MACE at 90 days. Age, BMI, duration of surgery and Hb were included in the model as linear terms and were assumed to be linear. As postoperative Hb, preoperative Hb, nadir Hb and transfusion would demonstrate co-linearity, four adjusted regression models were created. The first model was created for the outcome postoperative Hb, as exploring the association between postoperative Hb and adverse outcomes is the primary aim of this study. Candidate risk factors for adverse outcome were identified as age, ASA, sex, BMI, preoperative co-morbidities, duration of surgery, procedure type (TKA/THA) and backwards elimination was applied to these risk factors. Subsequent models for preoperative Hb and nadir Hb were created with the same covariables for comparison. The final model, red blood cell transfusion, was also created using backward elimination.

Risk factor selection was guided by likelihood ratios and Akaike's Information Criteria (AIC). A significance level of p-value < 0.05 was used. The association of risk factors was checked using correlation scatter matrices and correlation coefficients. Odds ratios (ORs) were reported with 95% confidence intervals (CIs). Any missing data was presented descriptively and depending on levels of missingness, imputation analysis was not performed. Given the small amount of missing data all analyses were complete case analyses. The analysis was conducted in STATA version 17 (StataCorp, College Station, Texas, USA)[69].

2.5 **Results**

2.5.1 Descriptive analysis

A total of 5378 patients were identified as having procedure codes associated with primary or revision hip or knee arthroplasty.

Table 2-1 Baseline characteristics of patients undergoing primary and revision total hip arthroplasty

Characteristics	**THA primary n = 2605**	**THA revision = 569**
Mean age, yrs. (SD; range)	67.8 (13.4; 16 to 100)	70.9 (13.0; 26 to 97)
Mean postoperative Hb, g/l (SD; range)**	120 (18.5; 51 to 189)	104.4; 68 to 177)
Mean preoperative Hb, g/l (SD; range)	136.5 (15.2; 81 to 190)	126 (20.3; 75 to 177)
Mean nadir Hb, g/l (SD; range)	103.9 (15.2; 51 to 189)	93.7 (13.4; 68 to 148)
Male sex, n (%)	1151 (44.2)	284 (49.9)
ASA, n (%)		
1 (low)	264 (9.4)	30 (5.3)
2	1845 (70.8)	309 (54.3)
3	508 (19.5)	212 (37.3)
4 (high)	6 (0.23)	14 (2.5)
Missing	*0 (0)*	*4 (0.7)*
BMI, n (%)		
Underweight	68 (2.6)	23 (4.0)
Normal	931 (35.7)	227 (39.9)
Overweight	948 (36.4)	190 (33.4)
Obese	657 (25.2)	125 (22.0)
Missing (height missing)	*1 (0.04)*	*4 (0.7)*
Patients with preop anaemia,* n (%)	761 (29.2)	318 (55.9)
Patients with postop anaemia, 7 days post-surgery n (%)**	2413 (92.6)	556 (97.7)
Comorbidities***		
0	321 (12.3)	37 (6.5)
1	658 (25.3)	118 (20.7)
2	635 (24.4)	120 (21.1)
3	469 (18.0)	129 (22.7)
4 or more	522 (20.0)	160 (28.1)
Missing	0	5 (0.9)
Received blood transfusion	338 (13.0)	209 (36.7)
Missing	34 (1.2)	56 (9.8)

Median operating time, mins (IQR)	80 (69 to 317)	132 (92 to 181)

*Male haemoglobin < 130 g/l, female haemoglobin < 130 g/l.
** Postoperative Hb defined as day one post-operative Hb
ASA, American Society for Anesthesiologists; BMI, body mass index; Hb, haemoglobin; IQR, interquartile range.
***Comorbidities included history of diabetes, heart murmur or rheumatic fever, angina or chest pain, heart attack, history of heart failure, pacemaker, hypertension, pulmonary embolism, deep vein thrombosis, recurrent urinary tract infections, liver disease, bowel disease, renal disease, chronic obstructive pulmonary disease (COPD), cerebrovascular event (CVA), asthma, peripheral arterial disease and high cholesterol.
Where not otherwise specified no data was missing

Table 2-2 Baseline characteristics of patients undergoing primary and revision total knee arthroplasty

Characteristics	TKA primary n = 1967	TKA revision = 237
Mean age, yrs. (SD; range)	70.6 (10.1; 47 to 96)	69.1 (11.8; 33 to 97)
Mean postoperative Hb, g/l (SD; range)**	119.2 (17.3; 67 to 174)	109.0 (20.6; 59 to 178)
Mean preoperative Hb, g/l (SD; range)	136.0 (14.3; 80 to 185)	127.0 (20.2; 63 to 178)
Mean nadir Hb, g/l (SD; range)	99.4 (13.9; 67 to 157)	94.9 (15.1; 59 to 150)
Male sex, n (%)	645 (32.8)	95 (40.1)
ASA, n (%)		
1 (low)	70 (3.6)	8 (3.4)
2	1457 (74.1)	129 (54.4)
3	437 (22.2)	95 (40.1)
4 (high)	3 (0.2)	5 (2.1)
Missing	*0 (0)*	*0 (0)*
BMI, n (%)		
Underweight	11 (0.6)	4 (1.7)
Normal	354 (18.0)	43 (18.1)
Overweight	693 (35.2)	88 (37.1)
Obese	909 (46.2)	101 (42.6)
Missing (height missing)	*0 (0)*	*1 (0.42)*
Patients with preop anaemia,* n (%)	595 (30.25)	128 (54.0)
Missing	36 (1.83)	2 (0.84)
Patients with postop anaemia, 7 days post-surgery n (%)**	1890 (96.1)	227 (95.8)
Comorbidities***		
0	123 (6.3)	10 (4.2)
1	325 (16.5)	33 (13.9)
2	500 (25.4)	57 (24.1)
3	455 (23.1)	49 (20.7)
4 or more	564 (28.7)	88 (37.1)

Received blood transfusion	348 (17.7)	63 (26.6)
Missing	25 (1.2)	22 (9.3)
Median operating time, mins (IQR)	120 (103 to 137)	140 (95 to 180)

*Male haemoglobin < 130 g/l, female haemoglobin < 130 g/l.
** Postoperative Hb defined as day one post-operative Hb
ASA, American Society for Anesthesiologists; BMI, body mass index; Hb, haemoglobin; IQR, interquartile range.
***Comorbidities included history of diabetes, heart murmur or rheumatic fever, angina or chest pain, heart attack, history of heart failure, pacemaker, hypertension, pulmonary embolism, deep vein thrombosis, recurrent urinary tract infections, liver disease, bowel disease, renal disease, chronic obstructive pulmonary disease (COPD), cerebrovascular event (CVA), asthma, peripheral arterial disease and high cholesterol.
Where not otherwise specified no data was missing

Across the entire cohort, 40.4% were male and mean age was 69 years (SD 12.3, range 16-100). Patients undergoing revision surgery had a lower preoperative Hb than patients undergoing a primary arthroplasty, and had an increased number of comorbidities (Table 2 -1). The majority of patients were anaemic seven days post-surgery (92.2-97.7%) (Table 2 -1, Table 2 -2).

The 90-day mortality rate for primary TKA was 0.25% (n = 5), revision TKA 3.0% (n=7), primary THA 0.4% (n=9), revision THA 3.3% (n=19). Myocardial infarction, cerebrovascular events and cardiac decompensation requiring readmission were all more common with revision procedures (Table 2 -3).

Table 2-3 The contribution of events with the 90-day MACE composite

90-day MACE composite*	THA primary n = 2605	THA revision = 569	TKA primary n = 1967	TKA revision = 237
Mortality (%)	6 (0.2)	18 (3.1)	0 (0.0)	0 (0.0)
Myocardial infarction (%)	10 (0.4)	6 (1.1)	7 (0.4)	3 (1.3)
Cerebrovascular event (%)	5 (0.2)	4 (0.7)	1 (0.1)	2 (0.8)

Cardiac decompensation requiring readmission (%)	10 (0.4)	8 (1.4)	6 (0.3)	4 (1.7)
Total (%)	31 (1.2)	36 (6.3)	14 (0.7)	9 (3.8)
*Where multiple MACE events occurred, the first was counted in the composite[68]				

Patients who developed a MACE were on average older, had a higher number of comorbidities and had a lower average preoperative Hb compared with those who did not suffer a MACE. All patients who suffered a MACE were anaemic following surgery. BMI was similar across both groups (Table 2 -4).

As expected, postoperative Hb, preoperative Hb and nadir Hb outcomes were found to be correlated (Figure 2 -1) and therefore three independent multivariable models were built.

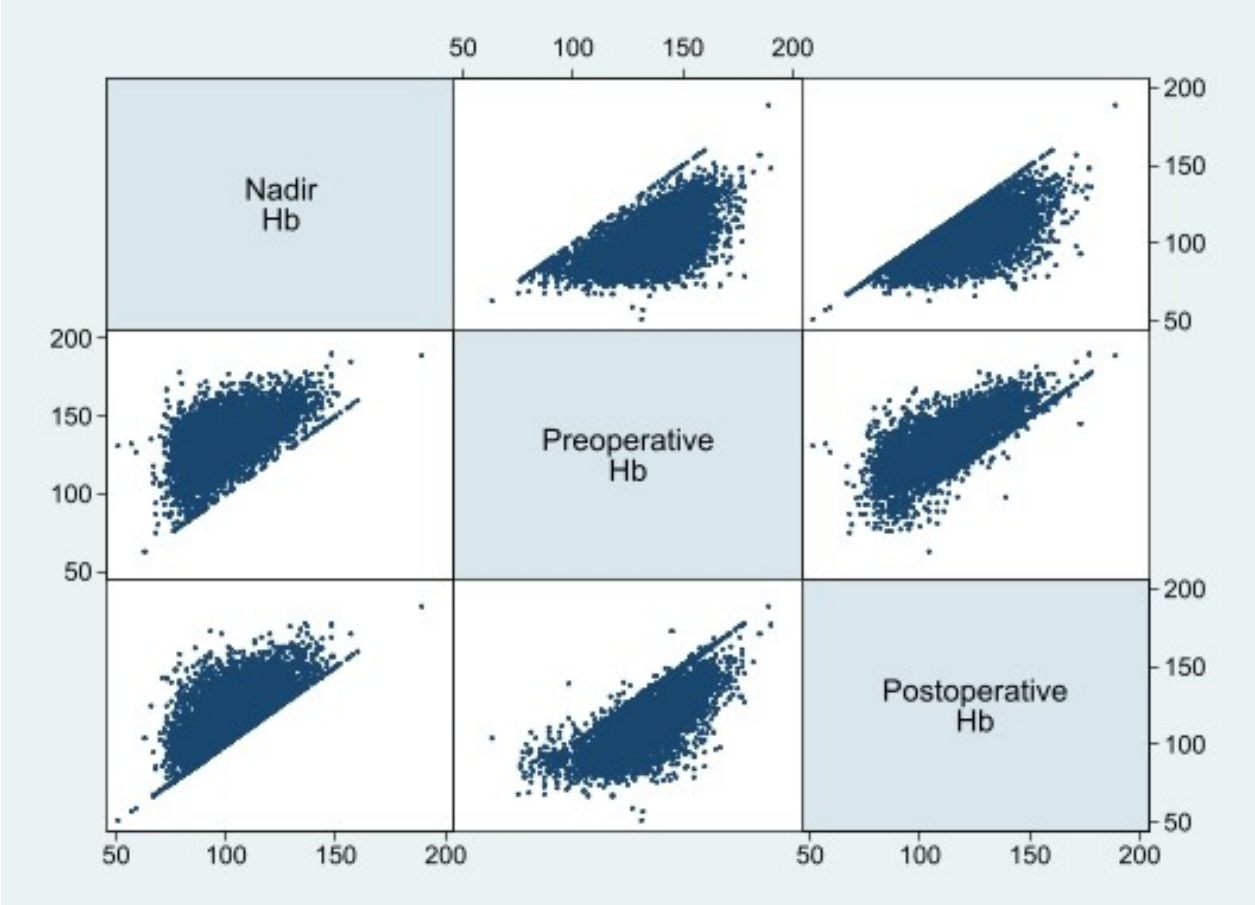


Figure 2-1 Scatter plots demonstrating co-linearity between postoperative, preoperative and nadir Hb

Table 2-4 Characteristics of patients undergoing primary/revision THA/TKA, by MACE within 90 days

Characteristics	Patients who suffered a MACE within 90 days (n=90)	Patients who did not suffer a MACE within 90 days (n=5288)
Mean age, yrs. (SD; range)	79.0 (10.9; 29 to 94)	69.1 (12.2; 16 to 100)
Mean postoperative Hb (SD; range)**	105.4 (17.9; 71 to 155)	117.8 (18.7; 79 to 189)
Mean preoperative Hb, g/l (SD; range)	123 (23.7; 81 to 174)	134.7 (16.0; 63 to 190)
Mean nadir Hb (SD; range)	93.1 (11.2; 71 to 129)	100 (15.0; 51 to 189)
Male sex, n (%)	43 (47.8)	2132 (40.3)
ASA, n (%)		
1 to 2	20 (22.2)	4074 (77.1)
3 to 4	70 (77.8)	1210 (22.9)
Preoperative anaemia,* n (%)	53 (58.9)	1749 (33.1)
Postoperative anaemia, 7 days post-surgery* n (%)	90 (100)	4996 (94.5)
]No	36 (40.0)	3446 (65.2)
Yes	53 (58.9)	1749 (33.1)
Missing	1 (1.1)	93 (1.8)
BMI, n (%)		
Underweight	1 (1.1)	105 (2.0)
Normal	34 (37.8)	1521 (28.8)
Overweight	30 (33.3)	1889 (35.7)
Obese	25 (27.8)	1767 (33.4)
Missing (height missing)	0 (0.0)	5 (0.1)
Comorbidities*		
0	2 (2.2)	489 (9.3)
1	6 (6.7)	1128 (21.3)
2	12 (13.3)	1300 (24.6)
3	23 (25.6)	1079 (20.4)
4 or more	47 (52.2)	1292 (24.4)
Missing	0	5 (0.1)
Received blood transfusion	33 (36.7)	925 (17.5)
Missing	27 (30.0)	110 (2.1)
Median operating time, mins (IQR)	120 (82 to 177)	104 (78 to 129)

*Male haemoglobin < 130 g/l, female haemoglobin < 130 g/l.
** Postoperative Hb defined as day one post-operative Hb
ASA, American Society for Anesthesiologists; BMI, body mass index; Hb, haemoglobin; IQR, interquartile range.
Where not otherwise specified no data was missing

2.5.2 Unadjusted and adjusted analyses

There was a small amount of missing data (4.6% n= 250, of patients had 1 or more missing variable) and therefore a complete case analysis was justified[70]. In the adjusted analysis, MACE was associated with a decrease in Hb in all haemoglobin models (postoperative Hb (OR; 0.98; CI 0.97 to 0.99) , preoperative Hb (OR; 0.98; CI 0.97 to 0.99) and nadir Hb (OR; 0.98; CI 0.97 to 0.99) (Table 2 -5).

The AIC for the models were postoperative Hb model: 762.5, preoperative Hb model: 754.4, nadir Hb model: 766.3, suggesting the preoperative model had a better fit, followed by postoperative Hb and nadir Hb. Age and ASA featured in all models, including the blood transfusion model, with ASA being an influential risk factor (Table 2 -6). Blood transfusion increased the risk of MACE by over two-fold (OR; 2.34 CI; 1.37 to 3.99). BMI, procedure type, operative time and the number of comorbidities a patient had were not included in the model in the presence of the other risk factors for MACE within 90 days.

Table 2-5 Unadjusted and adjusted analysis anaemia

Risk factors	Unadjusted (n= 5378)		Adjusted Postop Hb** (n=5282)		Adjusted preop Hb (n=5282)		Adjusted nadir Hb (n=5286)	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**	**OR (95% CI)**	**p-value**
Age, yrs.	1.09 (1.07 to 1.12)	< 0.001	1.06 (1.03 to 1.09)	<0.001	1.06 (1.03 to 1.08)	<0.001	1.06 (1.03 to 1.09)	<0.001
BMI	0.97 (0.93 to 1.01)	0.134	-	-	-	-	-	-
Sex		0.154		0.023		0.017		0.029
Female	Reference		Reference		Reference		Reference	
Male	0.74 (0.49 to 1.12)		0.60 (0.39 to 0.93)		0.58 (0.38 to 0.91)		0.61 (0.40 to 0.95)	
ASA		< 0.001		<0.001		<0.001		<0.001
1 to 2	Reference		Reference		Reference		Reference	
3 to 4	11.8 (7.13 to 19.45)		6.44 (3.78 to 10.98)		6.32 (3.70 to 10.80)		6.66 (3.92 to 11.31)	
Procedure type			-	-	-	-	-	-
THA	Reference	0.003						
TKA	0.49 (0.30 to 0.78)							
Postoperative Hb**	0.96 (0.95 to 0.98)	< 0.001	0.982 (0.971 to 0.994)	0.003	Not included	Not included	Not included	Not included
Preoperative Hb	0.96 (0.95 to 0.97)	<0.001	Not included	Not included	0.982 (0.971 to 0.993)	0.002	Not included	Not included
Nadir Hb	0.97 (0.95 to 0.99)	0.001	Not included	Not included	Not included	Not included	0.979 (0.965 to 0.994)	0.006
Operating time	1.01 (1.00 to 1.01)	<0.001	-	-	-	-	-	-
Number of comorbidities	1.60 (1.41 to 1.83)	<0.001	-	-	-	-	-	-
Blood transfusion*		0.251	Not included	Not included	Not included	Not included	Not included	Not included
No	Reference							
Yes	5.06 (3.07 to 8.33)							

*At intra and or post-surgery. **Defined as the day after surgery postoperative Hb
ASA, American Society for Anesthesiologists; CI, confidence interval; OR, odds ratio; THA Total hip arthroplasty; TKA total knee arthroplasty

Table 2-6 Unadjusted and multivariate analysis blood transfusion

Risk factors	Unadjusted (n= 5378)		Adjusted blood transfusion (n=5241)	
	OR (95% CI)	**p-value**	**OR (95% CI)**	**p-value**
Age, yrs.	1.09 (1.07 to 1.12)	< 0.001	1.05 (1.02 to 1.08)	<0.001
BMI	0.97 (0.93 to 1.01)	0.134	-	-
Sex		0.154	-	-
Female	Reference			
Male	0.74 (0.49 to 1.12)			
ASA		< 0.001		<0.001
1 to 2	Reference		Reference	
3 to 4	11.8 (7.13 to 19.45)		5.39 (2.96 to 9.81)	
Procedure type			-	-
THA	Reference	0.003		
TKA	0.49 (0.30 to 0.78)			
Postoperative Hb	0.96 (0.95 to 0.98)	< 0.001	Not included	Not included
Preoperative Hb	0.96 (0.95 to 0.97)	<0.001	Not included	Not included
Nadir Hb	0.97 (0.95 to 0.99)	0.001	Not included	Not included
Operating time	1.01 (1.00 to 1.01)	<0.001	-	-
Number of comorbidities	1.60 (1.41 to 1.83)	<0.001	-	-
Blood transfusion*		0.251		0.002
No	Reference		Reference	
Yes	5.06 (3.07 to 8.33)		2.34 (1.37 to 3.99)	

*At intra and or post-surgery. **Defined as the day after surgery postoperative Hb

ASA, American Society for Anesthesiologists; CI, confidence interval; OR, odds ratio; THA Total hip arthroplasty; TKA total knee arthroplasty

2.6 Discussion

This study demonstrates that a lower Hb level at any timepoint during the perioperative period is associated with an increased risk of MACE within 90 days. The odds ratio for all three haemoglobin models (preoperative Hb, postoperative Hb and nadir Hb) were found to be similar and the confidence intervals overlapped. Therefore, we did not find evidence of a difference between preoperative Hb, postoperative Hb and nadir Hb, as risk factors for MACE within 90 days. For all three haemoglobin models, the risk of MACE increased by approximately 2% for every 1g/L decrease in Hb. Blood transfusion was also found to be a risk factor for MACE within 90 days, along with increased age and ASA.

The absolute 90-day mortality rate for hip and knee arthroplasty remains low and our study is consistent with other published studies [71]. Anaemia is thought to lead to an increased likelihood of ischaemic events due to reduced tissue perfusion[72]. All patients who experienced a MACE event were anaemic post-operatively.

Anaemia is a modifiable risk factor and the majority of patients (>90%) were anaemic postoperatively. The observed prevalence of preoperative and postoperative anaemia in this study is consistent with other studies conducted in orthopaedic patients[73,74]. Anaemia should be optimised at every time point during the patient's surgical journey, including postoperatively. The focus of treatment is predominantly on iron

deficiency anaemia as this is one of the most common cause for a low Hb in the surgical patient population[52]. The National Institute for Health and Care Excellence (NICE) recommend pre and postoperative treatment of iron deficiency anaemia with oral or intravenous iron supplementation[75]. When identified in a timely manner, iron deficiency anaemia is readily treatable with iron supplementation.

However, there are several challenges to identifying and treating preoperative and postoperative anaemia. Despite recommendations published, the proportion of people assessed for iron status in the preoperative period remains generally low, with few patients being tested for ferritin levels or TSAT[8]. In one study, only two out of seven nations had national guidelines for the management of preoperative anaemia, the UK being one of those nations[76]. Furthermore a study based on data from 11 hospitals in Canada and Europe demonstrated that even if low Hb were identified, the initiation of treatment remained poor[77]. The barriers to treatment are thought to be those related to time and infrastructure.

Where treatment is enacted, the main stay of treatment is oral iron. However, it takes longer to increase iron stores with oral iron than intravenous iron and it has more reported side-effects[78]. Intravenous iron offers an alternative choice, due to the shorter time frame between supplementation and surgery[76]. Studies have demonstrated that intravenous iron can effectively and safely replenish depleted iron stores in a short time span, and is able to bypass the gastrointestinal barriers to

absorption, mediated by hepcidin, in patients with chronic disease[79]. However, it is unclear whether intravenous iron is effective at reducing the risk of blood transfusion or mortality in the perioperative period, which may be related to diagnosis of iron deficiency anaemia[80]. Erythropoietin, as part of preoperative anaemia management, is usually only indicated in certain patient populations such as those with chronic renal failure[76]. Erythropoietin is used widely in the USA prior to arthroplasty but it can be quite costly and there are concerns over thromboembolic risk[81].

Blood transfusions are a scarce resource, are expensive and associated with risks such as transfusion reactions[82]. This study found blood transfusion increased the risk of MACE by two-fold (OR 2.34; 95% CI 1.37 to 3.99). It is important to consider interventions to conserve blood such as preventing hypothermia, the use of intraoperative pharmacological agents to prevent bleeding and cell salvage where blood loss is expected to exceed 500ml[83]. One consequence to adopting restrictive transfusion threshold, is that more patients are being discharged with profound postoperative anaemia and the treatment and prevention of this is less certain.

This is the first study to explore whether preoperative Hb, nadir Hb or postoperative Hb are more strongly associated with outcome. The strengths of the study include a large cohort, specifically assessing the impact of anaemia in an orthopaedic population with minimal missing data. Limitations include that the data was derived from a single

institution and readmissions to other hospitals with complications may not have been captured. However, most patients within the dataset were likely to return to the centre as it is a tertiary centre. No formal sample size calculation was performed, and the size was informed by a time interval. Multiple imputation was not used, however there was a very small amount of missing data and therefore complete case analysis was justified[70].

In summary, this study shows that perioperative anaemia increases the risk of MACE at 90 days after primary and revision hip or knee arthroplasty. There was no strong evidence that either preoperative Hb, nadir Hb or postoperative Hb is a stronger risk factor for MACE at 90 days. Blood transfusion was also associated with MACE at 90 days. Healthcare workers should consider optimising and preventing anaemia along the pre, intra and post-operative pathway.

Chapter 3 Postoperative Anaemia Recovery Observational Study (PAROS)

3.1 Abstract

Introduction:

Preoperative anaemia has been associated with increased risk of adverse outcomes, however there has been limited research on the effect of postoperative anaemia on patient outcomes. More than 90% of patients are anaemic after hip or knee arthroplasty. Patients who are unable to recover their haemoglobin levels to preoperative levels may experience increased risk of fatigue and complications, through reduced tissue oxygenation. Therefore, in addition to optimising preoperative anaemia, patients may benefit from strategies to enhance their recovery from postoperative anaemia. Few studies explore recovery from postoperative anaemia, however in 30 patients undergoing primary total hip arthroplasty, 25% of patients had a haemoglobin at least 10g/L (considered clinically significant) below preoperative concentrations 56 days postoperatively. Postoperative anaemia recovery was identified as a research priority in a consensus status statement published in 2018 and with ‘how can we improve patient recovery from surgery’ a James Lind Alliance priority question.

Aim:

To develop and internally validate a prediction model to identify patients who do not recover their haemoglobin concentration (Hb) to within 10g/l of preoperative levels six weeks.

Methods:

A prospective cohort study was conducted of patients undergoing hip or knee arthroplasty with a primary objective to identify patients who do not restore their haemoglobin to preoperative levels at six weeks following hip or knee arthroplasty. Patients were excluded if they were under 18 years of age, were undergoing a unicompartmental or patellofemoral knee replacement, had active malignancy, had a known haematological disease, or had a previous renal transplant, or currently were requiring dialysis. Data was collected at several time points. The first was at the participant's routine preoperative assessment clinic 6 to 12 weeks prior to surgery, where blood test results, demographics and comorbidities were recorded (full blood count, urea and electrolytes and estimated glomerular filtration rate, iron studies, B12, folate, C-reactive protein). The second data collection point was the day of surgery and the day following surgery, where routine bloods had been performed, and finally research six-week blood tests were taken at the participants routine six-week appointment (full blood count, urea and electrolytes and estimated glomerular filtration rate, iron studies, B12, folate, C-reactive protein).

A prediction model was developed on eleven candidate predictors: age (years), sex (male/female), American society of anaesthesiology score

(ASA), preoperative transferrin saturation, preoperative folate levels (ng/mL) and preoperative B12 levels (pg/ml), preoperative CRP levels (mg/dL), discharge haemoglobin level (g/L), procedure type (THA or TKA), primary or revision surgery, and the presence of preoperative anaemia (<130g/l for both men and women). The model was developed and reported according to the TRIPOD statement (transparent reporting of a multivariable model for individual prognosis or diagnosis). Predictors were assessed for collinearity. Least absolute shrinkage and selection operator (LASSO) linear regression was used with six-week postoperative Hb as the outcome, and the specified eleven candidate predictors. Model performance measures used were R^2, adjusted R^2, calibration slope and calibration-in-the-large. The model was internally validated using bootstrapping and multiple imputation was used to handle missing data. The final regression coefficients across the imputed data sets and model performance measures were pooled using Rubin's rules.

Results:

327 participants were recruited, and **t**he postoperative six-week Hb was available for 243 patients. The median postoperative six-week Hb was 125 g/l (range 63 to 164). 151 (46.2%) patients remained anaemic post-operatively (threshold <130g/l for both men and women). 98 (40.5%) patients had a Hb more than 10g/l less than their preoperative Hb. Nine predictors were included in the final model: Age, sex, ASA, preoperative transferrin saturation, preoperative folate level, discharge Hb,

preoperative anaemia, procedure type (TKA or THA) and primary or revision surgery. Preoperative anaemia was the most influential predictor, followed by primary or revision surgery. The pooled estimate for R^2 = 0.606 (95% CI; 0.582 to 0.629), adjusted R^2 = 0.600 (95% CI; 0.576 to 0.972), C-slope = 1.024 (95% CI; 0.972 to 1.076) and calibration in the large = 0.156 (95% CI; -0.427 to 0.740).

Conclusions:

The developed model had good predictive ability of Hb levels at six weeks to determine whether patients recovered their Hb or not to within 10g/L of preoperative levels (R^2 value of greater than 60%). The prediction model is based on simple measures without the need for more complex forms of assessment and can be used to help to identify patients at greatest risk of prolonged anaemia, to guide postoperative care, and identification of patients for future clinical trials exploring the prevention, timing and optimal management of prolonged postoperative anaemia.

3.2 Approvals and Funding

This prospective cohort study was conducted according to a protocol approved the University of Oxford Clinical Trials and Research Governance. The project received ethical approval 11th February 2020 (REC reference 19/LO/2011) and is listed on the HRA website: HRA research summaries. I was responsible for study conception and design, successfully getting ethical approval for the study, patient screening,

consent and recruitment, organisation of patient and public involvement, data collection, analysis and drafting the final manuscript (submission pending). I collected all data from patient notes and conducted all research blood sampling at six weeks, and I also personally ensured questionnaire completion. I was a co-applicant for the grant proposal for the study (Royal College of Surgeons of England Pump Priming Award) and liaised with clinical laboratories for processing blood tests with the Oxford University Hospitals NHS Trust. I received support from a research nurse (Susan Morris) in questionnaire completion.

3.3 Background

Hip and knee arthroplasty are highly successful procedures in most patients with significant improvements in patient reported quality of life[84]. However, there are potential complications that can occur after surgery, including cardiovascular and cerebrovascular events, venous thromboembolism, surgical site infection, urinary tract infection, lower respiratory tract infection, and acute kidney injury.

The mortality rate within 90 days of lower limb surgery is 0.4% for a standard patient cohort and 2.9% in individuals aged over 85 years (median age at surgery is 70 years)[7]. The leading cause of death is ischaemic heart disease[53]. The risk of myocardial infarction is significantly elevated during the first 30 days after surgery (hazard ratio (HR) 8.75,

95% CI 3.11 to 24.62) and only returns to baseline levels after six months[85].

Hip and knee arthroplasty represent major surgery and total blood loss can exceed 2000ml[9]. Furthermore, patients often have multiple preoperative co-morbidities and at least a third are anaemic prior to surgery[52]. Cohort studies of over 500,000 patients demonstrate an independent association between preoperative anaemia and 30-day morbidity (odds ratio (OR) 1.41, 95% CI 1.30 to 1.40) and mortality (OR 1.42; 95% CI 1.31 to 1.54)[16,17].

Over two thirds of cases of preoperative anaemia are secondary to iron deficiency[63,64] and preoperative iron supplementation in these patients has shown to improve postoperative morbidity and mortality[59]. This suggests that preoperative anaemia is a modifiable risk factor for morbidity and mortality rather than purely a marker of comorbidity.

However, there are disadvantages to focusing only on treating preoperative anaemia. Firstly, there may be a limited time window before surgery to improve anaemia preoperatively for some procedures (e.g., revision hip arthroplasty requiring more urgent attention). Secondly, a significant proportion of patients treated for their preoperative anaemia remain anaemic. Thirdly, patients unable to restore their haemoglobin (Hb) postoperatively may not have been anaemic preoperatively. In the previous study (Chapter 2) over 90% of patients were anaemic

postoperatively compared with approximately 30% preoperatively (2.5.1 Descriptive analysis).

There has been limited research into the relationship between postoperative anaemia and patient health outcomes. It is often during this postoperative period when adverse events manifest, possibly as a result of reduced tissue oxygenation[86]. An improved understanding of postoperative anaemia was identified as a research priority in a recent consensus statement[87] and the diagnosis and treatment of anaemia is a top ten research priority question set by the James Lind Alliance blood transfusion and blood donation priority setting partnership[48].

Despite optimisation strategies for improving preoperative anaemia and employment of strategies to minimise intraoperative blood loss, over 90% patients are anaemic when discharged from hospital following hip or knee replacement[8]. Few studies have explored the recovery of postoperative anaemia, however a recent cohort study of 30 patients undergoing primary hip replacement found 25% of patients continued to have an Hb at least 10g/L (considered clinically significant) below preoperative concentrations, 56 days after surgery[88].

Investigating the effect of postoperative anaemia on patient outcomes is particularly important given the adoption of restrictive transfusion thresholds of 70g/L since recognition of the adverse outcomes associated with allogeneic blood transfusion[89]. Allogeneic blood transfusion rates have fallen below 5% for primary hip and knee replacement[59] but as a

consequence, patients are likely to be discharged with more severe anaemia. Postoperative anaemia is associated with an increased risk of adverse events, including an increased risk of myocardial infarction which lasts for up to six months after surgery[85].

Potentially, there are several modifiable reasons why patients may not be able to restore their Hb postoperatively. For example, patients may have adequate iron stores for steady state erythropoiesis (process by which red blood cells are produced), but inadequate stores to compensate for significant blood loss. Therefore, although not anaemic preoperatively, they may still benefit from iron supplementation. Alternatively, post-operative inflammation is known to blunt erythropoiesis, and this effect may be more prominent in specific patient populations. These patients may benefit from treatment with erythropoiesis-stimulating agents such as recombinant human erythropoietin. Patients who are found to have low B12 and folate levels may benefit from the administration of B12 and folate to restore their haemoglobin levels. However, it is worth noting that in some conditions, such as sickle cell anaemia, haemoglobin levels are not easily correctable[90].

Guidelines have been published which recommend the treatment of postoperative anaemia[87], although it is not clear which patients may be at risk of prolonged postoperative anaemia, the optimal treatment of postoperative anaemia and whether this is associated with adverse outcomes. This cohort study will identify patient groups exposed to

prolonged postoperative anaemia, who fail to recover their Hb to preoperative levels postoperatively and establish the patient population who are at greatest risk.

3.4 Objectives

The objective of this study was to develop and internally validate a prediction model to identify patients who do not recover their haemoglobin concentration (Hb) to within 10g/l of preoperative levels six weeks.

3.5 Methods

3.5.1 Study Procedures

A prospective observational cohort study at a single site (Nuffield Orthopaedic Centre, Oxford) was conducted. The protocol was reviewed by the Clinical Trials & Research Governance department at the University of Oxford and received a favourable ethical outcome 11.02.2020 (REC reference 19/LO/2011). Participants were recruited from 03.03.2020 – 05.05.2022. An amendment to increase the sample size from 300 to 400 was granted by the same ethics committee 20.12.2020 due to lost to follow up secondary to the COVID-19 pandemic. A further amendment was

approved to increase the duration of recruitment to 10.03.2021 due to the on-going COVID-19 pandemic.

Patient participation lasted between 18-24 weeks. The participant completed two study visits. The first study visit took place at the same time as the routine preoperative assessment clinic (POAC) between 6-12 weeks prior to surgery where the participant had a routine preoperative assessment and blood tests. The second study visit took place six weeks following surgery, which coincided with the routine six week follow up clinic. At this appointment the participant had research blood tests (full blood count (FBC), urea and electrolytes (U&E) and estimated glomerular filtration rate (eGFR), Iron studies, B12, folate, C-reactive protein (CRP)) and undertook routine questionnaires. Demographic data (age, sex, bmi) preoperative and postoperative clinical data (comorbidities, ASA, adverse events, length of hospital stay) and blood test results (FBC, U&Es, CRP, B12 & folate, Iron status), results of blood tests (FBC, U&E, eGFR) performed on the day of surgery and one day after were collected. Medical notes, demographic data and health status was accessed via the information held and maintained by NHS Digital following participants' consent given to the study team. Patient flow diagram 5.2.1.1A.1.1 in the appendix summarises the participant journey in a study flowchart.

3.5.2 Inclusion/Exclusion Criteria

Patients who were listed for a primary or revision total hip arthroplasty/total knee arthroplasty were approached for the study. To be included in the study the patient had to be:

- Willing and able to give informed consent for participation in the study
- Able to understand English
- An adult over 18 years of age
- Undergoing a primary or revision (for any indication) THA or TKA
- Were local to the Thames Valley region (able to return for six-week follow-up appointment)

The patient was excluded if they were undergoing a unicompartmental or patellofemoral knee replacement, had active malignancy, had a known haematological disease (anticoagulated patients not excluded), or had a renal transplant, or were on dialysis.

3.5.3 Patient and public involvement (PPI)

Patients and the public were consulted early in the research process. The PPI meeting was held at the Botnar Research Center 16.09.2019 and included 10 patients and members of the public who donate blood regularly or have recently undergone primary or revision hip and knee arthroplasty. The group helped to develop the research question and outcome measures, and were involved in developing the study design. The patient group consisted of patients who had undergone a primary or

revision hip or knee arthroplasty and patients who regularly donated blood. There are plans to disseminate the results of the research to the study participants and the patient and public involvement group.

3.5.4 Defining the outcome of prediction model

The primary outcome measure was to develop a model to identify patients who do not recover their haemoglobin concentration (Hb) to within 10g/l of preoperative levels at six weeks. Firstly, the outcome was defined as “recovered” (patients who recovered to within 10g/l of preoperative levels) versus “not recovered” (patients who did not recover to within 10g/l of preoperative levels) and a prediction model was developed using logistic regression. This model had very poor performance (the apparent c-statistic, used to evaluate discrimination, was 0.61, 95% CI 0.54-0.69 (range 0.5-1) where a higher score is better and the Brier score was 0.23 (range 0-0.25) where a lower score is better (see Prediction model logistic regression 5.2.1.1A.1.3 for the full calculation in the appendix). This was likely due to the binary outcome definition and loss of information from the continuous Hb measurement. Therefore, an alternative strategy was employed to answer the original research question, through the development of a linear regression prediction model to predict continuous postoperative Hb at six weeks. This model allows the prediction of postoperative Hb, which can then be used to assess whether the participant recovered to within 10g/l of their observed baseline Hb using an additional calculation (observed preoperative Hb result minus the

predicted six-week postoperative Hb result, with result greater than or equal to 10g/l as not recovered and those with less than 10g/l indicating recovery).

3.5.5 Sample Size Determination

The study was powered on the objective to develop a prediction model. The sample size was calculated prior to the study commencement and was conducted using the best-known methods at the time (see Original sample size calculation 5.2.1.1A.1.2 in the appendix). Newer methods to calculate the minimum required sample size to develop a prediction model have since become available[91] and therefore the sample size was adjusted accordingly for a prediction model for a continuous outcome. The sample size for developing the continuous outcome prediction model (for six week postoperative Hb) was calculated in STATA[69] using the "pmsampsize" command to compute the minimum sample size required using the criteria proposed by Riley et al. 2018[91].

For the sample size calculation, an expected mean post-operative Hb value of 109g/L and standard deviation 15.51g/L was assumed, informed by a published cohort study[92], which studied a similar population of patients undergoing elective total hip and knee arthroplasty, at the Nuffield Orthopaedic Centre. The department had existing data from the cohort study and therefore provided an estimate for the R^2 value. Based on the information provided by the research team and clinical judgment, a conservative R^2 of 0.3 was assumed for the prediction modelling scenario.

This information was entered into the Riley et al calculations and a number of 11 predictors was also specified, yielding a total minimum sample size requirement of 243 patients.

Excluding unicompartmental and patellofemoral knee replacements, 1200 primary hip and knee replacements are performed at the Nuffield Orthopaedic Centre each year. Accounting for potential logistical challenges to recruitment (e.g., failure to attend appointment, timing of appointment significantly different to that of study protocol), a conservative recruitment rate of 50% of eligible patients was assumed. Based on this, it was estimated that recruitment would have been complete in six months, with 12 months allowed for follow up and data collection. However due to the COVID-19 pandemic the recruitment period was extended by a further 12 months.

3.5.6 Candidate predictors

Eleven candidate predictors were used in the development of the model. These were selected on the basis of previous published literature[92] and clinical judgment. The predictors were age (years), sex (male/female), American society of anaesthesiology score (ASA), preoperative transferrin saturation (measured as a %, the ratio of serum iron to total iron-binding capacity, considered an important biochemical marker of overall iron status, with a value of less than 20% suggesting iron deficiency), preoperative folate levels (ng/mL) and preoperative B12 levels (pg/ml) (deficiencies in both result in anaemia), preoperative CRP levels (mg/dL)

(increased inflammation results in high hepcidin levels which block intestinal iron absorption and macrophage iron recycling causing iron deficiency anaemia[19]), discharge haemoglobin level (g/L), procedure type (THA or TKA), primary or revision surgery, and the presence of preoperative anaemia (<130g/l for both men and women.) Ferritin was not selected due to being an acute phase protein and therefore transferrin saturation was used instead. Age, preoperative transferrin saturation, preoperative folate levels, preoperative B12 levels, preoperative CRP levels and Hb were included in the model as linear terms.

3.5.7 Statistical analysis for model development

Stata version 17 was used for all analyses[69]. The model was developed and reported according to the TRIPOD (transparent reporting of a multivariable model for individual prognosis or diagnosis) guidance[93]. A scatterplot matrix and correlation coefficients were used to assess whether there were any correlations between linear predictors. Correlation coefficients were used to look for correlations between binary predictors. Least absolute shrinkage and selection operator (LASSO) regression was used with six-week postoperative Hb as the outcome, and the specified 11 candidate predictors. The LASSO regression identifies variables and corresponding regression coefficients to create a model that reduces prediction error, leading to a lower mean squared error[94]. LASSO achieves this by shrinking the regression coefficients towards zero, which constrains the model. The “tuning” parameter, lambda, was selected by

cross validation. An increase in lambda results in shrinkage towards zero, and therefore variables with a regression coefficient of zero are thus removed from the model.

3.5.8 Model performance measures

Model performance measures are based on the agreement between the model prediction and observed values within the dataset, and is used to quantify the predictive performance of the prediction model[93]. The performance of the final model was assessed using three values. The first statistic used was the R^2, which is the proportion of the variation of six-week postoperative Hb explained by the included predictors. The calibration slope, which is based on the agreement between observed and predicted values of six-week postoperative Hb (a value of 1 is most optimal) and finally calibration-in-the-large which denotes the intercept from the model observed and predictive values of six-week postoperative Hb (a value of 0 is most optimal). Calibration was also assessed graphically on a calibration plot.

3.5.9 Internal validation

The model was internally validated using bootstrapping which sampled 500 samples of the derivation data with replacement.[93] Bootstrapping mimics sampling from the population, and randomly selects patients with replacement until a dataset of the same size is obtained.. Each bootstrap sample allows the development of a model and the ability to test its performance on the original data. The LASSO process was repeated within

each of the 500 bootstrap samples, leading to 500 bootstrap models derived using the same methods as the original model development.

Each of these bootstrap sample models were applied within the original dataset to estimate optimism. Overfitting leads to optimism in the model performance estimates in the new data. Optimism can occur when a larger number of predictors are available for statistical analysis and included in model development.[93] An advantage of bootstrapping is that the degree of optimism can be calculated in each bootstrap sample in the repeated predictor selection process, and can be used as an adjunct to performance measures.

The values of R^2, calibration slope, and calibration-in-the-large were obtained for each 500 bootstrap sample and the average values subtracted from the original R^2, calibration slope, and calibration-in-the-large to obtain the adjusted R^2, adjusted calibration slope, and adjusted calibration-in-the-large.

3.5.10 Missing data and multiple imputation

Missing data was described. Multiple imputation was then used to handle missing data. Multiple imputation uses the observed information to impute missing values multiple times rather than singularly. This permits the ability to capture a degree of uncertainty through quantifying variability across the imputations. Data was not imputed if more than 50% of the data was missing. Assuming the data is missing at random, multiple imputation is able to give less biased estimates and standard errors[95,96].

Missing values were imputed 10 times resulting in 10 imputed datasets. The analysis was performed on each of the 10 datasets, including internal validation using bootstrapping before pooling the imputed results. The adjusted R^2, adjusted calibration slope, and adjusted calibration-in-the-large were pooled across the 10 datasets using Rubin's rules[97-99] to obtain the final results. Rubin developed rules for combining estimates and standard errors (SE) from imputed datasets to provide an overall estimate and SE. The rules are based on asymptotic theory, a framework for assessing properties of statistical tests[99].

3.6 Results

3.6.1 Descriptive analysis

A total of 349 patients met the inclusion criteria for the study and were recruited. Of those, 327 proceeded with surgery. Their details are shown in (Table 3 -7). The postoperative six-week Hb was available for 242 patients. Unfortunately, the large amount of missing data was due to participants not able to return for their six-week Hb blood test due to restrictions surrounding the COVID-19 pandemic, or declining to return for their six-week Hb blood test for infection control purposes. The median postoperative six-week Hb was 125 g/l (range 63 to 164). 151 (46.2%) patients remained anaemic post-operatively (threshold <130g/l for both men and women). 98 patients (40.5%) did not recover their Hb to within 10g/L of their preoperative Hb. One (0.3%) patient died within 90 days of

surgery. Myocardial infarction, cerebrovascular events and deep vein thrombosis rates observed in the cohort was low (<1%) (Table 3 -8).

Table 3-7 Baseline characteristics of patients undergoing primary or revision THA or TKA

Characteristics	**n = 327**
Median age, yrs. (range)	69 (30 to 95)
Median preoperative Hb, g/l (range)	134.5 (78 to 180)
Male sex, n (%)	128 (39.14)
ASA, n (%)	
1 (low)	18 (5.5)
2	198 (59.0)
3	105 (32.1)
4 (high)	5 (1.53)
*Missing**	6 (1.83)
BMI, n (%)	
Underweight	1 (0.31)
Normal	61 (18.7)
Overweight	109 (33.3)
Obese	152 (46.5)
Missing (height missing)	4 (1.2)
Patients with preop anaemia, n (%)	123 (37.6)
Median discharge Hb, g/l (range)	110 (71 to 165)
Median preoperative CRP mg/l (range)	3.8 (0 to 162.5)
Median preoperative B12 pg/ml (range)	371.5 (5.4 to 1711)
Median preoperative folate ng/ml (range)	7 (0 to137)
Median preoperative transferrin saturation	24 (6 to 66)
Received an allogeneic transfusion during admission, n (%)	23 (7.1)
Procedure, n (%)	
Primary TKA/THA procedure	221 (67.6)
Revision TKA/THA procedure	106 (32.4)
Primary TKA	55 (16.8)
Primary THA	166 (50.8)
Revision TKA aseptic	24 (7.3)

Revision THA aseptic	49 (15)
Revision TKA (infection)	16 (4.9)
Revision THA (infection)	17 (5.2)
Median length of hospital stay (range)	4 (0 to 49)
**Where not otherwise specified no data was missing*	

Table 3-8 Adverse events of patients undergoing primary or revision THA or TKA

Adverse events	**n = 327**
Readmission (for any reason) within 12 months, n (%)	49 (15%)
Myocardial infarction within 90 days of surgery, n (%)	3 (0.9)
Cerebrovascular event within 90 days of surgery, n (%)	1 (0.3)
Deep vein thrombosis within 90 days of surgery, n (%)	4 (1.2)
Acute kidney injury within 90 days of surgery, n (%)	6 (1.8)
Died within 90 days of surgery	1 (0.3)

3.3.2 The final model

Prior to model development, continuous predictors were assessed for collinearity using scatter matrix plots () and correlation coefficients (Table 3 -9), and no collinearity was found. No associations were found between categorical predictors.

The final LASSO model was applied to 10 imputed datasets and bootstrap internal validation was used per dataset. The predictor co-efficients were pooled using Rubin's Rules[96,98]. Nine predictors remained in the final model, with a very small contribution from preoperative transferrin saturation and preoperative folate.

Table 3-9 Correlation coefficients for continuous candidate predictors

	preop B12	preop folate	preop crp	discharge hb	preop transferrin saturation
preop B12	1				
preop folate	0.03	1			
preop crp	-0.04	0	1		
discharge hb	-0.07	0.03	-0.26	1	
preop transferrin saturation	-0.03	-0.04	-0.4	0.29	1

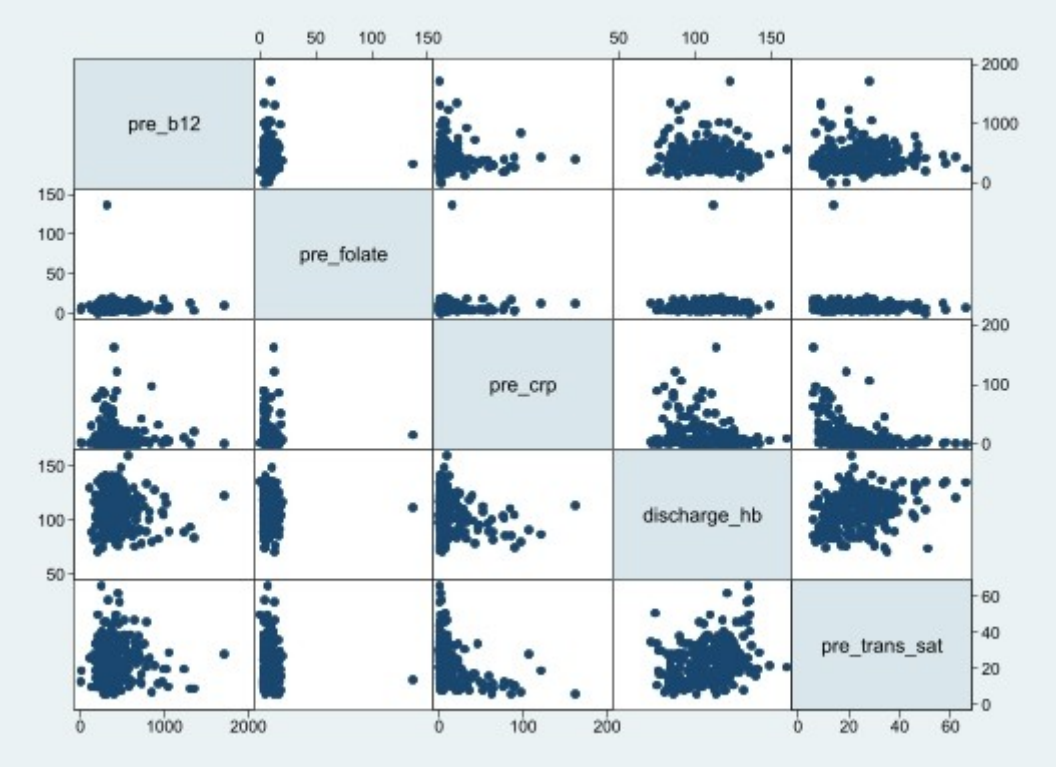


Figure 3-2 Scatter matrix plot for continuous candidate predictors

Preoperative anaemia remained the strongest predictor, along with primary or revision surgery (Table 3 -11). Based on the final pooled estimates the model is thus:

Predicted six week postoperative Hb = (-0.13 x age) + (-2.08 x (male 0, female 1)) + (-1.14 x (ASA 1&2 0, ASA 3&4 1)) + (0.03 x preop transferrin saturation) + (0.04 x preop folate) + (0.44 x discharge Hb) + (-9.76 x (no preoperative anaemia 0, preoperative anaemia 1)) + (0.18 x (TKA 0, THA 1)) + (-6.03 x primary 0, revision 1)) + 98.68

3.6.3 The final model pooled performance measures

The resulting ten R^2, adjusted R^2, adjusted CITL and adjusted C-slope were pooled using Rubin's Rules (for full calculation and equations see 5.2.1.1A.1.4 Rubins rules for pooling performance measures in the appendix). The confidence intervals for the adjusted R^2, R^2 and the C-slope are quite narrow, compared with calibration in the large (Table 3 -10).

Table 3-10 Pooled final performance measures

	R^2	Adjusted R^2	C-slope	Calibration in the large
Pooled estimate	0.606	0.600	1.024	0.156
Lower CI	0.583	0.576	0.972	-0.427
Higher CI	0.629	0.623	1.076	0.740

3.6.4 Sensitivity analysis: complete case analysis model development

The complete case LASSO model (model developed on original dataset) included 6 candidate predictors, age, sex, preoperative transferrin saturation, discharge haemoglobin level, the presence of preoperative

anaemia and whether a primary or revision procedure was performed. The strongest predictor selected was preoperative anaemia and primary or revision surgery, with a small contribution from preoperative transferring saturation (Table 3 -12). The remaining 5 were excluded.

Multiple imputation dataset number	**Predictor co-efficients**									
	Age	Sex	ASA	Preop transferrin saturation	Preop folate	Discharge Hb	Preop anaemia	Procedure (TKA or THA)	Primary/revision	Constant
1	-0.11	-2.03	-0.98	0.04	0.00	0.42	-9.86	0.00	-6.10	99.83
2	-0.13	-1.86	-0.62	0.09	0.08	0.47	-8.95	0.00	-5.38	91.68
3	-0.15	-2.39	-1.15	0.08	0.07	0.43	-9.67	0.46	-6.10	99.93
4	-0.13	-2.10	-1.38	0.00	0.05	0.46	-9.78	0.00	-6.26	98.88
5	-0.15	-2.39	-0.98	0.00	0.10	0.43	-10.46	0.56	-6.71	103.29
6	-0.12	-2.59	-1.99	0.00	0.07	0.43	-10.22	0.37	-6.40	102.09
7	-0.10	-1.62	-0.70	0.00	0.00	0.42	-10.26	0.00	-5.71	98.25
8	-0.15	-1.78	-1.20	0.01	0.01	0.46	-9.48	0.00	-6.13	100.33
9	-0.15	-2.20	-1.18	0.05	0.07	0.46	-9.56	0.39	-5.71	96.46
10	-0.12	-1.83	-1.19	0.00	0.00	0.47	-9.36	0.00	-5.76	96.08
Final pooled co-efficients	**-0.13**	**-2.08**	**-1.14**	**0.03**	**0.04**	**0.44**	**-9.76**	**0.18**	**-6.03**	**98.68**

Table 3-11 Final model pooled predictor co-efficients

Table 3-12 LASSO linear model complete case analysis

	Coefficient (selected by cross validation)
Age	-0.15
Sex	-1.16
Pre-transferrin saturation	0.06
Discharge Hb	0.43
Preop anaemia	-9.11
Primary or revision procedure	-5.36
constant	98.15
λ	0.65

The model showed good apparent predictive performance for postoperative Hb (Figure 3-2; R^2=0.62, adjusted R^2 = 0.61) and was calibrated in the development data (apparent slope=1.1, apparent calibration-in-the-large=-0.81). This was confirmed by the calibration plot which assessed the observed and the mean expected values of postoperative Hb (Figure 3 -3).

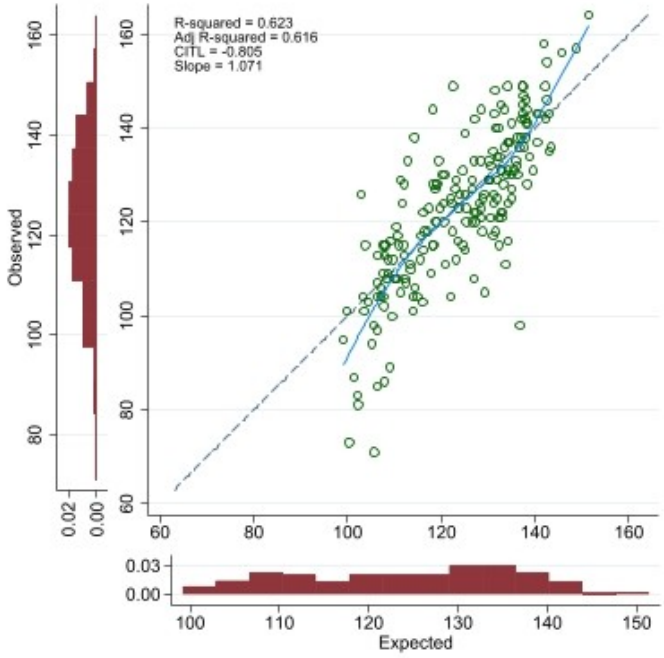


Figure 3-3 Calibration plot LASSO prediction model

3.6.5 Sensitivity analysis: complete case analysis internal validation

Bootstrap internal validation was performed using the complete case analysis (original dataset). The optimism corrected R^2 was 0.57, the optimism adjusted R^2 was 0.56, the optimism adjusted CITL was -0.88, and the optimism adjusted C-slope was 1.03. There was low optimism, reflected in the similar apparent and optimism adjusted performance measures. Following adjustment for optimism, the prediction model maintained a reasonable adjusted R^2 (0.56%).

3.6.6 Differences between predicted and actual values

The final model, with pooled coefficients was then applied to the original dataset and compared with those patients who actually recovered their Hb to within 10g/l compared with those who were predicted to recover their Hb to within 10g/L. 243 patients had an actual postoperative Hb value at six weeks and for 209 patients a predicted Hb was calculated. There were 153 patients who had both an actual postoperative Hb value and a predicted Hb. Table 3 -13 demonstrates the concordance between those predicted and those not predicted to recover compared to actual values.

Table 3-13 The differences between predicted and actual six-week postoperative Hb

	Actual six-week postoperative Hb		
Predicted six-week postoperative	Recovered*	Not recovered*	Total

Hb			
Recovered*	56	20	76
Not recovered*	37	40	77
Total	93	60	153
Accuracy (%) (95% CI)	**Sensitvity** (%) (95% CI)	**Specificity** (%) (95% CI)	
63 (54 to 70)	60 (50 to 70)	67 (53 to 78)	
**to within 10g/l of preoperative Hb*			

The differences between those who predicted not to recover and did, and those who were predicted to recover and did not recover are outlined in Table 3 -14. There was a larger proportion of men predicted to recover who did not recover compared with the overall proportion of men in the cohort (60% vs 39.14%, Table 3 -14 and Table 3 -7 respectively). Similarly, there was a higher number of THA procedures in those who were predicted to recover who did not recover. There was a similar spread of age, ASA, BMI, preoperative anaemia, discharge Hb, preoperative CRP, B12 and folate, and transferrin saturation across both groups and compared with the overall cohort. Patients who were predicted not to recover and did recover, had a higher median preoperative Hb level compared with the overall cohort (142 vs 134.5, Table 3 -14 and Table 3 -7 respectively). Blood transfusion rates for both groups were lower compared with the overall cohort.

Table 3-14 Characteristics of those predicted not to recover and did recover, and vice versa

Characteristics	Predicted not to recover and did actually recover* n=37	Predicted to recover and did not actually recover* n=20
Median age, yrs. (range)	71 (40 to 92)	74 (55 to 85)
Median preoperative Hb, g/l (range)	142 (114 to 162)	133.5 (102 to 148)
Male sex, n (%)	16 (43.2)	12 (60)
ASA, n (%)		
1 (low)	0 (0)	0 (0)
2	23 (62.2)	12 (60)
3	14 (37.8)	7 (35)
4 (high)	0 (0)	1 (5)
BMI, n (%)		
Underweight	0 (0)	0 (0)
Normal	4 (10.8)	4 (20)
Overweight	20 (54.1)	5 (25)
Obese	13 (35.1)	11 (55)
Patients with preop anaemia, n (%)	13 (35.1)	6 (30)
Median discharge Hb, g/l (range)	109 (80 to 136)	116.5 (84 to 136)
Median preoperative CRP mg/l (range)	2.9 (0.7 to 59)	2.2 (0.7 to 79)
Median preoperative B12 pg/ml (range)	355.5 (120 to 676)	279 (202 to 825)
Median preoperative folate ng/ml (range)	6.7 (0 to 14.4)	8.25 (4.1 to 16.4)

Median preoperative transferrin saturation	24 (8 to 58)	22.5 (8 to 47)
Received an allogeneic transfusion during admission, n (%)	1 (2.7)	0 (0)
Procedure, n (%)		
Primary TKA	5 (13.5)	2 (10)
Primary THA	18 (48.7)	14 (70)
Revision TKA aseptic	4 (11.0)	1 (5)
Revision THA aseptic	9 (24.3)	2 (10)
Revision TKA (infection)	1 (2.7)	1 (5)
Revision THA (infection)	0 (0)	0 (0)
**Recovery defined as to within 10g/L of preoperative Hb*		

3.7 **Discussion**

This study successfully developed a novel prediction model to predict postoperative Hb at six weeks following hip or knee arthroplasty. The model is based on readily available measures: age, sex, ASA, preoperative transferrin saturation level, preoperative folate level, discharge Hb, the presence or absence of preoperative anaemia, procedure type (TKA or THA) and whether the surgery was a primary or revision procedure. The model was internally validated via bootstrapping and showed good predictive ability with a useful R^2 value of greater than 60% from the derivation and cross validation datasets. This study also found that a significant proportion of patients failed to recover their Hb levels to within 10g/L of preoperative Hb levels (41%; n=98), and the adverse event rate within 90 days of surgery was low (<1% for mortaility, myocardial infarction and cerebrovascular event).

The majority of studies focus on predicting the risk of blood transfusion following surgery[100-102]. There has been only one study identified in the published literature that has developed and validated a prediction model to estimate postoperative anaemia in an orthopaedic population, and that study predicted immediate postoperative anaemia (within 3 days) in only TKA patients[103]. The model was developed on a retrospectively reviewed cohort study and they found five important predictors: sex, relatively low BMI, low levels of preoperative haemoglobin, abnormally high levels of ESR, and simultaneously two sides of TKA in the same surgery. The authors found that preoperative anaemia was the most influential predictor in their model, which was consistent with the findings from this study. Interestingly, BMI was not found to be important in the prediction of postoperative Hb at six weeks. The authors acknowledged in their paper that this was not consistent with previously published models predicting the risk of transfusion[100].

This study found that a higher ASA, age and patients undergoing a revision procedure compared with a primary procedure were influential predictors, likely due to the increased complexity of surgery, time duration and associated blood loss. These patients are at higher risk of suffering from prolonged anaemia.

The development of this model is important as the model will enable patients and clinicians to be better informed regarding individuals at greatest risk of prolonged anaemia and associated risk of adverse outcomes, and will aid with future clinical studies which may aim to

better understand the effect of prolonged anaemia on outcome and how best to treat postoperative anaemia. Currently, the optimal correction of postoperative anaemia is not clear. There is currently limited data regarding the appropriate timing for the management of postoperative anaemia, along with treatment choice. The best available guidance for clinicians are published consensus statements, which suggest starting iron supplementation in the early postoperative period for patients with iron deficiency where there are no major complications[23]. For patients who have serious postoperative anaemia and blunted erythropoiesis caused by inflammation, or those who refuse blood transfusions, treatment with a medication that stimulates erythropoiesis may be an option[104].

The UK's National Institute for Health and Care Excellence (NICE) suggests providing oral iron to patients with iron-deficiency anaemia after surgery[75]. However, following surgery patients often struggle to tolerate or absorb oral iron, resulting in frequent gastrointestinal side effects and low compliance with treatment. Furthermore, the inflammation caused by surgery increases the production and release of hepcidin, which decreases iron absorption in the intestine and makes oral iron therapy largely ineffective[105]. Intravenous iron may bypass some of these pathways and offer more effective treatment for patients with postoperative iron deficiency anaemia. However, intravenous iron is more costly, and is more likely to be associated with side-effects such as anaphylaxis[106].

There is an urgent need to establish the optimal treatment for patients at risk of prolonged anaemia given its association with adverse outcomes. The results of this cohort study and future clinical trial are likely to be transferrable across all surgical specialties.

This study has several strengths. The data was prospectively collected for the purpose of developing a prediction model and the data quality is high, recently collected and therefore reflective of current clinical practice, with little missing data. The dataset was sufficiently large to develop the model and the model is based on readily available measures. The study followed all recommended methodological guidance as provided in the TRIPOD and PROBAST guidelines explanation and elaboration documents[93,107].

It was not possible to develop a model with optimal model performance to predict the probability of recovering 6-week postoperative Hb to within 10g/L of pre-operative Hb (original aim). This is likely due to predicting a change outcome (post-op Hb minus pre-operative Hb) which was then categorised to recovery to with 10g/L, or not, both of which results in a loss of statistical information and is more at risk of diminishing predictor-outcome associations. A model predicting continuous 6-week postoperative Hb was therefore developed and was used to predict post-op Hb and then identify patients who did or did not recover to within 10g/L of their pre-op Hb value. Based on this altered approach from the original aim, the continuous outcome prediction model would correctly identify 63% of patients recovering their Hb to within 10g/L, or not. However, 37% of patients were not correctly identified. Given these results, it may be

that the recovery to within 10g/L outcome may not be the best outcome to use clinically, and that the model in its current form needs further adjustment prior to clinical use (e.g. a larger sample size, and exploration of additional intraoperative predictors). There is also scope to use artificial intelligence or machine learning to predict the recovery and continuous postoperative Hb outcomes. However, using artificial intelligence and machine learning still may not mean better predicting models and would risk clinical interpretability of the model and the outcome-predictor associations[108]. Future research should include possibly model updating through adding additional predictors and externally validating the model to ensure the model may be used more widely within the orthopaedic population, and separate validations studies would be needed to ensure applicability to the wider surgical population.

Chapter 4 Pharmacological interventions to prevent bleeding in hip and knee arthroplasty

4.1 **Introduction**

This review was conducted according to the published Cochrane protocol "Pharmacological interventions to prevent bleeding in people undergoing elective hip or knee surgery: a systematic review and network meta-analysis"[109] and according to recommendations by the Cochrane Collaboration[110]. The full review is under peer review by the Cochrane Injuries Group. I was responsible for the study concept and design, data acquisition, analysis, interpretation of data, drafting of the work and revising the manuscript for both protocol and final review. I had support from an information specialist (Carolyn Doree) in developing the electronic search and a systematic reviewer (Rita Champaneria) for independent double data extraction. My statistical analyses were reviewed by statisticians Dr. Josie Sandercock and Professor Nicky Welton. This review was conducted according to the published Cochrane protocol "Pharmacological interventions to prevent bleeding in people undergoing elective hip or knee surgery: a systematic review and network meta-analysis"[109] and according to recommendations by the Cochrane Collaboration[110].

4.2 **Abstract**

Introduction:

Hip and knee arthroplasty are well-established means of improving quality of life. However, surgery is associated with a significant risk of bleeding. One third of patients are estimated to be anaemic prior to undergoing hip or knee replacement surgery. Preoperative anaemia coupled with the blood lost during surgery results in up to 90% of patients being anaemic postoperatively. As a result, people undergoing orthopaedic surgery receive 3.9% of all packed red blood-cell transfusions in the United Kingdom. Bleeding and the need for allogenic blood transfusions has been shown to increase the risk of surgical site infection, mortality, is associated with an increased duration of hospital stay, and increased costs associated with surgery.

Reducing blood loss during surgery offers the opportunity to reduce the risk of allogenic blood transfusion, reduce cost and improve patients' outcomes following surgery. Several pharmacological interventions are available and are currently employed as part of routine clinical care. These include antifibrinolytics (Tranexamic acid, Aprotinin and Epsilon-aminocaproic acid), Desmopressin, Recombinant factor VIIa and factor XIII, Fibrinogen, Fibrin sealants, Non-fibrin sealants. The aim of this review is to determine the relative efficacy of pharmacological interventions for preventing blood loss in elective primary or revision hip or knee

arthroplasty, and to identify optimal administration of interventions regarding timing, dose and route.

Methods:

A Cochrane review with network meta-analysis (NMA) was conducted. The following databases were searched for randomised controlled trials of people who had undergone elective hip or knee arthroplasty from database inception to September 2021: CENTRAL (*The Cochrane Library*), MEDLINE (Ovid), Embase (Ovid), CINAHL (EBSCO*host*), Transfusion Evidence Library (Evidentia), ClinicalTrials.gov and WHO International Clinical Trials Registry Platform (ICTRP). Non-elective or emergency procedures were excluded. Studies published after the year 2010 that had not been prospectively registered (Cochrane Injuries group policy) were also excluded. There were no restrictions on gender, ethnicity, or age (adults only). Eligible interventions included: antifibrinolytics (tranexamic acid, aprotinin, epsilon-aminocaproic acid), desmopressin, factor VIIa and XIII, fibrinogen, fibrin sealants, and non-fibrin sealants. Two review authors (Victoria Gibbs and Rita Champaneria) independently screened all titles and abstracts identified by the electronic searches for eligibility using Covidence systematic review software[111] and excluded any citations deemed irrelevant. The texts were screened and all potentially relevant trials for eligibility studied against the criteria set out in the methods section (Two review authors (Victoria Gibbs and Rita Champaneria) independently screened all titles and abstracts identified by the electronic

searches for eligibility using Covidence systematic review software[111] and excluded any citations deemed irrelevant (4.5). Two primary outcomes (risk of an allogenic blood transfusion and all-cause mortality within 30 days of surgery) and four secondary outcomes were studied. Confidence in network meta-analysis (CINeMA) framework was used to assess the certainty of evidence and evidence was assigned as low, medium or high certainty evidence.

Results:

A total of 97 studies were included, with a total of 7835 randomised participants. Trials included more women (63%) than men (37%). 43 studies (3621 participants, 46%) were included in the NMA. The majority of included studies examined tranexamic acid (138 arms, 82%), followed by aprotinin (17 arms, 10%), epsilon-aminocaproic acid (EACA) (7 arms, 4%), desmopressin (5 arms, 3%) and fibrin (2 arms, 1%).

43 studies were combined in the NMA for the primary outcome risk of an allogenic blood transfusion. TXA given intra-articularly and orally at a total dose of greater than 3g pre-incision, intraoperatively and postoperatively ranked the highest (50.5% chance of ranking 1st) within the NMA with a 93% decrease in blood transfusion compared to placebo (relative risk (RR) 0.07, 95% credible interval (CrI) 0 to 1.78; low-certainty evidence) and an anticipated absolute effect of 140 fewer blood transfusions per 1000 people undergoing hip and knee replacement surgery (150 fewer to 117 more) compared with placebo. This was followed by TXA given

intravenously and orally at a total dose of greater than 3g intraoperatively and postoperatively (RR 0.17, 95% CrI 0.02 to 1.14; low-certainty evidence) absolute effect of 125 fewer per 1000 (147 fewer to 21 more) and TXA given intravenously and intra-articularly at a total dose of 2g intraoperatively (RR 0.17, 95% CrI 0.03 to 0.83; high-certainty evidence) absolute effect of 125 fewer per 1000 (146 fewer to 26 fewer). Aprotinin (RR 0.65 95% CrI 0.4 to 1.01) and Epsilon-aminocaproic acid (EACA) (RR 0.68 95% CrI 0.31 to 1.46) were not shown to be effective compared with TXA.

There was not enough data to perform an NMA for the second primary outcome mortality within 30 days of surgery, due to the large number of studies with zero events, or because the outcome was not reported.

Conclusions:

Tranexamic acid was the most effective intervention for preventing the risk of a blood transfusion in people undergoing hip or knee arthroplasty of all the interventions studied. Aprotinin and epsilon-aminocaproic acid (EACA) were not as effective as TXA at preventing the need for allogenic blood transfusion. It was not possible to draw strong conclusions on the optimal dose, route and timing of administration due to the quality of evidence included within the review and the variability of doses, routes and timings of the interventions studied. In general, tranexamic acid given at higher doses tended to rank higher in the treatment hierarchy, and it may be more beneficial to use a mixed route of administration (oral and

intra-articular, oral and intravenous, or intravenous and intra-articular) rather than a single route. Intravenous administration did not rank more highly than oral administration. However, it was not possible to draw these conclusions based on the trials included within this review.

4.3 **Background**

The safe access to blood products and minimising unnecessary blood transfusions to preserve a limited resource is a global priority[112], and the prevention of bleeding has been identified as an important research priority by the James Lind Alliance (JLA). The JLA for transfusion has specified the need to better understand 'the best drug alternatives to blood transfusion to reduce and prevent bleeding.'[45] Blood transfusion is associated with an increased risk of adverse events[11,55], and is costly to administer. Currently a unit of red blood cells in the United Kingdom costs £153.30, an increase of £24.30 since 2019[31]. This significant increase in cost is multifactorial, with some increased funds required for marketing purposes to increase donor numbers for individual blood groups[113].

Drugs to prevent bleeding in arthroplasty are considerably cheaper than a blood transfusion[114] and may reduce the need for transfusion, offering a lower risk profile for patients. There are several drugs licensed for use in surgery which aim to reduce bleeding. The most widely used are antifibrinolytic drugs, which act to competitively inhibit plasminogen

activation, which in turn attenuates the process of fibrinolysis. This results in stabilisation of the fibrin clot and a reduction in bleeding.

One of the most common antifibrinolytic drugs used in the United Kingdom is tranexamic acid (TXA). TXA is often recommended for intraoperative use in lower limb arthroplasty[115]. TXA has been shown to reduce the need for transfusion by 69%[116] in elective hip and knee arthroplasty, and costs £3.09 per 10ml ampoule[114]. Other popular antifibrinolytics include Epsilon-aminocaproic acid (EACA) and Aprotinin. EACA belongs to the lysine class of antifibrinolytics, similar to TXA and is thought to act via a similar mechanism. EACA has become increasingly popular in the USA as it is significantly cheaper than TXA[117], however the efficacy of EACA compared with TXA is not clear[118]. Aprotinin is a naturally occurring single-chain amino acid polypeptide and is a proteinase inhibitor with antifibrinolytic properties[119] and is frequently used during cardiac surgery[120]. Aprotinin had a period of disuse when a series of small observational studies suggested that it could increase the risk of mortality[121,122], however more recent studies have concluded that Aprotinin is safe for use in surgery and it has seen a resurgence in recent years[123,124].

Less well studied drugs available for use to prevent bleeding include desmopressin a vasopressin analogue, fibrinogen, and topical fibrin based and non-fibrin-based sealants. Many of these pharmacological

interventions can be administered in a variety of different ways, including orally, intravenously, topically and intra-nasally.

The timing of administration of drugs to reduce bleeding has been shown to be of great significance. The CRASH-2 trial, a large RCT assessing TXA efficacy in trauma patients, concluded that TXA given within three hours of injury reduced the risk of death, however if administered after three hours, may increase mortality[125]. Similarly ensuring the correct dose of the drug administered is important from a side-effect profile, and cost.

There is a large evidence base investigating the effectiveness of many of these drugs for reducing blood loss[126,127]. However despite national guidance on the use of TXA, there is significant variability in its use, with 67.5% of planned surgical cases with expected moderate blood loss (greater than 500 ml) receiving the drug in 2021[128]. Barriers to use include uncertainty of the optimal route, dose and timing of administration. Furthermore, there is concern around the theoretical risk of blood clots which is unclear in certain high risk groups, including patients undergoing major orthopaedic surgery[129].

There is no trial design which would enable the comparison of all of these drugs, doses, routes and timings in hip and knee arthroplasty patients. This provides uncertainty to clinicians, as it is unclear which pharmacological interventions are most effective for reducing bleeding and the method by which to administer those interventions. Therefore, a Cochrane review with network meta-analysis (NMA) of RCTs was

conducted in order to provide the highest level of evidence for clinicians, and provide more clarity on the optimal drug, dose route and timing for preventing bleeding in arthroplasty patients. NMA enables the comparison of more than two treatments and allows the generation of a treatment hierarchy, useful for clinical decision making.

4.4 **Objectives**

The primary objective of this study was to determine the relative effectiveness of pharmacological interventions for preventing blood loss in elective primary or revision hip or knee replacement, and to identify the optimal administration of interventions regarding timing, dose and route.

4.5 **Methodology**

4.5.1 Study Procedures

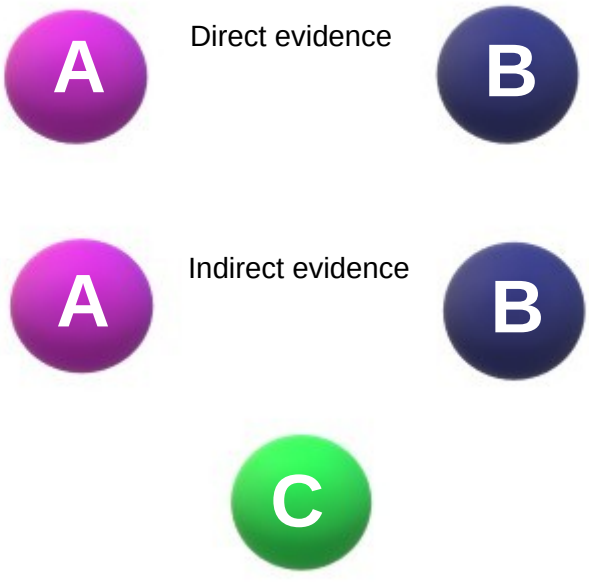


Figure 4-4 Contribution of direct and indirect evidence in an NMA between RCTs A, B & C

Network meta-analysis (NMA) of randomised controlled trials (RCTs) provides the highest level of evidence where direct comparisons in RCTs are not possible and also where direct comparisons have not been made. NMA is a statistical method which enables the comparison of more than two treatments[130]. The comparisons are presented in a network map, where nodes represent treatments and lines connecting nodes represent treatments that have been directly compared in RCTs. Absent lines represent 'indirect' comparisons where no RCTs have directly made that comparison[131] (Figure 4 -4).

NMA uses data from direct comparisons to indirectly estimate treatment effects of missing comparisons to produce treatment estimates[49,132]. The NMA works from the principal that all trials and participants are similar enough across the different comparisons to draw meaningful conclusions.

4.5.2 Inclusion/Exclusion Criteria

The network meta-analysis included only RCTs to ensure only the highest level of evidence was used in evidence synthesis, and included patients who had an elective total hip or total knee arthroplasty, unicondylar or partial knee arthroplasty or revision hip or knee arthroplasty. RCTs needed to be prospectively registered if the final report was published after 2010 to be included. By 2010 all RCTs were mandated to have

prospective registration globally by National Institutes of Health to prevent reporting bias[133,134]. RCTs included in the network had to compare one or more of the following interventions:

- Antifibrinolytics: Tranexamic acid, Aprotinin or Epsilon-aminocaproic acid (EACA)
- Desmopressin
- Factor VIIa and Factor XIII
- Fibrinogen
- Fibrin sealants
- Non-fibrin sealants

Studies comparing an intervention against standard care were excluded to reduce the risk of bias associated with blinding. Patients with a higher risk of bleeding, such as haemophilia were also excluded at the study level. There were no restrictions on gender or ethnicity. Where trials contained a mixed trauma and elective population, data from elective subgroups were used. If subgroup data were not reported, then elective data needed to comprise at least 80% of the sample size in order to be included to assist with ensuring the transivity assumption would not be compromised.

4.5.3 Outcome Measures

There were two primary outcome measures and four secondary outcome measures. The first primary outcome measure was risk of an allogenic red blood transfusion within 30 days of surgery. This was selected over blood loss, as although many studies were likely to report blood loss,

quantification of blood loss in Orthopaedics is highly subjective and has poor inter-rater reliability. This is due to the use of gauzes and hidden losses[135,136]. Formulae exist to help improve the estimation of blood loss, however these remain unreliable[137]. The second primary outcome selected was all-cause mortality up to 30 days within surgery.

Secondary outcome measures included the mean number of transfusion episodes within 30 days of surgery, length of hospital stay (LOHS), re-operation due to bleeding within seven days of surgery and adverse events. LOHS was chosen as the 30 day mortality rate following hip and knee arthroplasty is low (0.08%)[138]. Adverse events included thromboembolic events (deep vein thrombosis (DVT), pulmonary embolism (PE), myocardial infarction (MI), and cerebral vascular accident (CVA)) within 30 days of surgery, any acute transfusion reactions within 24 hours of blood administration and serious suspected drug reactions within 30 days of drug administration. Serious drug reactions were defined using the International Conference on Harmonisation Good Clinical Practice.[139]

Cost and patient reported outcome measures (PROMS) data was also collected from studies, although no formal economic evaluation was performed. This data may be useful for those involved in decision making.

4.5.4 Electronic Search Strategy (update search conducted 19.09.2021)

A search strategy was developed in conjunction with a senior information specialist. The search strategy consisted of index terms, words and word variations for the population (hip and knee) and interventions (pharmacological interventions to prevent bleeding). There was no limit on searches by language, publication type, or year of publication. The databases were searched through the OVID platform, from database inception to 18 October 2022, and included: CENTRAL, MEDLINE, Embase, CINAHL, Transfusion Evidence Library, ClinicalTrials.gov, and World Health Organization International Clinical Trials Registry Platform (ICTRP). Each reference was screened and double extracted by two independent reviewers VNG and Rita Solanki (systematic reviewer) as per the methods described in the Cochrane Handbook for Systematic Reviews [140]. The full search strategy is detailed in appendix (Cochrane Electronic Search Strategy 5.2.1.1B.1.1.)

Relevant review articles were reviewed to collect as much evidence as possible and references were hand searched to supplement the database searches to confirm that no additional trials were missed. The most recent published systematic reviews (2020-2021) were identified and authors in the area were contacted to ascertain to whether there were any further trials known to them. Authors of on-going trials were contacted to request any additional unpublished data. Any relevant errata and retractions for studies which were included were also examined.

4.5.5 Data Collection

Trial information data, characteristics of participants (including age, sex, and ethnicity) type of surgery, lost to follow-up, dropouts with reasons, protocol violations, co-morbidities, characteristics of interventions, outcomes and quality assessment were collected. The data extraction form was piloted on 10 studies and refined as necessary. A copy of the data extraction form is included in the appendix (5.2.1.1B.1.2 Data extraction form). Information was requested from the trial authors if there was insufficient information. Arm-level data was used rather than study-level data. Articles in different languages were translated using the Cochrane “Task Exchange”.

4.5.6 Potential risk modifiers

From every included trial data was extracted on the following characteristics which may act as treatment risk modifiers:

1) Type of procedure: revision arthroplasty surgery typically results in more blood loss[9], and an increase in the need for allogenic blood transfusion. This is likely to be related to the increased complexity of revision surgery and subsequent duration of surgery.

2) Indication for surgery: Surgery performed for malignancy is likely to result in more blood loss due to increased vasculature of tumours[141].

3) Duration of surgery: will result in increased bleeding.

4) Proportion of trial participants with preoperative anaemia: preoperative anaemia is a strong risk factor for blood transfusion following surgery[142].

5) Type of anaesthetic: general anaesthesia may result in the loss of venous vasoconstriction and has been associated with an increased risk of transfusion[143].

6) Use of tourniquet in knee arthroplasty: it is currently unclear whether tourniquet use affects blood loss following knee arthroplasty. Several meta-analyses suggest that tourniquet use may increase blood loss through the activation of inflammatory cytokines from tissue ischemia [144,145]. However, a more recent RCT suggested tourniquets may not affect total blood loss [146].

7) Use of anticoagulation: patients taking anticoagulant therapy will have increased blood loss.

4.5.7 Risk of bias

Risk of bias was assessed using the Cochrane “Risk of bias” one tool as per the Cochrane Handbook of Systematic Reviews of Interventions[140,147]. Risk of bias was conducted independently by VNG and RS, and conflicts were resolved by Prof. Lise Estcourt. The following domains were assessed: selection bias (random sequence generation and allocation concealment), reporting bias (selective reporting), attrition (incomplete outcome data), performance bias (blinding of participants, personnel and outcome assessors), detection bias (blinding of outcome assessment) and

other forms of bias (such as pharmaceutical or charitable funding). A dropout rate of less than 20% was considered to be at low risk of attrition. A low risk of bias was assigned when all domains had been adequately fulfilled in the study and unclear if the study did not provide enough information for a clear decision. The consensus decisions were included in the 'Characteristics of included studies' table (Characteristics of included studies). Confidence in Network Meta-Analysis (CINeMA) framework was used to assess the certainty of evidence, using the online tool. Confidence In Network Meta-Analysis (CINeMA) framework was used to assess the certainty of evidence, using the online tool[148]. The software was developed from the GRADE framework[49] CINeMA has been shown to improve transparency and considers six domains: within-study bias (this refers to the impact of risk of bias of the included studies, such as short-comings in the trial design or conduct), reporting bias (refers to publication and other reporting bias), indirectness (refers to the relevance of the included trials to the research question), imprecision (assessed by 95% confidence intervals with treatment effects within the range of equivalence), heterogeneity (where there is genuine differences in variability between studies, rather than random variation) and incoherence (variation between direct and indirect sources of evidence)[149]. Indirectness was assessed by evaluating the distribution of potential effect modifiers and relevance of each study to the research question.

4.5.8 Statistical analysis

Binary outcomes were recorded as number and percentage of events and participants in the intervention and control arms. Continuous outcomes were recorded as mean and standard deviation (SD), and total number of participants in the intervention and control arms. The amount of between study variability was assess through the Tau^2 statistic and 95% CI.

All comparisons were included where data existed. The analysis was performed using the participant as the unit of analysis. To assess for heterogeneity in the network, the variance parameter Tau^2 was estimated. The total I^2 value for the whole network was also estimated.

The nodes were decided by a blinded independent expert panel (two consultant haematologists, two consultant orthopaedic surgeons, two consultant anaesthetists) into clinically meaningful groups following data extraction. The panel were blinded to the outcome data and was given information on the study design, types of studies included, and additional information needed to decide the network nodes. The information given to the panel is listed in the Appendix (Information Given to Expert Blinded Panel 5.2.1.1B.1.3). Nodes were coded with drug name, route, dose and timing.

The panel recommended nodes consisting of intervention name, mode of administration, total dose of intervention and timing. The panel recommended each node to consist only of one type of pharmacological

intervention. They felt the following groupings for TXA would result in a pharmacologically similar predicted effect (Table 4 -15).

Table 4-15 Panel recommended nodes for drug TXA

Drug	Dose	Route	Time
Tranexamic acid	1g 2g 3g >3g	Intravenous Intra-articular Topical Oral	Pre-incision Intra-operative Post-operative

For EACA, Aprotinin and Desmopressin the panel recommended grouping all doses together, as they are likely to be weight adjusted doses.

A Bayesian NMA was conducted in 'metainsight' using the method of multivariate meta-analysis which treated different comparisons as different outcomes[150]. The estimated treatment effect for each comparison along with 95% CI was documented. A Bayesian approach was selected as it has several advantages over a frequentist analysis. The analysis can cope with more sparse timings and incorporates uncertainty in the heterogeneity parameter. The NMA was constructed by excluding studies with some-zero (e.g., a zero in one or more arm of the trial but not all arms) and all zero event arms. Zero event studies are highly likely to lead to numerical instability and lack of convergence which can affect connectivity[151].

The NMA included all the expert panel groupings. Timing was divided by the expert panel into pre-incision (intervention administered any time prior to surgical incision), intraoperative (intervention administered anytime between surgical incision and wound closure) and post-operative administration (intervention administered any time after wound closure). The NMA network diagram was performed using STATA 17[69] and the SUCRA plot was performed using R package "ggplot2"[152]. The SUCRA plot demonstrates the cumulative ranking probability for each intervention with those having the largest area under the curve ranking highest.

Where insufficient data existed to conduct NMA, pairwise analysis was conducted. In pairwise meta-analyses, all trials with multiple treatment group comparisons were treated as individual, independent two-arm studies. In pairwise meta-analyses, statistical heterogeneity was assessed using the I^2 statistic with 95% CI. For the primary outcome risk of an allogenic blood transfusion within 30 days of surgery, a "Summary of Findings" table was created as recommended by Yepes-Nuez et al[153]. The top five ranking interventions were presented as well as EACA, Aprotinin, Desmopressin and Fibrin. Results were expressed as median nodal point, with 95% credible intervals. Rank statistics were used to define the probability that a treatment out of n treatments in the NMA were best, second, the third and so on until the least effective treatment.

4.5.9 Sensitivity analysis

The main analysis was performed using all studies. The strength of the overall results was assessed by performing sensitivity analyses where appropriate with respect to excluding trials deemed to be at high risk of bias. The influence of participant dropout was explored where possible and RCTs were categorised into those with less than 20% dropout, those with 20% to 50% dropout, and those with more than 50% dropout, and these groups were analysed if data allowed.

4.6 Results

4.6.1 Description of studies

Following abstract and full text screening 97 RCTs met the inclusion criteria for analysis (Figure 4 -5). Following exclusion of duplicate records and those clearly not relevant at the abstract screening stage, the majority of studies were excluded due to being retrospectively registered (156) or had no trial registration (128). There was a global spread of trials, with the highest number conducted in Europe (35%) and Asia (34%) (Table 4 -16). TXA was the most common drug studied (82%). The trials were mostly conducted in primary hips and knees and by far the most common route studied was intravenous alone, followed by intra articular and then combined. The full characteristics of each included studies are detailed in the appendix (Characteristics of included studies). All included trials were RCTs. There were no quasi-randomised or crossover RCTs. The

included trials were published between 1992 and 2021. Ten included studies were multicentre studies[136,154-162]. Four studies included were translated into English for the review[163-166]. The number of participants ranged from 16[162] to 300[167] and the mean age of participants included ranged from 50[168] to 77[169] years of age. Trials included more women (n=4930/7835 (63%)) than men (n=2905, 7835; 37%) (Table 4 -17).

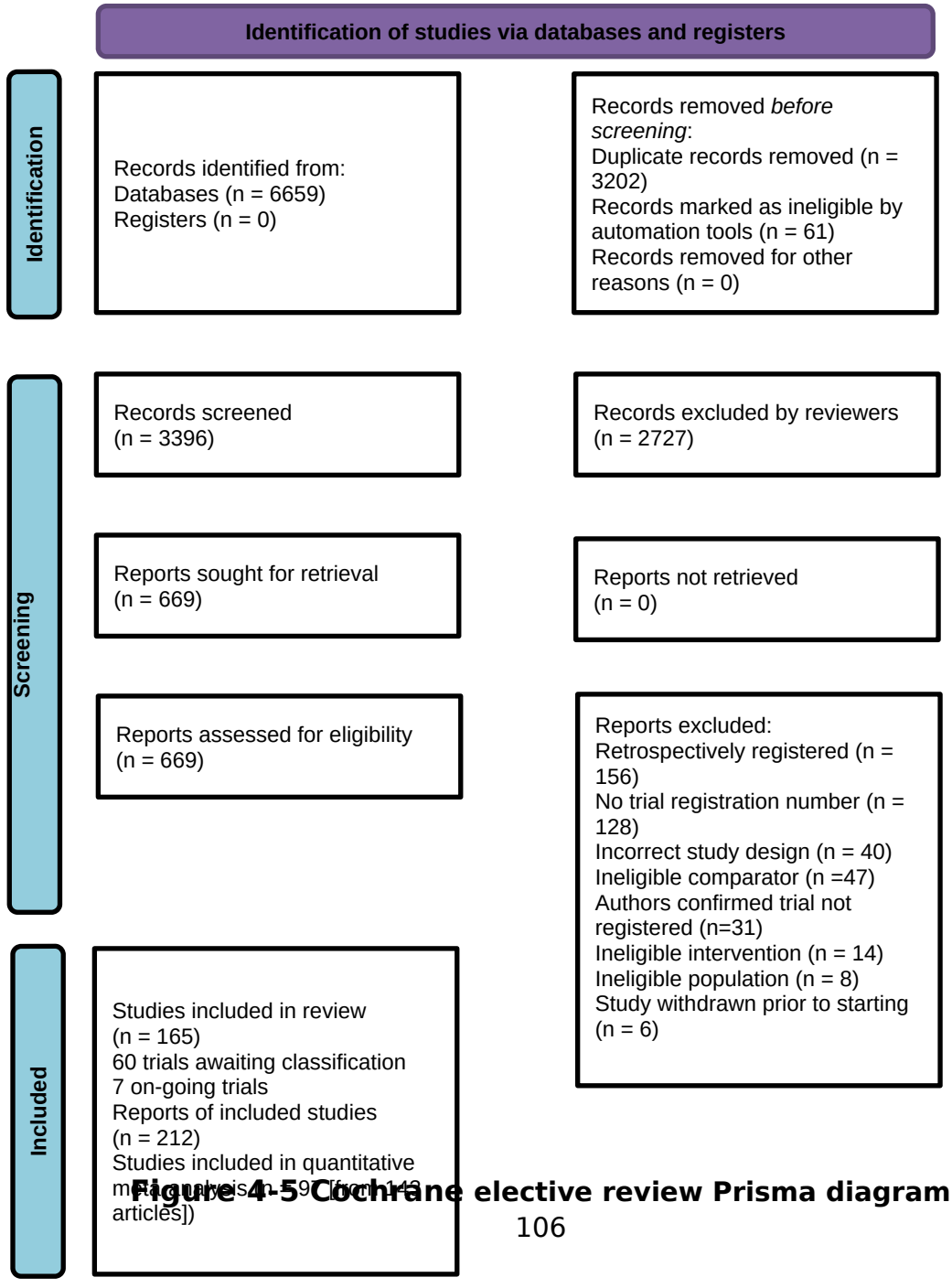


Figure 4-5 Cochrane elective review Prisma diagram

Table 4-16 Baseline characteristics of included studies Cochrane elective review

Study population	***Frequency***	***%***
Primary THA	45	46
Primary TKA	39	41
Mixed Primary THA and TKA	1	1
Revision THA	4	4
Mixed revision THA and TKA	2	2
Bilateral TKA	1	1
Mixed Primary and unilateral TKA	1	1
Mixed Primary and Revision THA and TKA	4	4
RCT origin	***Number of studies***	
Europe	34	35
Asia	33	34
North America	21	22
Australia	6	6
South America	1	1
New Zealand	2	2
Routes of interventions	***Study arms***	
Intravenous (IV)	159	71
Intra-articular (IA)	22	10
IV and IA	17	8
Oral and IA	12	5
Oral	11	5
IV and Oral	3	1
IV, IA and Oral	1	<1
Drug type	***Study arms***	
Tranexamic acid	138	82
Aprotinin	17	10
EACA	7	4
Desmopressin	5	3
Fibrin	2	1

Few studies (19 (19.6%)) reported the primary outcome mortality within 30 days and most studies reported the primary outcome of risk of

requiring a blood transfusion within 30 days (81 (83.5%)). There was little evidence of inconsistency and no evidence that transitivity assumptions had been breached in all networks presented.

Table 4-17 Overview of characteristics of included studies

Study	No. Males	No. females	Total no. people	Ethnicity	Outcomes reported							
					All-cause mortality	Blood trans	Mean units RBC	CVA	DVT	MI	PE	LOHS
Alvarez 2008	17	78	95	NR	N	Y	Y*	N	Y	N	Y	N
Alvarez 2019a	7	15	22	NR	Y	Y	N	Y	Y	Y	Y	N
Alvarez 2019b	5	17	22	NR	Y	Y	N	Y	Y	Y	Y	N
Benoni 1996	23	63	86	NR	N	Y	Y*	N	Y	N	Y	N
Benoni 2000	17	22	39	NR	N	Y	N	N	Y	N	Y	N
Benoni 2001	19	19	38	NR	N	Y	Y*	Y	Y	Y	Y	N
Boese 2017	54	140	194	NR	N	Y	Y*	Y	Y*	N	Y	Y
Bradley 2019a	42	48	90	White 74, African American 13, Other 3	N	Y	N	Y	Y	Y	Y	Y
Bradley 2019b	53	92	145	White 109 African American 33, Other 3	N	Y	N	Y	Y	Y	Y	Y
Camarasa 2006	25	102	127	NR	N	Y	Y	Y	Y	Y	Y	N
Cao 2018	69	83	152	NR	N	Y	Y*	Y	Y	Y	Y	N
Chin 2020	NR	NR	NR	NR	N	Y	Y*	N	N	Y	Y	Y*
Claeys 2007	12	28	40	NR	N	Y	Y*	N	Y	N	N	N
Clave 2019	98	131	229	NR	N	Y	N	N	Y	Y	Y	Y
Colwell 2007	172	180	352	White 334	Y	Y	Y	Y	Y	Y	Y	N
Compostella 1997	NR	NR	NR	NR	N	N	Y*	N	N	N	N	N
Cui 2019	35	37	72	NR	N	Y	N	N	Y	N	Y	N
D'Ambrosio 1999	14	16	30	NR	N	Y	Y*	N	N	N	N	N
Dorji 2021	20	11	31	NR	N	Y	N	N	N	N	N	N
Ekback 2000	20	20	40	NR	N	Y	Y*	N	Y	Y	N	N
Ellis 2001	11	29	40	NR	N	Y	Y*	N	Y	N	Y	Y
Engel 2001	7	17	24	NR	N	Y	Y*	N	Y	N	N	N
Flordal 1992	24	26	50	NR	N	N	Y	N	N	N	N	N
Garcia Enguita 1998	NR	NR	NR	NR	N	N	Y	N	N	N	N	N
Garneti 2004	NR	NR	NR	NR	N	Y	Y	N	Y	N	Y	N
Georgiadis 2013	31	70	101	NR	N	Y	Y*	N	Y	N	Y	Y

Ghijselings 2015	NR	NR	NR	NR	N	N	N	N	N	N	N	N
Gill 2009	3	7	10	NR	N	Y	Y	N	Y	N	Y	Y*
Gomez Barrena 2014	27	51	78	NR	Y	Y	Y*	N	Y	N	Y	Y
Good 2003	15	36	51	NR	N	Y	Y*	N	Y	N	N	N
Goyal 2017	78	90	168	NR	N	Y	Y*	N	Y	N	N	Y
Harley 2002	21	34	55	NR	N	Y	Y*	N	Y	N	Y	N
Hayes 1996	15	27	42	NR	N	N	Y	N	Y	N	N	N
Hiippala 1995	5	23	28	NR	N	Y	Y	N	Y	Y	N	N
Hiippala 1997	12	65	77	NR	Y	Y	Y	N	Y	Y	Y	N
Husted 2003	6	14	20	NR	N	Y	Y*	N	Y	N	Y	N
Jansen 1999	8	34	42	NR	N	Y	Y	N	Y	N	N	N
Janssens 1994	16	24	40	NR	N	Y*	Y	N	Y	N	Y	Y
Jeserschek 2003	7	9	16	NR	N	Y	Y	N	Y	N	N	N
Johansson 2005	53	47	100	NR	N	Y	Y*	N	Y	N	Y	N
Jules-Elysee 2019	31	32	63	Hispanic: 4; Not Hispanic 59;	Y	N	N	N	N	N	N	Y*
Kakar 2009 Bilateral TKR	14	36	50	NR	N	N	Y*	N	Y	N	N	N
Kakar 2009 Unilateral TKR	14	36	50	NR	N	N	Y*	N	Y	N	N	N
Kang 2021	10	87	97	NR	N	Y	Y*	N	Y	Y	Y	N
Kang 2021a	56	244	300	NR	N	Y	Y*	N	Y	N	Y	N
Karnezis 1994	16	20	36	NR	Y	N	N	N	Y	Y	N	Y
Karnezis 1994a	26	30	56	NR	Y	N	N	N	Y	Y	N	Y
Kayupov 2017	24	47	71	NR	N	Y	Y	N	Y	N	Y	Y
Kayupov 2017a	42	41	83	NR	N	Y	N	N	Y	N	Y	Y
King 2019	26	27	53	NR	N	Y	N	N	Y	N	N	Y*
Langdown 2000	NR	NR	NR	NR	N	N	N	N	N	N	N	N
Lei 2017a	27	132	159	NR	N	Y	Y*	Y	Y	Y	Y	Y
Lei 2018b	61	89	150	NR	N	Y	Y*	Y	Y	Y	Y	Y
Lei 2020	26	124	150	NR	N	Y	N	Y	Y	Y	Y	Y*
Lemay 2004	25	14	39	NR	N	Y	N	N	Y	N	Y	N
Levine 2014	15	25	40	NR	Y	Y	Y*	N	Y	N	Y	N
Llau 1998	NR	NR	NR	NR	N	Y	Y*	N	Y	N	N	N
Lopez Picado 2017	57	51	108	NR	N	Y	Y	N	Y	N	N	Y
Molloy 2007	NR	NR	NR	NR	Y	Y	Y	N	Y	N	Y	Y
Morales-Avalos 2021	50	52	102	NR	Y	Y	N	Y	Y	Y	Y	N
Murkin 1995	20	33	53	NR	N	Y	Y	Y	Y	N	N	Y
Murkin 2000	139	141	280	White: 270; Black: 6; Hispanic: 4	Y	Y	N	N	Y	Y	N	N

NCT02922582	6	9	15	Hispanic 0 NOT Hispanic 15	Y	Y	N	Y	N	N	N	N
Niskanen 2005	13	26	39	NR	N	Y	Y*	N	Y	N	Y	Y*
North 2016	77	61	138	NR	N	Y	N	N	Y	Y	Y	N
Orpen 2006	11	18	29	NR	N	Y	N	N	Y	N	Y	N
Painter 2018	65	75	140	NR	Y	Y	N	Y	Y	Y	Y	Y
Peng 2021	13	80	93	NR	N	Y	N	Y	Y	Y	Y	N
Petsatodis 2006	NR	NR	NR	NR	N	Y	Y	N	Y	N	N	N
Ray 2005	NR	NR	NR	NR	N	Y	N	N	Y	N	Y	N
Schott 1995	35	44	79	NR	N	N	Y	N	N	Y	Y	N
Sershon 2020	86	89	175	NR	N	Y	N	Y	Y	N	Y	Y*
Staniforth 2017	NR	NR	NR	NR	N	N	N	N	N	N	N	N
Stowers 2017	59	75	134	NR	N	Y	Y*	N	Y	N	Y	Y
Tanaka 2001	31	68	99	NR	N	Y	Y	N	Y	N	Y	N
Tsukada 2019	16	61	77	NR	N	Y	N	N	Y	N	Y	N
Tsukada 2020	23	77	100	NR	N	Y	Y*	Y	Y	Y	Y	N
Utada 1997	3	18	21	NR	N	N	Y	N	N	N	N	N
Veien 2002	5	25	30	NR	N	Y	Y*	N	Y	N	Y	N
Veien 2005	14	17	31	NR	N	Y	Y*	N	Y	N	Y	N
Wang 2018	61	139	200	NR	N	Y	N	Y	Y	Y	Y	Y
Wang 2019a	59	141	200	NR	Y	Y	N	Y	Y	N	Y	Y*
Wang 2019b	112	188	300	NR	Y	Y	N	Y	Y	Y	Y	Y*
Wang 2019	26	92	118	NR	Y	Y	N	N	Y	N	N	Y*
Wu 2018	59	41	100	NR	N	Y	Y*	N	Y	N	Y	Y
Xie 2017	60	90	150	NR	N	Y	N	Y	Y	Y	Y	Y
Xie 2017a	41	110	151	NR	N	Y	Y*	Y	Y	Y	Y	Y
Yamasaki 2004	37	3	40	NR	N	Y	Y*	N	Y	N	Y	N
Yang 2020	24	70	94	NR	N	Y	N	N	Y	N	Y	N
Yasli 2019	40	20	60	NR	N	N	N	N	Y	N	Y	Y
Yen 2017	23	70	93	NR	Y	Y	N	N	Y	N	Y	Y
Yen 2021	15	88	103	NR	Y	Y	Y*	Y	Y	N	Y	Y*
Zeng 2017	60	40	100	NR	N	Y	Y*	N	Y	N	Y	Y
Zeng 2018	23	37	60	NR	N	Y	Y*	N	Y	N	Y	Y
Zhang 2007	NR	NR	NR	NR	N	Y	Y	N	Y	N	N	N
Zhao 2018	70	50	120	NR	N	Y	Y*	N	Y	N	Y	Y
Zohar 2004	18	42	60	NR	N	Y	Y	N	Y	N	Y	Y

Abbreviations: LOHS: Length of hospital stay, CVA: Cerebrovasuclar event, DVT: Deep vein thrombosis, MI: Myocardial infarction, PE: Pulmonary embolism, Y: Yes, outcome reported, N: No outcome reported, NR: Characteristic not reported

Y*: Yes reported*: Represents where data were not included in the analysis due to being either incomplete or unusable (for example due to differing units or unable to transform data to mean and standard deviation)

4.6.2 Risk of Bias

The main source of bias was selective reporting bias (32 (33%)), followed by other (16, (16.5%)) (Figure 4 -6). Other potential biases considered included assessing baseline imbalances, block randomisation in an unblinded trial, funding and conflict reporting.

There was a range of quality amongst the studies analysed. In general more recent studies (those published after 2017) had a lower risk of bias (Figure 4 -7). 39 trials (40.2%) did not provide sufficient information on sequence generation and therefore were judged as having unclear risk of bias and 60 trials (80.8%) provided clear and detailed information on sequence generation and were judged as having low risk of bias. Blinding for performance bias and detection bias was assessed for objective and subjective outcomes separately. The majority of trials were rated at low risk of subjective blinding bias (52, (59.8%)).

All objective outcomes were rated at low risk of bias as it was felt that blinding would not affect objective outcomes stated in the review. Objective outcomes included mortality, incidence of myocardial infarction (MI), cerebrovascular accident (CVA) or stroke, and pulmonary embolism (PE) due to clear diagnostic criteria in wide use. Most trials reported all outcome data (69;71%).

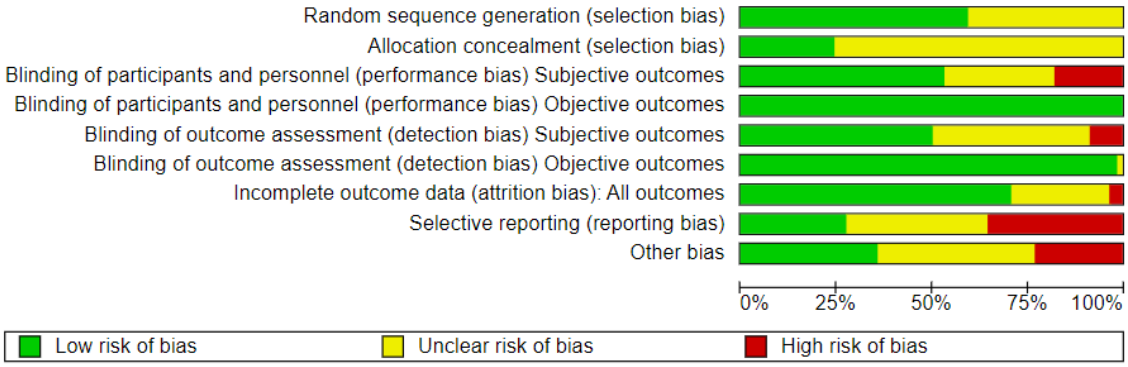


Figure 4-6 Risk of bias graph





Figure 4-7 Risk of bias summary

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Table 4-18 CiNEMA grading for comparisons intervention versus placebo

Comparison	Number of studies	Within-study bias	Reporting bias	Indirectness	Imprecision	Heterogeneity	Incoherence	Confidence rating	Reason(s) for downgrading
Aprotinin: **Placebo**	6	Some concerns	Major concerns	Some concerns	No concerns	Major concerns	No concerns	Low	Reporting bias, heterogeneity
EACA: **Placebo**	3	Some concerns	Some concerns	No concerns	Major concerns	No concerns	No concerns	Low	Imprecision
Fibrin top: **Placebo**	0	Major concerns	Some concerns	Some concerns	Major concerns	No concerns	No concerns	Low	Imprecision
Placebo: **TXA_IA_1g_intra**	1	Some concerns	Some concerns	Some concerns	No concerns	Some concerns	No concerns	Med	Within-study bias, Reporting bias, Indirectness, Heterogeneity
Placebo: **TXA_IA_oral_ grt_than_3g_prel_intra_post**	0	Some concerns	No concerns	Some concerns	Major concerns	No concerns	No concerns	Low	Imprecision
Placebo: **TXA_IV_1g_intra**	3	Some concerns	No concerns	Some concerns	Some concerns	Some concerns	No concerns	Med	Within-study bias, Indirectness, Imprecision, Heterogeneity
Placebo: **TXA_IV_1g_intra_post**	3	Major concerns	No concerns	Some concerns	No concerns	No concerns	Major concerns	Low	Incoherence
Placebo: **TXA_IV_1g_prel**	7	Some concerns	Some concerns	Some concerns	No concerns	Major concerns	Some concerns	Low	Heterogeneity
Placebo:	2	Some	No	Some	No concerns	No concerns	Some	Med	Within-study bias,

TXA_IV_1g_prel_intra		concerns	concerns	concerns			concerns		Indirectness, Incoherence
Placebo: **TXA_IV_1g_prel_post**	1	Some concerns	No concerns	Some concerns	Major concerns	No concerns	No concerns	Low	Imprecision
Placebo: **TXA_IV_2g_intra_post**	5	Some concerns	No concerns	Some concerns	No concerns	Major concerns	No concerns	Low	Heterogeneity
Placebo: **TXA_IV_2g_prel_intra**	1	Some concerns	Major concerns	No concerns	No concerns	Some concerns	Major concerns	Low	Incoherence
Placebo: **TXA_IV_2g_prel_post**	4	Some concerns	No concerns	No concerns	No concerns	Some concerns	No concerns	High	
Placebo: **TXA_IV_grt_than_3g _intra_post**	2	No concerns	No concerns	Some concerns	No concerns	No concerns	No concerns	High	
Placebo: **TXA_IV_grt_than_3g _prel_post**	1	Some concerns	No concerns	No concerns	Major concerns	No concerns	No concerns	Low	Imprecision
Placebo: **TXA_IV_IA_2g_intra**	0	Some concerns	No concerns	Some concerns	No concerns	Some concerns	No concerns	High	
Placebo: **TXA_IV_IA_2g_prel_intra**	0	Major concerns	Some concerns	No concerns	Some concerns	Some concerns	No concerns	Low	Within-study bias
Placebo: **TXA_IV_oral_grt_than_3g _intra_post**	0	Major concerns	No concerns	No concerns	Major concerns	No concerns	No concerns	Low	Within-study bias, Imprecision
Placebo:	0	Some	No	No concerns	Major	No concerns	No concerns	Low	Imprecision

TXA_IV_oral_grt_than_3g _preI_post		concerns	concerns		concerns				
Placebo: TXA_oral_2g_preI	0	Major concerns	Major concerns	No concerns	Major concerns	No concerns	No concerns	Low	Imprecision
Placebo: TXA_oral_2g_preI_post	1	Some concerns	No concerns	No concerns	No concerns	Some concerns	No concerns	High	
Placebo: TXA_oral_grt_than_3g _preI_post	0	Some concerns	No concerns	No concerns	Major concerns	No concerns	No concerns	Low	Imprecision
Footnotes IA: Intraarticular grt_than_3g: greater than 3g IV: Intravenous post: Postoperative dose top: Topical intra: Intraoperative dose preI: Pre-incision dose									

4.6.2.1CiNEMA grading for comparisons intervention versus placebo

The CiNEMA gradings for the nodes against placebo are shown in Table 4 -18. Three comparisons had a high confidence rating. Imprecision and within study bias were common reasons for downgrading comparisons.

4.6.3 Primary outcome: risk of blood transfusion

Primary analysis was conducted according to the expert panel groupings. There was a total of 43 RCTs, involving 3621 participants (46%) in the Bayesian NMA for the primary outcome (Table 4 -19). Nineteen trials were excluded from the analysis due to some zero or all zero event arms[170]. Two studies were also excluded as they did not connect with the network [171,172]. These excluded trials had 1665 participants (21% of participants included in the review).

Table 4-19: Network plot characteristics for risk of blood transfusion NMA

Characteristics	Value
Number of interventions	23
Number of Studies	43
Total number of patients	3621
Total possible pairwise comparisons	253
Total number of pairwise with direct data	39
Number of two arm studies	35
Number of multi-arm studies	8

Total number of events	879

Table 4-20 Summary of findings table

BENEFITS							
Estimates of effects, credible intervals, and certainty of the evidence for the prevention of bleeding in hip and knee replacement patients							
Patient or population: Individuals undergoing planned hip or knee replacement surgery **Interventions: Antifibrinolytics (Tranexamic acid, Aprotinin or Epsilon-aminocaproic acid (EACA)), Fibrin sealants** **Comparator (reference): Placebo** **Outcome: risk of requiring a blood transfusion** **Setting: Within 30 days of surgery**							
Total studies: 43 **Total participants: 3621**	Relative effect* (95% CrI)	Anticipated absolute effect**			Certainty of evidence	Median nodal ranking (95% CrI) ***	Probability of ranking 1st (%)
		Without intervention	*With* intervention	Difference			
TXA given intra-articular and orally at a total dose of greater than 3g pre-incision, intraoperatively & postoperatively	0.07 (0, 1.78)	150 per 1000	11 per 1000	140 fewer per 1000 (150 fewer to 117 more)	Low (Due to imprecision)	1 (1-21)	50.5
TXA given intravenously and orally at a total dose of greater than 3g intraoperatively and postoperatively	0.17 (0.02, 1.14)	150 per 1000	26 per 1000	125 fewer per 1000 (147 fewer to 21 more)	Low (Due to within-study bias, imprecision)	1 (4-20)	14.1
TXA given intravenously and intra-articular at a total dose of 2g intraoperatively	0.17 (0.03, 0.83)	150 per 1000	26 per 1000	125 fewer per 1000 (146 fewer to 26	High	5 (1-20)	9.0

				fewer)			
TXA given intravenously and orally at a total dose of greater than 3g pre-incision and postoperatively	0.42 (0.04, 4.97)	150 per 1000	63 per 1000	87 fewer per 1000 (144 fewer to 596 fewer)	Low (Due to imprecision)	8 (1-23)	7.8
TXA given intravenously at a total dose of greater than 3g pre-incision and postoperatively	0.26 (0.03, 1.37)	150 per 1000	39 per 1000	111 fewer per 1000 (146 fewer to 56 more)	Low (Due to imprecision)	8 (1-22)	5.9
TXA given intravenously at a total dose of 1g pre-incision and postoperatively	0.25 (0.03, 1.29)	150 per 1000	38 per 1000	113 fewer per 1000 (146 fewer to 44 more)	Low (Due to imprecision)	8 (1-22)	5.8
Aprotinin given intravenously	0.65 (0.4, 1.01)	150 per 1000	98 per 1000	53 fewer per 1000 (90 fewer to 2 more)	Low (Due to reporting bias, heterogeneity)	19 (12-22)	0.00
EACA given intravenously	0.68 (0.31, 1.46)	150 per 1000	102 per 1000	48 more per 1000 (104 fewer to 69 more)	Low (Due to imprecision)	19 (10-23)	0.00
Fibrin given topically	0.47 (0.09, 2.35)	150 per 1000	71 per 1000	137 fewer per 1000 (80 fewer to 203 more)	Low (Due to imprecision)	16 (3-23)	0.3
Results are expressed as risk ratios with credible intervals as opposed to the confidence intervals since a Bayesian analysis has been conducted** * Anticipated absolute effect. The anticipated absolute effect compares two risks by calculating the difference between the risks of the intervention group with the risk of the control group** *****Results expressed as median nodal point, with 95% credible intervals. Rank statistics are defined as the probability that a treatment out of n treatments in a network meta-analysis are the best, second, the third and so until the least effective treatment.**							

**** Probability of treatment ranking first

Network plot risk of blood transfusion data code

IA	Intraarticular	grt_than_3g	Greater than 3g
IV	Intravenous	post	Postoperative dose within 24 hours of wound closure
top	Topical	preI	Pre-incision dose
intra	Intraoperative dose		

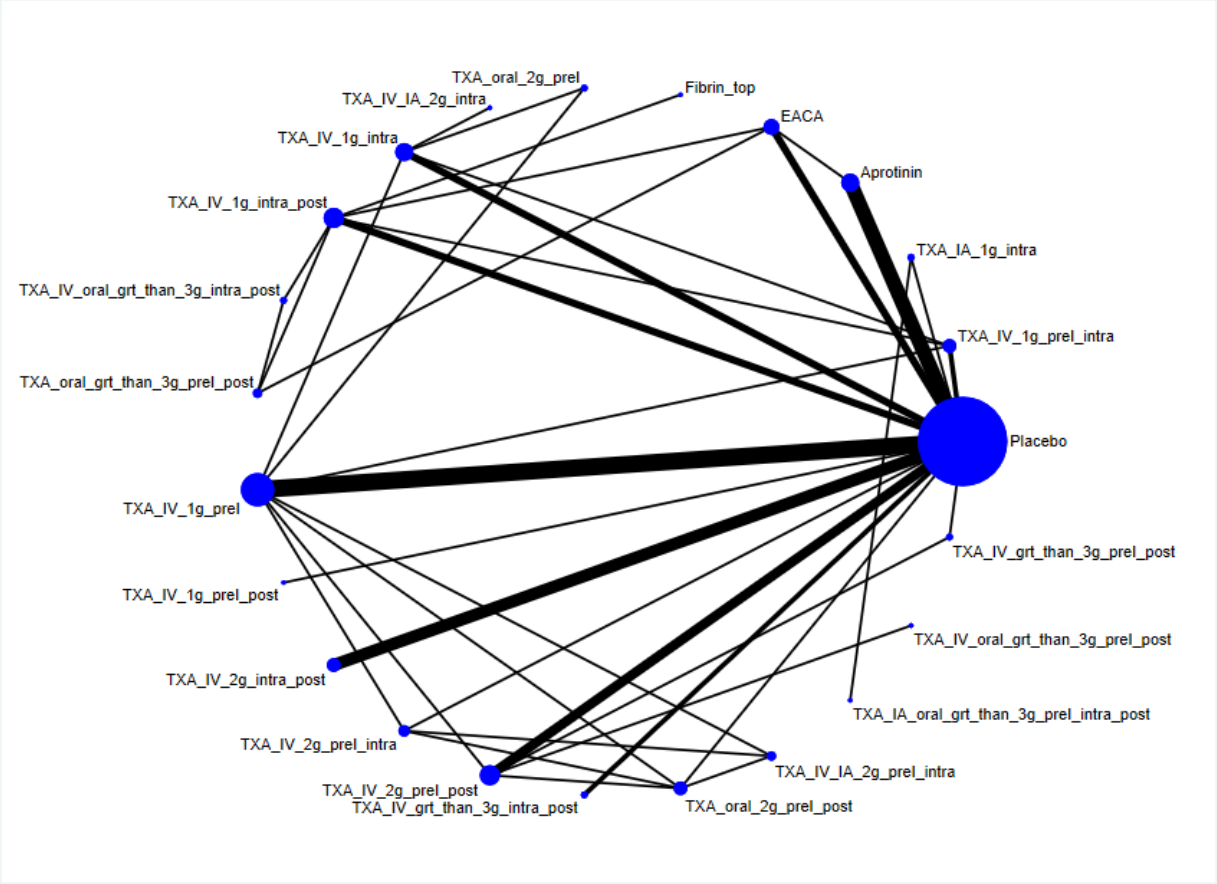
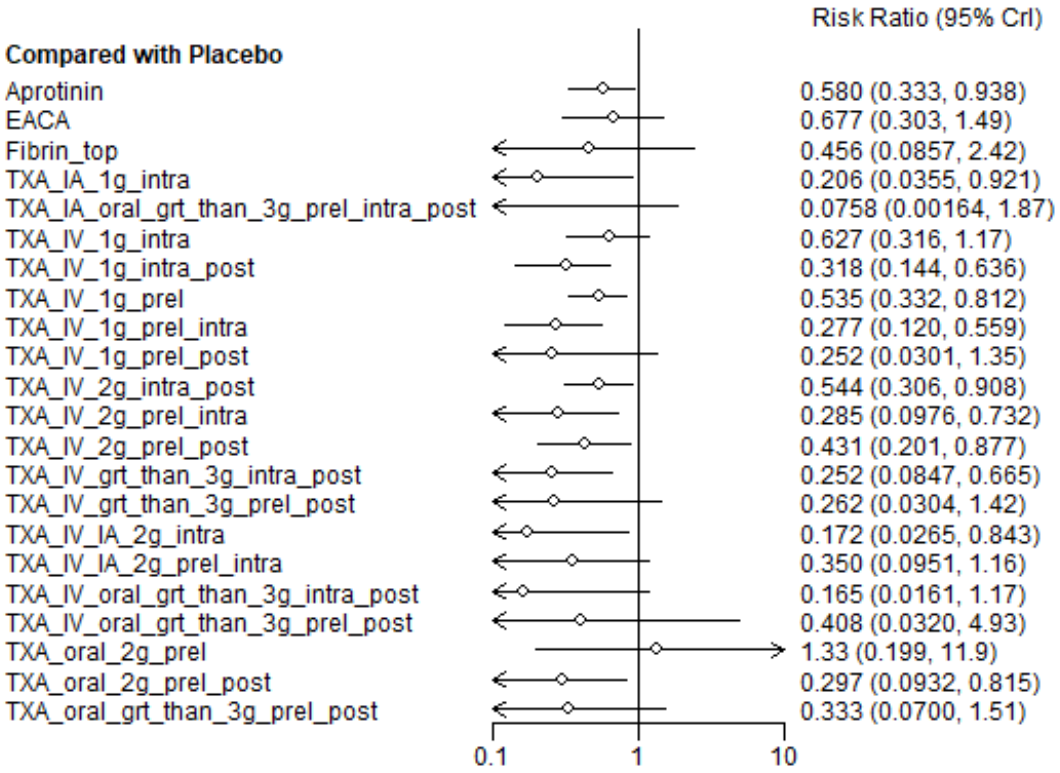


Figure 4-8 Network plot risk of blood transfusion

All included participants had either a primary total hip or knee replacement, unicompartmental knee replacement, bilateral replacements or a revision of a hip or knee replacement. The network meta-analysis results are summarised in the summary of findings table (Table 4 -20) for

the main comparisons, and provides overall estimates of treatment effects compared with placebo and the certainty of available evidence for the risk of blood transfusion within 30 days. Figure 4 -8 Network plot risk of blood transfusion demonstrates the network diagram for the risk of blood transfusion within 30 days. The size of the nodes is proportionate to the total number of participants receiving each intervention, and the line thickness is proportionate to the number of studies directly comparing those interventions.

Figure 4 -9 shows the forest plot of all interventions included within the network with relative risk (RR) and 95% credible intervals (CrI). There is some evidence of benefit for all but one of the included interventions but the credible intervals are wide and certainty of the evidence is low.



IA	Intraarticular	grt_than_3g	Greater than 3g
IV	Intravenous	post	Postoperative dose within 24 hours of wound closure
top	Topical	prel	Pre-incision dose
intra	Intraoperative dose		

Figure 4-9 NMA forest plot risk of blood transfusion

The model was a reasonable fit, with the Dbar (measure of fit) well within five data points (Table 4 -21). The deviance plot represents each data points' contribution to the deviance for the NMA. There were few poorly fitting data points on the equality line (Figure 4 -10). The stem plot (Figure 4 -11) represents the residual deviance per study arm. The total number of stems equals the number of data points and each stem corresponds to the residual deviance associated with each arm in each study. Similarly, there were few arms with large residual deviance suggesting a good model fit.

Table 4-21: Model fit statistics for risk of transfusion NMA

Model fit	
Dbar	96.33
pD	75.77
DIC	172.12
Data points	96.00
Between-study standard deviation (log-odds scale): 0.45. 95% credible interval: 0.21, 0.8.	

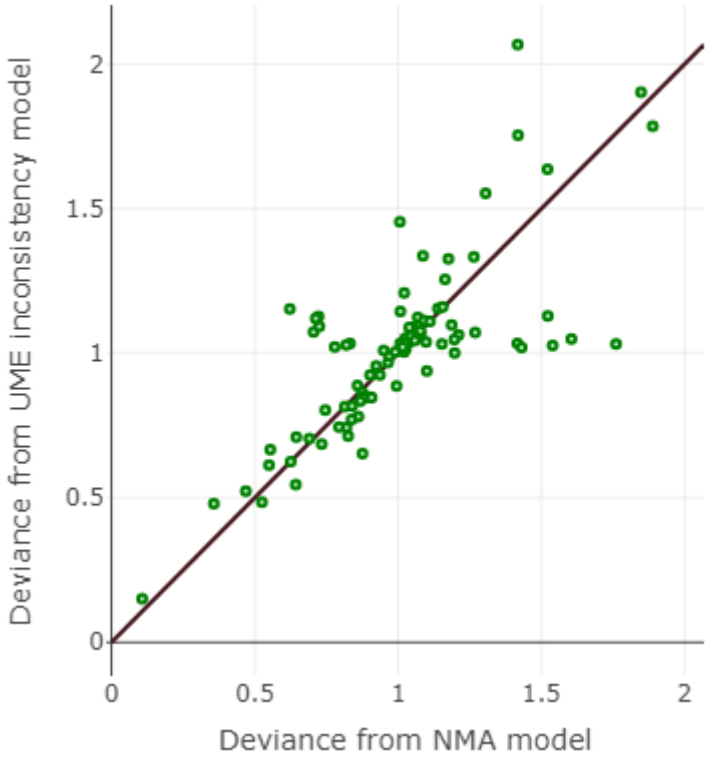


Figure 4-10 Deviance-deviance plot blood transfusion NMA

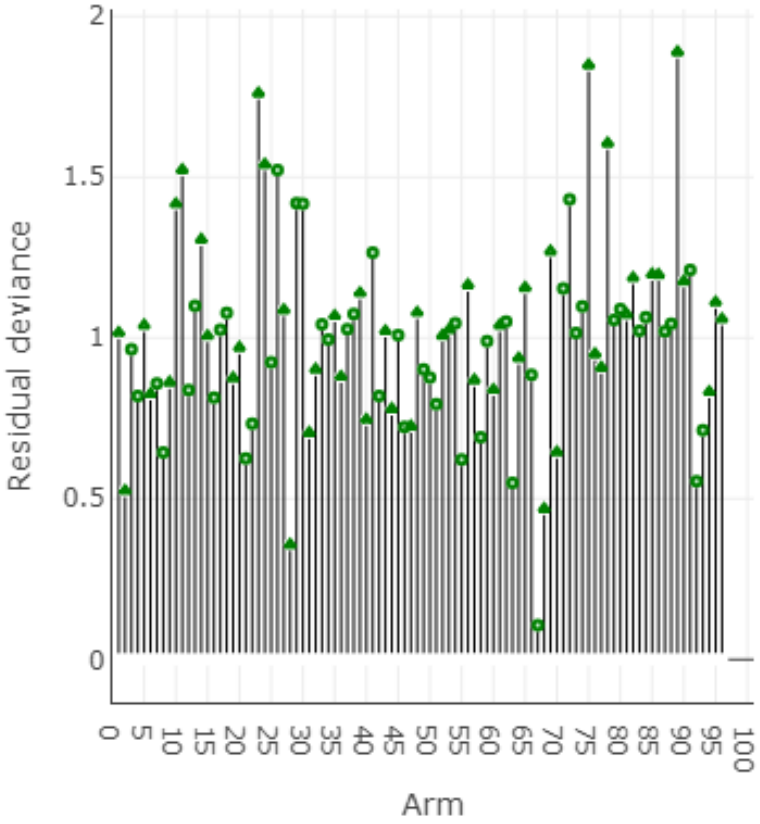


Figure 4-11 Per-arm residual deviance blood transfusion NMA

4.6.3.1Treatment ranking: risk of blood transfusion

The SUCRA plot (Figure 4 -12) shows the cumulative ranking probability for each intervention with higher ranking treatments having the largest area under the curve. The thickness of the lines represents the dose used, the greyscale colours represent the non-TXA interventions, the different colours represent different routes of TXA and the line style (long dash, short dash, dots) represent the different timings of administration. Placebo is represented by the black dotted line.

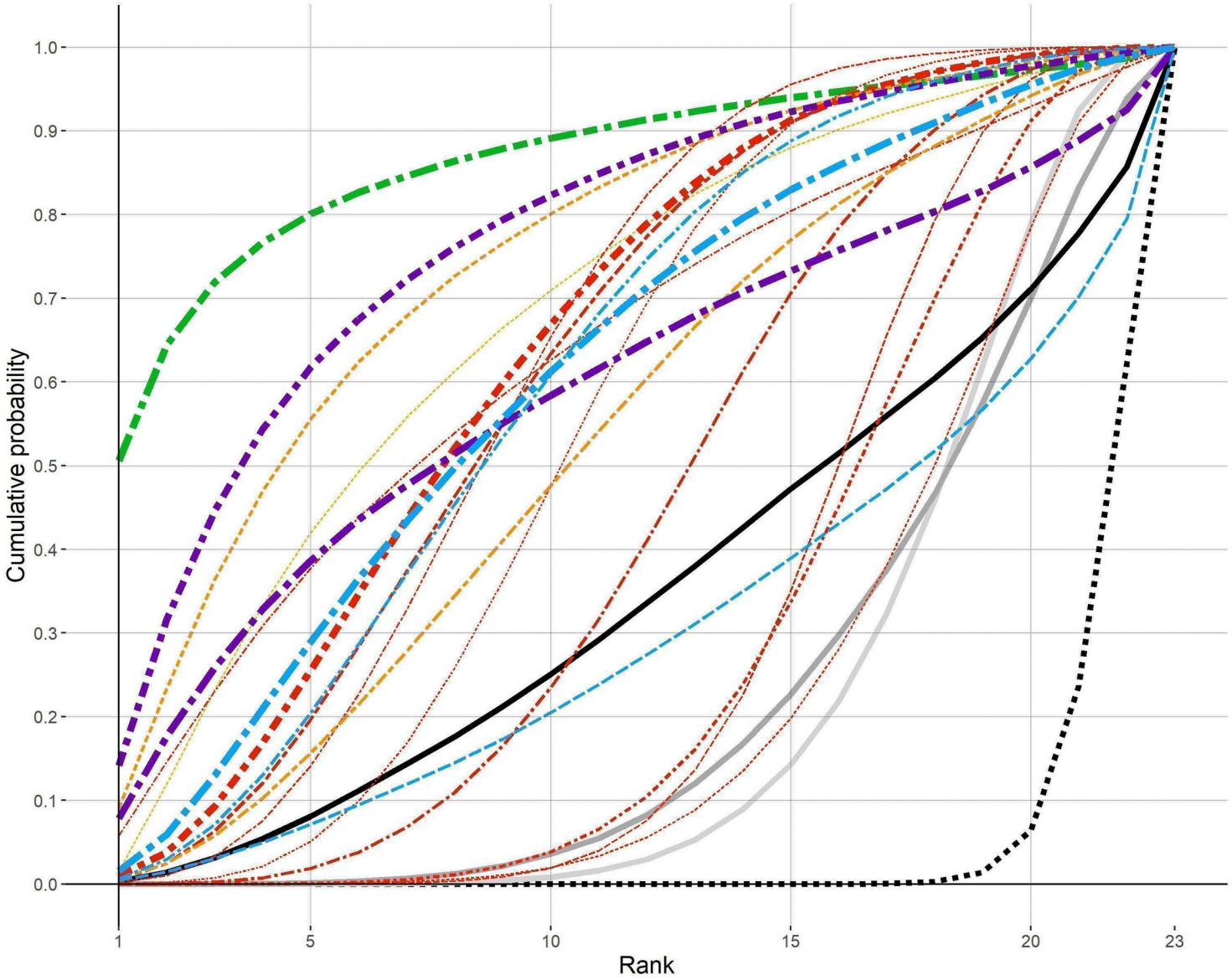
TXA given intra-articular and orally at a total dose of greater than 3g pre-incision, intraoperatively & postoperatively ranked first (50.5% probability) in the network versus placebo with a relative 93% decrease in blood transfusions compared with placebo (RR 0.07, 95% CrI 0 to 1.78), although this is rated as low-certainty evidence; the estimate is extreme, based on indirect evidence alone, and the confidence interval is wide.

This was followed by TXA given intravenously and orally at a total dose of greater than 3g intraoperatively and postoperatively, with a relative 83% decrease in blood transfusion compared with placebo (RR 0.17, 95% CrI 0.02 to 1.14; low-certainty evidence) and TXA given intravenously and intra-articular at a total dose of 2g intraoperatively with a relative 83% decrease in blood transfusion compared with placebo (RR 0.17, 95% CrI 0.03 to 0.83; high-certainty evidence).

The ranking effects of other top 6 TXA interventions are presented in Summary of findings Table 4 -20. Aprotinin (RR 0.65 95% CrI 0.4, 1.01) and EACA (RR 0.68 95% CrI 0.31, 1.46) had a median rank of 19 (95% CrI 12 to 22) and 19 (95% CrI 10 to 23) respectively, while fibrin given topically (RR 0.47, 95% CrI 0.09 to 2.35) had a median rank of 16 (95% CrI 3 to 23). The network is sparsely populated, with not many more trials than there are treatments to compare, with all the trials being small or very small.

The SUCRA plot (Figure 4 -12) is useful for identifying the features of interventions which appear to be more beneficial. The cumulative ranking probability for each intervention with higher ranking treatments, and therefore more likely to be beneficial, have the largest area under the curve. The thickness of the lines represents the dose used, the greyscale colours represent the non-TXA interventions, the different colours represent different routes of TXA and the line style (long dash, short dash, dots) represent the different timings of administration. Placebo is represented by the black dotted line.

The SUCRA plot suggests higher doses of TXA may be beneficial (are clustered in the upper left diagonal of the plot, and have the greatest area under the curve), as are all the interventions including intra-articular administration and all but one of the oral TXA regimens. Lower doses and IV TXA have more mixed results in terms of benefit, appearing in both upper left and bottom right diagonals of the plot.



Placebo is the black dotted line.

Aprotinin: light grey
EACA: dark grey
Fibrin_top: black

TXA regimens are coded as follows:
Dose (1g, 2g, 3g, >3g) is indicated by the thickness of the line.
Route of administration is indicated by colour: red for IV, yellow for IA, blue for oral, and combinations (orange, green, purple).
Timing is indicated by line style: long dash for pre-incision, short dash for intra-surgical, dotted for post, and combinations for multiple timepoints.

Figure 4-12 SUCRA plot risk of transfusion

4.6.4 Primary outcome mortality

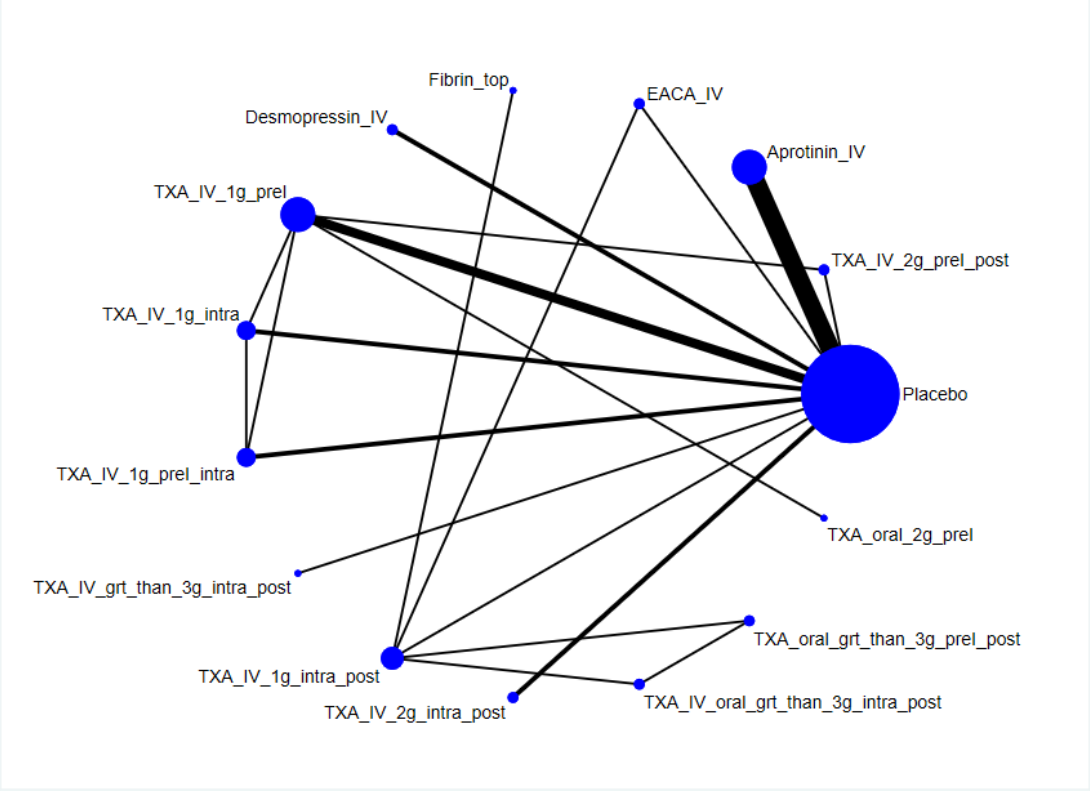
There was not enough data to present a network meta-analysis for the primary outcome of mortality within 30 days of surgery. Therefore, a pair-wise meta-analysis was conducted. There was no indication of increased mortality in any of the pairwise comparisons analysed. All confidence intervals for the pairwise comparisons for mortality included the null effect 0.

The following pairwise comparisons were possible: TXA IV versus placebo (Appendix B.1.5.1); TXA oral versus placebo (Appendix B.1.5.2); TXA topical versus placebo (Appendix B.1.5.3); TXA IV given at a lower dose versus TXA IV given at a higher dose (Appendix B.1.5.4); TXA IV versus TXA topical (Appendix B.1.5.5); TXA oral lower dose versus TXA oral higher dose (Appendix B.1.5.6); TXA topical lower dose versus TXA topical higher dose (Appendix B.1.5.7); TXA oral versus EACA oral (Appendix B.1.5.8); TXA IV versus Fibrin topical (Appendix B.1.5.9); TXA topical versus Fibrin topical (Appendix B.1.5.10); Aprotinin versus placebo (Appendix B.1.5.11); Desmopressin versus placebo (Appendix B.1.5.12); Fibrin topical versus placebo (Appendix B.1.5.13); TXA IV and TXA oral versus TXA IV (Appendix B.1.5.14); TXA topical versus TXA oral and TXA topical (Appendix B.1.5.15); TXA oral and topical lower dose versus TXA oral and topical higher dose (Appendix B.1.5.16).

4.6.5 Secondary outcomes

4.6.5.1 Mean number of transfusion episodes up to 30 days

There was enough data to conduct a Bayesian NMA for the secondary outcome mean number of red cell units transfused per person up to 30 days (Figure 4 -13). The number of units per person randomised was analysed, using reported means and standard deviations. A reasonable number of studies reported this outcome (23) and 15 interventions were explored (Table 4 -22).



Network plot risk of blood transfusion data code

IA	Intraarticular	grt_than_3g	greater than 3g
IV	Intravenous	post	Postoperative dose within 24 hours of wound closure
top	Topical	prel	Preincision dose

Figure 4-13 Mean number of units Network plot

Table 4-22 Network plot characteristics Mean number of transfusion episodes

Characteristics	Value
Number of interventions	15
Number of Studies	23
Total number of patients	1698
Total possible pairwise comparisons	105
Total number of pairwise with direct data	20
Number of two arm studies	19
Number of multi-arm studies	4
Average outcome	1.07

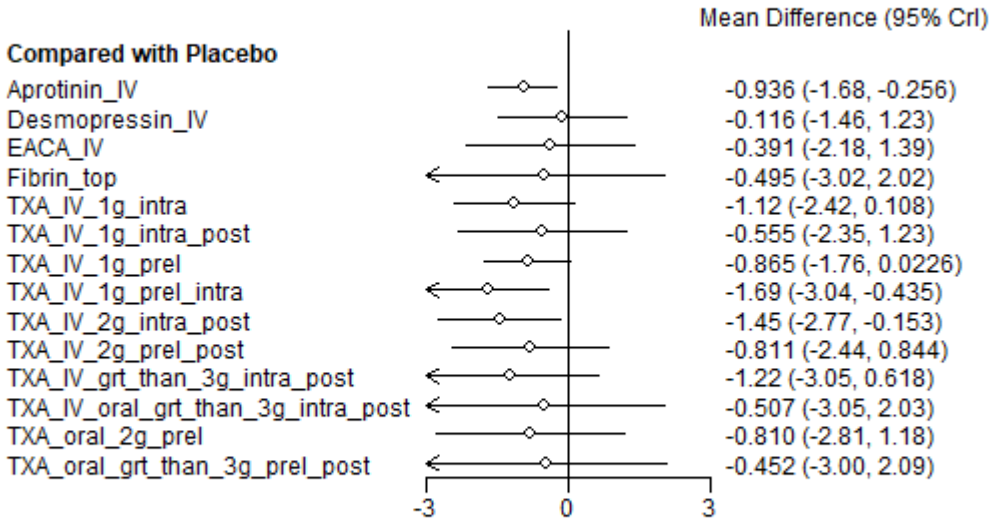


Figure 4-14 Mean number of transfusion episodes NMA forest plot

There is some evidence of reduced volume of blood transfusion in favour of aprotinin and some TXA regimens, with no evidence of benefit for desmopressin, EACA or fibrin, although all the confidence intervals were

wide (Figure 4 -14). There were over 1600 participants in the network, with over 100 possible pairwise comparisons, 20 of which contained direct data. There was just over 1 unit transfused per participant included within the network (Table 4 -22). There were three interventions which were favourable compared with placebo. TXA given intravenously at a total dose of 1g pre-incision and intraoperatively (RR -1.69 95% CrI -3.04, -0.435), TXA given intravenously at a total dose of 2g intraoperatively and postoperatively (RR -1.45, 95% CrI -2.77, -0.153) and intravenous aprotinin (RR -0.935 95% CrI -1.68 to -0.26) (Figure 4 -14).

4.6.5.2Mean number of transfusion episodes model fit

The model fit for the mean number of transfusion episodes NMA was very good, with the data points and Dbar within 1 point of each other, all studies along the equality line and little difference in study arm residual deviance (Table 4 -23, Figure 4 -15).

Table 4-23 Mean number of transfusion episodes model fit statistics

Model fit mean number of transfusion episodes NMA	
Dbar	51.65
pD	48.38
DIC	100.03
Data points	51.00
Between-study standard deviation: 0.86. 95% credible interval: 0.51, 1.4	

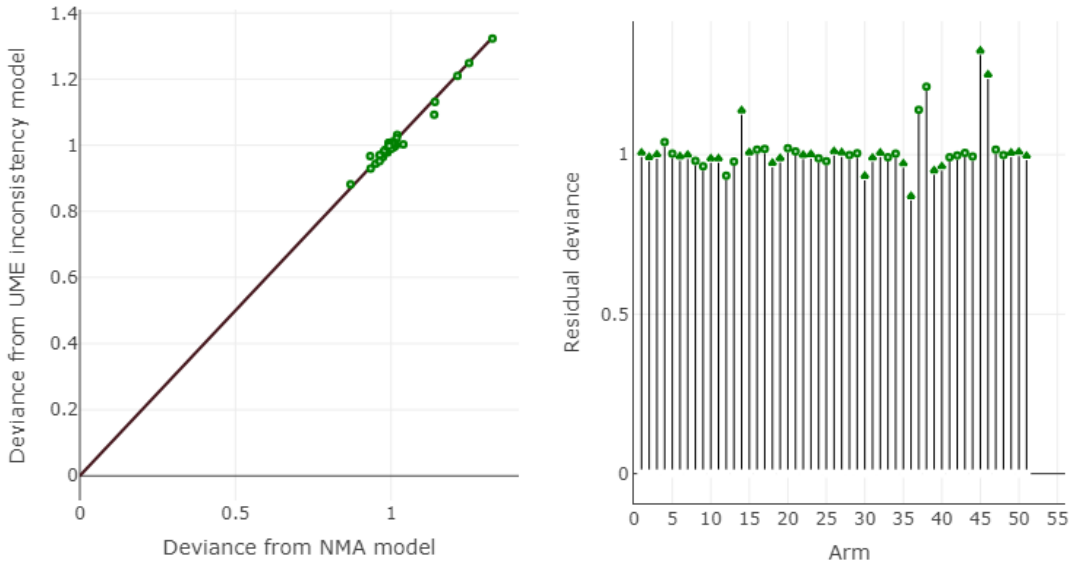


Figure 4-15 Mean number of transfusion episodes dev-dev plot and stem plot

4.6.5.3Length of hospital stay

There were several studies which reported length of hospital stay (LOHS) and of those, the average in patient stay was over 5 days (Table 4 -24). The network connected with the exclusion of four studies[172-174] (Figure 4 -16). The network encompassed 2842 people, 378 possible pairwise comparisons with 39 direct data comparison and the average length of stay was 4.6 days (Table 4 -24). Compared with placebo no treatments were found to increase the length of hospital stay. Two treatments, both tranexamic acid, demonstrated a small reduction in length of hospital stay. The interventions were TXA given intra-articular at a dose of 3g (RR -1.93 95% CrI -3.66, -0.19) and TXA given intravenously 3g pre-incision and intraoperatively (-1.23 (-2.09, -0.35) (Figure 4 -17).

Figure 4-16 Length of hospital stay network plot

Network plot risk of blood transfusion data code

IA	Intraarticular	grt_than_3g	greater than 3g
IV	Intravenous	post	Postoperative dose within 24 hours of wound closure
top	Topical	prel	Preincision dose

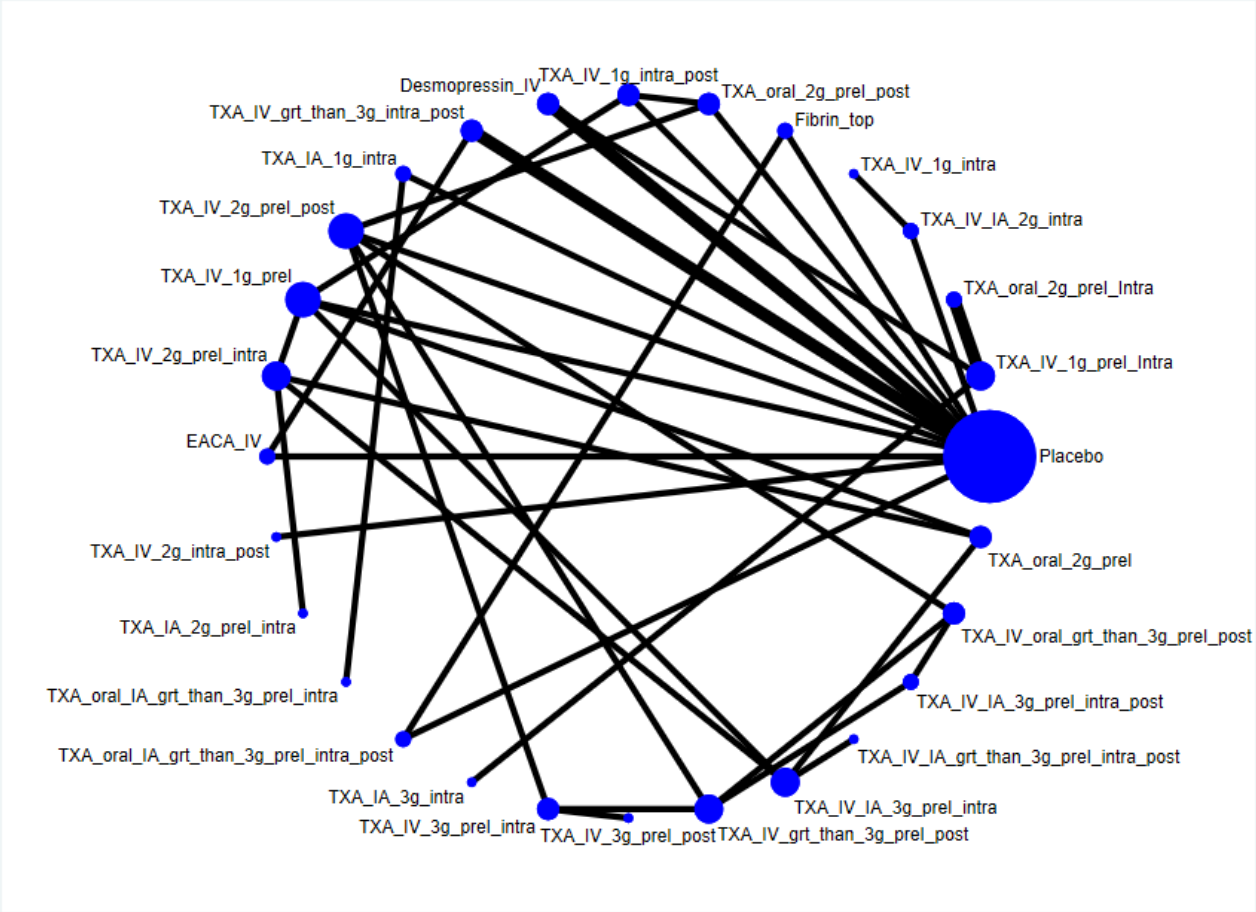

Desmopressin_IV
TXA_IV_1g_intra_post
TXA_oral_2g_prel_post
TXA_IV_grt_than_3g_intra_post
Fibrin_top
TXA_IA_1g_intra
TXA_IV_1g_intra
TXA_IV_2g_prel_post
TXA_IV_IA_2g_intra
TXA_IV_1g_prel
TXA_oral_2g_prel_Intra
TXA_IV_2g_prel_intra
TXA_IV_1g_prel_Intra
EACA_IV
Placebo
TXA_IV_2g_intra_post
TXA_oral_2g_prel
TXA_IA_2g_prel_intra
TXA_IV_oral_grt_than_3g_prel_post
TXA_oral_IA_grt_than_3g_prel_intra
TXA_IV_IA_3g_prel_intra_post
TXA_oral_IA_grt_than_3g_prel_intra_post
TXA_IV_IA_grt_than_3g_prel_intra_post
TXA_IA_3g_intra
TXA_IV_IA_3g_prel_intra
TXA_IV_3g_prel_intra
TXA_IV_3g_prel_post
TXA_IV_grt_than_3g_prel_post

Table 4-24 Network plot characteristics length of hospital stay

Characteristics	Value
Number of interventions	28
Number of Studies	25
Total number of patients	2842
Total possible pairwise comparisons	378
Total number of pairwise with direct data	39
Number of two arm studies	18
Number of multi-arm studies	17
Average outcome	4.59

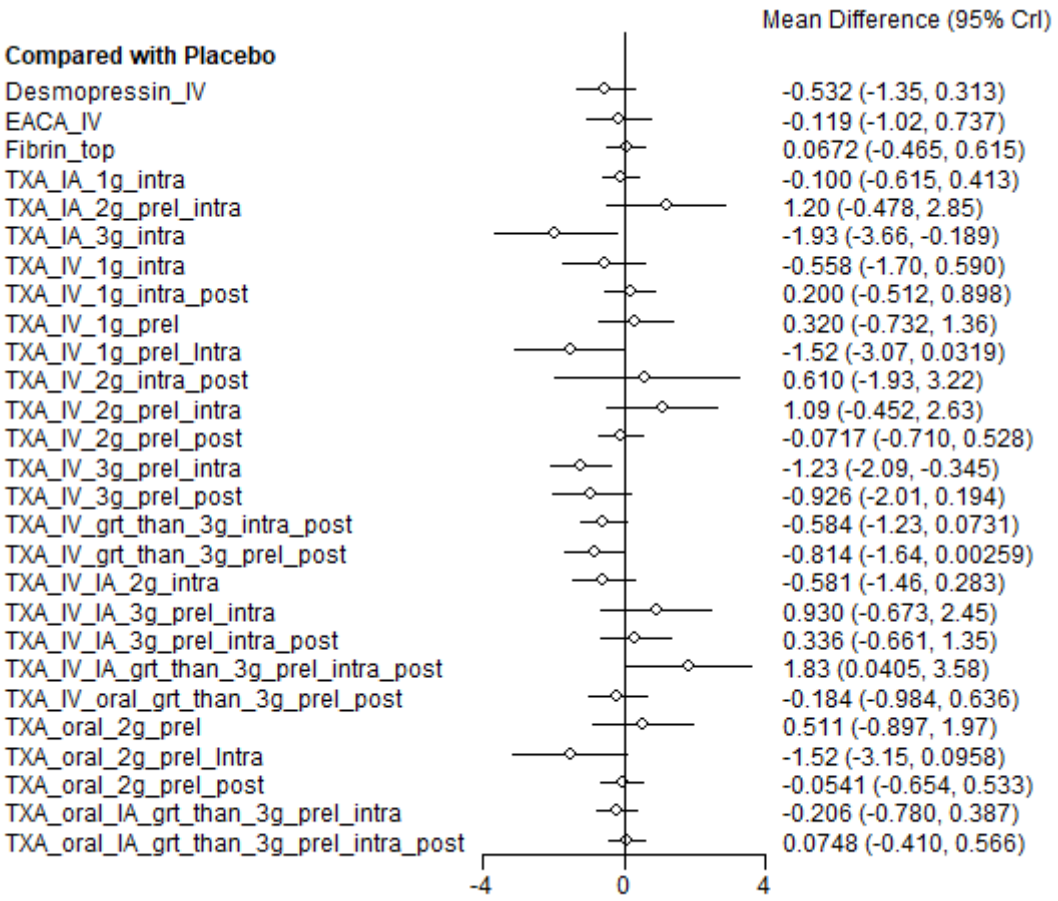


Figure 4-17 Length of hospital stay NMA forest plot

4.6.5.4 Length of hospital stay model fit

Table 4-25 Length of hospital stay model fit statistics

Model fit length of hospital stay NMA	
Dbar	55.67
pD	53.95
DIC	109.62
Data points	58.00
Between-study standard deviation: 0.18. 95% credible interval: 0.01, 0.68	

The Dbar and data points were within 5 of each other (Table 4 -25) and there was minimal evidence of deviance within the network (Figure 4 -18)

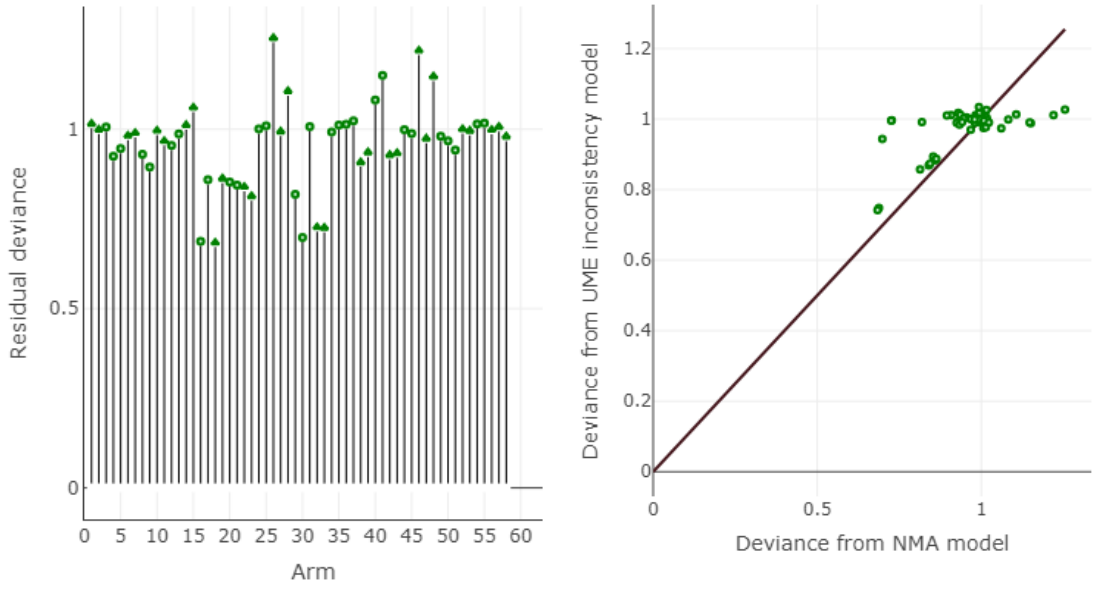


Figure 4-18 Length of hospital stay dev-dev plot and stem plot

4.6.5.5Adverse events

There was only enough data to conduct a Bayesian NMA for deep vein thrombosis (DVT) and therefore pairwise analyses were conducted for pulmonary embolism (PE), myocardial infarction (MI), and cerebrovascular accident (CVA).

4.6.5.6Deep vein thrombosis

17 studies were included in the network with a total of 140 events between 1817 people (Table 4 -26, Figure 4 -19).

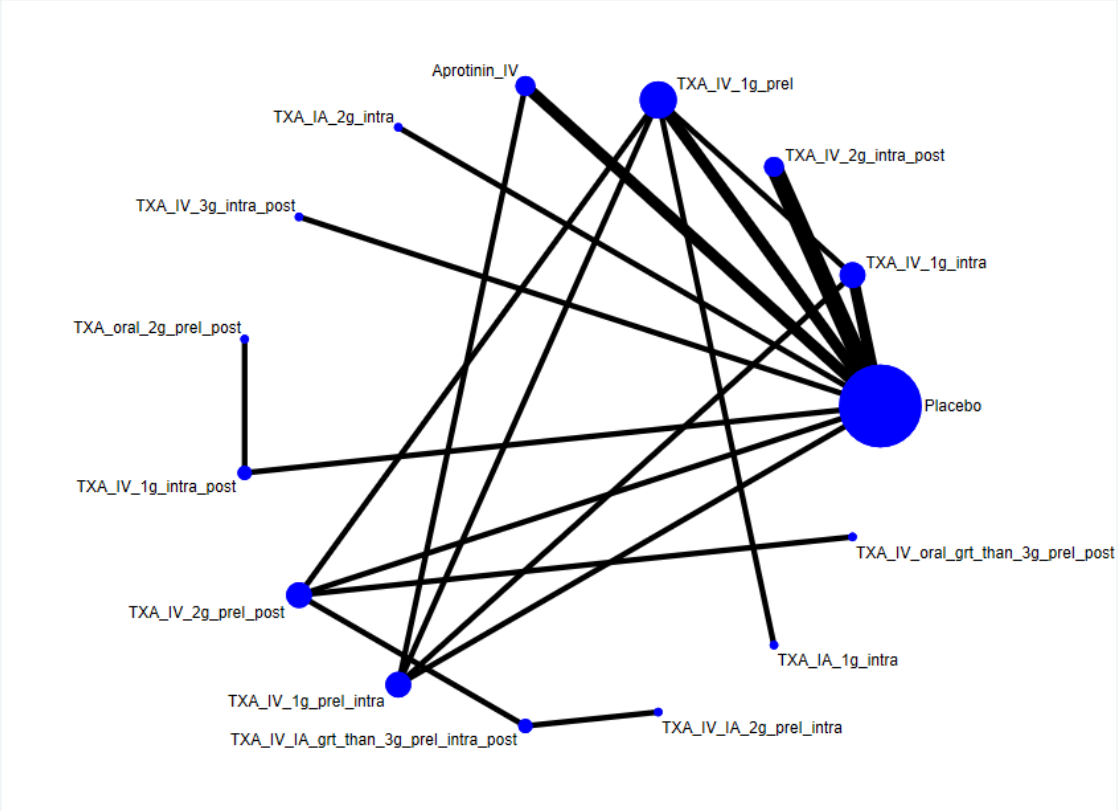


Figure 4-19 Network plot deep vein thrombosis

Figure 4-20 DVT NMA forest plot

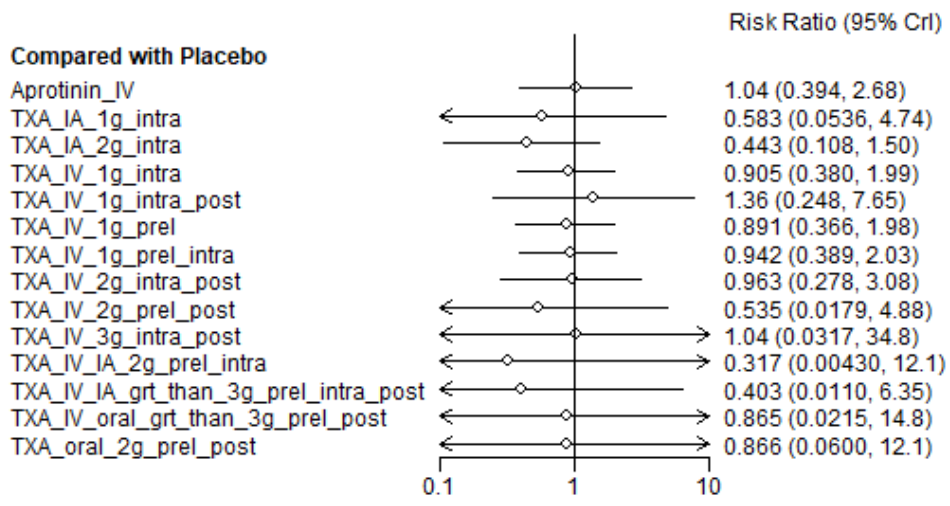


Table 4-26 Network plot characteristics deep vein thrombosis

Characteristics	DVT
Number of interventions	15
Number of Studies	17
Total number of patients	1817
Total possible pairwise comparisons	105
Total number of pairwise with direct data	19
Number of two arm studies	15
Number of multi-arm studies	2
Total number of events	140

There was no evidence of harm from any of the interventions within the network compared with placebo (Figure 4 -20).

4.6.5.7Deep vein thrombosis model fit

The model fit details are shown in Table 4 -27. The residual deviance and deviance from the inconsistency models were acceptable.

Table 4-27 Deep vein thrombosis model fit

Model fit subgroup	DVT
Dbar	33.90
pD	32.96
DIC	66.75
Data points	37.00
Between-study standard deviation (log-odds scale): 0.28. 95% credible interval: 0.01, 0.68	

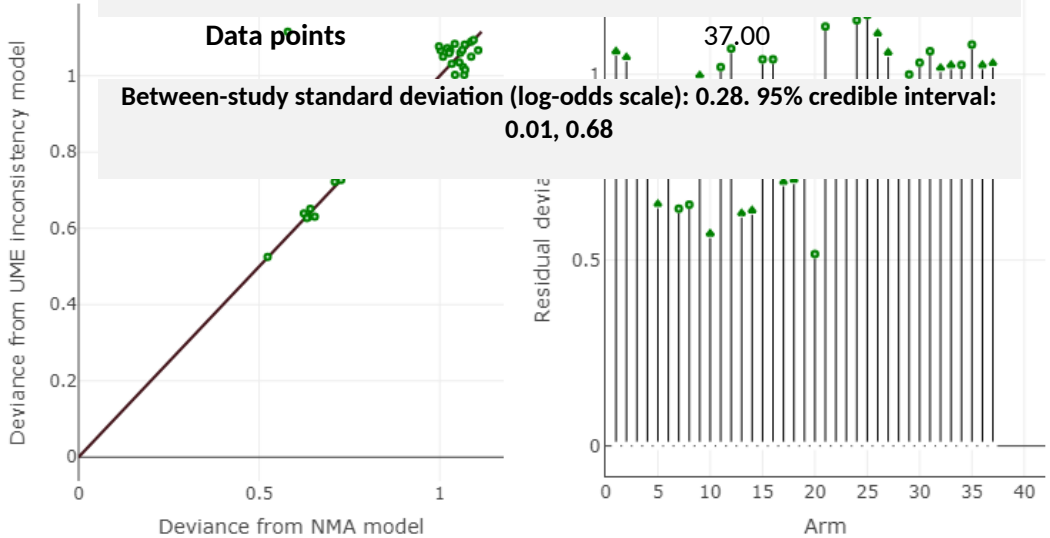


Figure 4-21 DVT dev-dev plot and stem plot

One study Engel et al.[175] was responsible for the outlier seen in the dev-dev plot (

), however exclusion of this study did not result in any significantly improved difference to the NMA and therefore was included.

4.6.5.8 Pulmonary embolism, myocardial infarction and cerebrovascular event within 30 days

There was no evidence of increased risk of pulmonary embolism, myocardial infarction or cerebrovascular events within 30 days in any of the comparisons analysed. The pairwise comparisons for these outcomes are presented in the Appendix (5.2.1.1B.1.6 Pairwise comparisons for pulmonary embolism, 5.2.1.1B.1.7 Pairwise comparisons for Myocardial Infarction, 5.2.1.1B.1.8 Pairwise comparisons for Cerebrovascular event)

4.6.5.9 Transfusion reactions within 24 hours, Suspected serious drug reactions within 30 days, Reoperation due to bleeding within 7 days

Few studies reported these outcomes. Only one study [176] reported on transfusion reactions within 24 hours and a pairwise analysis was conducted. Pairwise comparisons for all studies that reported the secondary outcomes transfusion reactions within 24 hours, suspected

serious drug reactions within 30 days, reoperation due to bleeding within 7 days are presented in the Appendix (5.2.1.1B.1.9 5.2.1.1B.1.11Transfusion reactions within 24 hours, 5.2.1.1B.1.10 Re-operation due to bleeding 5.2.1.1B.1.11 Suspected serious drug reactions: within 30 days). Compared with placebo there was no evidence of increased transfusion reactions, increased drug reactions or increased reoperation rates.

4.6.5.10 Cost and quality of life data

Information on cost of interventions and quality of life measures were collected where they were reported. None of the included studies reported on quantitative cost data, however 31 studies reported descripted information on cost. Five studies reported any quality of life data. The information is summarised in Appendix (5.2.1.1B.1.12 Descriptive cost information and 5.2.1.1B.1.13 Descriptive health related quality of life information).

4.6.6 Subgroup analysis and sensitivity analysis

Unfortunately, there was not enough data to perform any subgroup analyses for our primary outcome risk of blood transfusions detailed in the methodology due to a lack of data and number of interventions (23) included within the NMA compared with the studies (43). No included study reported a dropout rate of more than 20%; therefore, no further sensitivity analysis was performed with regard to dropout rate. Sensitivity

analyses by risk of bias could not be performed as planned as exclusion of studies with high risk of bias resulted loss of network connectivity.

4.7 **Discussion**

This review found that Tranexamic acid was the most effective pharmacological intervention for reducing bleeding in hip and knee arthroplasty patients. Tranexamic acid interventions consistently ranked higher than other treatments such as Aprotinin, EACA and topical fibrin sealants compared with placebo. There were a large number of tranexamic acid treatment regimens identified and relatively little data to support individual treatment regimens, therefore the ranking of individual treatments should be interpreted with a degree of caution given the limited amount of evidence contributing to each comparison. However, mixed routes of administration (oral and intra-articular, intravenous and intra-articular) appear to be more effective than single routes of administration and higher doses tranexamic acid feature higher up the treatment ranking hierarchy. Oral tranexamic acid appeared to perform well, which is an important finding as oral tranexamic acid is cheaper and easier to administer than intravenous tranexamic acid (£6.01 for sixty 500mg tablets (30g) versus £15.47 for five 1g ampoules (5g)[114]).

This review found that EACA was not effective compared with placebo, and this is a significant finding given the increasingly popular use of EACA in the United States for arthroplasty patients due to its lower cost[117].

Similarly, Aprotinin and topical fibrin are not effective for preventing bleeding compared with placebo, and therefore not recommend for use in arthroplasty patients over tranexamic acid.

Mortality was not reported by many trials, which is likely due to the low risk of death in people undergoing hip or knee replacement surgery. However, there was no evidence of harm associated with any of the interventions compared with placebo. In particular, the rate of thromboembolic events was low on all arms and there is no evidence that higher doses of tranexamic acid increased this risk; while the estimates are imprecise what evidence there is suggests that the risk may actually be reduced. This may be due to anti-inflammatory effects of TXA among people undergoing orthopaedic procedures on reducing the levels of C-reactive protein and interleukin-6 in patients receiving TXA compared with patients receiving no or lower doses of TXA[177].

Some RCTs within the NMAs included very large doses of Tranexamic acid, for example Jansen et al[178] and Wang et al[179], with total doses in some of the arms exceeding 9 and 6.5 grams respectively. A recent pharmacokinetic review suggested that concentrations of between 10mg/l and 15 mg/l resulted in substantial inhibition of fibrinolysis, with partial inhibition with 5mg/l to 10mg/l[180]. These plasma concentrations can be achieved with significantly smaller doses than those explored in some of the included studies and may be achieved with doses less than 1g in some patients[180]. Reassuringly, there was no increase in mortality,

adverse events (deep vein thromboses, pulmonary embolism, cerebrovascular events, and myocardial infarctions) or length of hospital stay with the use of any interventions investigated, including with the use of larger doses of tranexamic acid. However, certain high-risk groups may not have been adequately represented in this analysis, as some studies excluded patients with previous thromboembolic events, and this may represent an area for future research. In addition, this review found few RCTs examining Tranexamic acid in the prevention of bleeding in revision surgery and this may also represent an area of recommended future research.

TXA has been shown to be effective for preventing bleeding in people undergoing hip or knee replacement surgery in other reviews. Fillingham et al.[181] conducted a network meta-analysis of randomised trials using tranexamic acid in people having a primary hip replacement and included 34 studies in their review. They similarly concluded that there was strong evidence to support the use of TXA to reduce blood loss and risk of transfusion, however they were not able to clearly identify superior routes of administration, dosage, dosing regimen, or time of administration. They found that oral TXA may not have been as effective as other routes of intervention, a finding which this review did not conclude. As with our review, the authors found many treatments relied on a limited number of studies connecting the nodes and therefore relied more heavily on indirect comparisons. Importantly, this review also found that the use of

tranexamic acid did not result in the increased risk of adverse events compared with placebo.

There are several limitations with the review. Although the probability of missing an eligible trial was low, given the wide search strategy, pharmaceutical companies were not contacted regarding any relevant trials that were not publicly available. There were also a large number of studies (38 studies) awaiting classification which may be a source of bias. Some studies did not provide enough details to adequately assess risk of bias, particularly those conducted prior to 2010. Despite attempting to contact those authors, few replied and therefore there may be some bias in the review process due to incomplete reporting. The trials included in this review were small with a large number of interventions tested, resulting in a sparsely populated network, and low certainty in the evidence for any specific treatment. Evidence of some of the interventions studied was informed by a single trial, which led to imprecision and low certainty of evidence. However, we identified 8 on-going trials which may allow firmer conclusions to be drawn in future. The included population was quite homogeneous, as it was limited to people who had undergone a hip or knee replacement. However, the transitivity assumption may have been affected by transfusion thresholds. The variations in the criteria to trigger a transfusion could have an influence on the pooled studies for analysis especially if in the presence of a network with fewer connections.

The overall degree of certainty of the evidence evaluated ranged from low to high based on grading using the CiNEMA assessment. However, in general there was not enough good evidence to draw definitive conclusions. The degree of certainty of the evidence of our top ranking TXA treatments was assessed as low except for TXA given IV at a total dose of 2g pre-incision and postoperatively. The main reason for downgrading the certainty of evidence was imprecision (wide credible and/or confidence intervals), and within-study bias. Many comparisons yielded low certainty evidence due to these concerns.

The planned subgroup analyses could not be performed as the data were too limited to allow informative subgroup analyses. Similarly, the sensitivity analyses by risk of bias could not be performed as planned. Exclusion of studies with high risk of bias resulted in loss of connectivity. Studies were also excluded that were not prospectively registered after 2010 which should mean that the data used in this review are likely to be less biased, however it also resulted in fewer trials for analysis and may have resulted in older treatment regimens being excluded.

In conclusion, the findings from this review provide robust evidence for the use of tranexamic acid in hip and knee arthroplasty patients, with no evidence of harm with its use. Surgical teams still not using tranexamic acid should strongly consider its use to prevent bleeding and the need for blood transfusion in hip and knee arthroplasty. It is likely that tranexamic acid used at higher doses and mixed routes of administration (oral and

intra-articular, or intravenous and intra-articular) is most effective at reducing the risk of blood transfusion.

Chapter 5 Conclusions

5.1 Summary of Findings

The aim of this thesis was to explore the effect of anaemia on patient outcome, identify patients at greatest risk of prolonged anaemia and explore pharmacological strategies to prevent bleeding. There were three main objectives:

i) Investigate whether preoperative anaemia, nadir haemoglobin or postoperative anaemia was more strongly associated with outcome

ii) Identify the patient group at greatest risk of prolonged anaemia and predict which patients were most likely to recover their haemoglobin concentration by six weeks following surgery

iii) Determine the most effective drug for preventing bleeding intraoperatively and the optimal route, dose and timing of administration of that drug in arthroplasty patients

Evidence on the associations between perioperative anaemia and adverse outcomes are unclear for orthopaedic patients. In addressing the first objective, results from this thesis found there was likely no strong evidence of a difference between preoperative anaemia, nadir haemoglobin or postoperative anaemia on outcome. All three haemoglobin models resulted in a 2% increase in the risk of MACE (Major adverse cardiac events) for every unit decrease in haemoglobin and all

the confidence intervals overlapped. Anaemia regardless of timepoint increased the risk of adverse outcomes.

Anaemia is a modifiable risk factor. Strategies to prevent and treat anaemia are important in reducing the risk of adverse outcomes. There is an urgent need to increase awareness and publish national guidelines for the management and identification of perioperative anaemia in developed countries.[76] One study found that less than 25% of the 706 surveyed physicians from ten European countries routinely assess patients for anaemia[182]. Another study conducted across 11 hospitals from Europe and Canada, found even if low Hb levels were diagnosed preoperatively, treatment rates remained low[77]. Barriers to the implementation of guidelines to prevent and treat anaemia include those associated with infrastructure, time and cost.

Blood transfusion was also found to be a risk factor for adverse outcome, increasing the risk of MACE within 90 days by more than two-fold. Blood transfusions are associated with adverse events, are scarce and costly. Clinicians are becoming increasingly aware of these adverse events such as infection and are beginning to adopt restrictive transfusion thresholds of 70g/L for non-cardiac patients and 80g/L for cardiac patients, although practice still varies[92]. Although preventing the number of blood transfusions given, this has led to patients being discharged with more severe anaemia than before and anaemia itself is associated with adverse outcome.

The second objective of this thesis was to predict which individuals were at risk of not recovering their haemoglobin levels by six-weeks following surgery. The prevalence of patients recovering their haemoglobin levels by six-weeks following surgery is not known. The majority of patients are anaemic immediately following surgery, however less is understood about recovery from anaemia in the postoperative period. It was observed in this study that 41% (n=98) of the cohort did not recover their Hb to within 10g/L of preoperative levels. This early postoperative period (within 90 days) is particularly important as it is often during this postoperative period when adverse events manifest, possibly as a result of reduced tissue oxygenation[86]. A prediction model was successfully developed with good predictive ability (R^2 0.60). The study found that a higher ASA, age and patients undergoing a revision procedure compared with a primary procedure were the strongest predictors. This is the first prediction model to be developed to predict postoperative haemoglobin levels at six weeks following surgery. The availability of such a model will enable patients to be counselled as to their risk of prolonged anaemia and will be useful for future trials to identify these individuals to determine optimal treatment regimens for these patients, which currently remain unknown.

The final objective of this thesis was to determine the relative effectiveness of drugs used to prevent bleeding and establish the optimal dose route and time of administration. From this study tranexamic acid was found to be the most effective intervention for preventing the risk of a blood transfusion in people undergoing hip or knee arthroplasty of all the

interventions studied. From the available evidence, other antifibrinolytics (aprotinin and epsilon-aminocaproic acid) did not reduce the need for allogenic blood transfusion compared with tranexamic acid. Aprotinin, epsilon-aminocaproic acid and topical fibrin was found not to be effective compared with placebo, and therefore should not be recommended for use over tranexamic acid. This is a substantial finding as EACA is increasingly used in the United states for arthroplasty patients due to its lower cost compared with tranexamic acid[117].

Unfortunately, no strong conclusions on the optimal dose, route and timing of administrations were able to be drawn from the evidence currently published globally. Tranexamic acid given at a higher dose tended to rank higher in the treatment hierarchy, and it may be more beneficial to use a mixed route of administration (oral and intra-articular, or intravenous and intra-articular). Oral tranexamic acid is cheaper than intravenous tranexamic acid and this may provide a cheaper alternative to intravenous tranexamic acid with similar efficacy. However, these conclusions could not conclusively be drawn based on the trials included within the review. Barriers to using tranexamic acid are thought to centre around concerns for the risk of thrombosis. This study found no increase in the risk of mortality or adverse events such as deep vein thromboses, pulmonary embolism, cerebrovascular events, and myocardial infarctions or length of hospital stay with any interventions studies, and in some studies exceedingly large doses of tranexamic acid were used (>9 grams in total[178,179]). However, it should be noted that some high-risk patient

groups were often excluded from trials and therefore these results may not be translatable to these patient cohorts.

5.2 **Future directions**

The prediction model developed through the PAROS prospective cohort study identifies a population of adults who fail to recover their Hb at six weeks. However, the model in its current form likely needs adjustment, and this may include exploring a larger sample size and additional intraoperative predictors such as intraoperative blood loss. Artificial intelligence and machine learning may be effective in predicting Hb recovery to within 10g/L however comes with its own limitations, including loss of clinical interpretability[108]. Externally validating the model would ensure the model could be used more widely within the orthopaedic population. The development of a robust prediction model will enable individuals who may not recover their haemoglobin levels to be targeted for future potential randomised controlled trials, to help establish the optimal treatment for patients with prolonged anaemia. These studies could explore whether the administration of iron postoperatively, via intravenous or oral routes to address iron deficiency anaemia in postoperative patients may improve their outcome and Hb recovery.

The majority of trials included in the Cochrane review were small and had few participants which resulted in a sparsely populated network, wide credible intervals, and low certainty in the evidence for any specific

treatment. Evidence of some of the interventions studied was informed by a single trial, which led to imprecision and low certainty of evidence. The included population was quite homogeneous, as it was limited to people who had undergone a hip or knee replacement. Larger, adequately powered randomised controlled trials, conducted in a way that reduces bias need to be conducted to ascertain the optimal dose route and timing of administration of tranexamic acid. Studies including people undergoing revision hip and knee replacement, for whom blood loss is higher, are also needed to evaluate the optimal dose route and timing of TXA. Currently there are no on-going trials identified studying patients undergoing revision hip or knee replacement surgery. The most common reason for exclusion of trials from this review was the lack of prospective trial registration, whether the trial remained unregistered, or was registered retrospectively (after recruitment or randomisation, or both, had already started). Prospective trial registration for drug interventions became compulsory in 2005, and it was an unexpected find to identify such a high number of trials that did not fulfil this requirement.

It is the hope that future research will include prospective registration on national and international databases actively, to allow complete transparency in the design, and an audit trail for any changes that may have been made (with rationale for those changes) during the various study phases (active recruitment, through to data analysis and publication or dissemination, or both). Several ongoing studies exploring TXA are yet to be completed and published, and may provide more insight into the

most effective route, dose, and timing of administration. Therefore, following publication of some of these studies an update review should be considered.

5.3 Impact of COVID-19 pandemic

The COVID-19 pandemic was an unprecedented challenge to the world and impacted research. Unfortunately, the COVID-19 pandemic had a negative impact on the research conducted during this DPhil.

5.3.1 PAROS

As a response to the COVID-19 pandemic, there was a 5-month suspension of all research not related to COVID-19 by the University of Oxford from April 2020 which hampered recruitment and follow up of PAROS patients. There were several periods during 2020, 2021 and 2022 due to on-going restrictions, recurrent lockdowns and NHS capacity issues where elective services were cancelled in the NHS, which affected recruitment rates. In addition, more patients withdrew from the study than anticipated due to the concern surrounding attending hospitals for their research blood tests. As a result of the pandemic, PAROS underwent two ethical amendments. The first was to increase study duration and increase the recruitment number, and the second was to include telephone consent to prevent the need for face-to-face contact and reduce the spread of infection. This disruption unfortunately resulted in some missing data and fewer patients than planned included within the

study. However, attempts were made to mitigate the effects of lower recruitment and missing data through the prediction of a continuous outcome and the use of multiple imputation in the development of the prediction model.

5.3.2 Pharmacological interventions to prevent bleeding in hip and knee arthroplasty

Several issues were identified with Covidence, the software package used to complete Cochrane reviews. Unfortunately, due to technical problems and the pandemic there were significant delays in exporting data into revman web. Due to the pandemic there was limited access to the NMA systematic reviewer, librarian and Covidence technicians to resolve the software problems. This unfortunately resulted in a delay of approximately 2 months to the Cochrane review project. However, despite these setbacks the review is still on target to be published in 2023.

5.1 Skills acquired

During the DPhil I have been able to develop a wide range of skills. I developed, designed and successfully conducted a clinical cohort study, requiring ethical approval and feel confident to conduct future cohort studies. I better understand the logistical processes of obtaining necessary approvals, recruiting patients and collecting data in the framework of the NHS, as well as setting realistic targets and timelines. There were several challenges which I had not initially anticipated, such

as losing patients to follow up and moving to digital consent, however I feel better placed to plan future clinical studies having overcome them with PAROS.

My statistical skills have vastly improved throughout the DPhil. I attended several courses (Oxford NMA 5-day course, Oxford Biostatistics course, Keele prediction model course, the Cochrane methodology online course) and became proficient with using STATA and Metainsight with guidance and a degree of trial and error. I am able to develop and internally validate a prediction model according to TRIPOD guidelines and able to perform multiple imputation. I have learnt the thorough and rigorous Cochrane methodology for conducting reviews and will take these skills forward for future reviews. I feel more confident to conduct future network meta-analyses using Metainsight. I firmly believe the skills I have acquired throughout this DPhil will stand me in good stead to conduct future high-quality research.

5.2 **Publications**

1. Gibbs VN, McCulloch RA, Dhiman P, McGill A, Taylor AH, Palmer AJR, Kendrick BJL. Modifiable risk factors for mortality in revision total hip arthroplasty for periprosthetic fracture. The Bone & Joint Journal 2020; 102-B(5): 580-5.

2. Gibbs VN, Champaneria R, Novak A, Doree C, Palmer AJR, Estcourt LJ. Pharmacological interventions for the prevention of bleeding in people undergoing definitive fixation of hip, pelvic and long bone fractures: a systematic review and network meta-analysis. *Cochrane Database of Systematic Reviews* 2019; (12).

3. Gibbs VN, Champaneria R, Palmer A, Doree C, Estcourt LJ. Pharmacological interventions for the prevention of bleeding in people undergoing elective hip or knee surgery: a systematic review and network meta-analysis. *Cochrane Database of Systematic Reviews* 2019; (3).

4. Palmer AJR, Lloyd TD, Gibbs VN, Shah A, Dhiman P, Booth R, Murphy MF, Taylor AH, Kendrick BJL, collaborators. The role of intra-operative cell salvage in patient blood management for revision hip arthroplasty: a prospective cohort study. *Anaesthesia* 2020; **75**(4): 479-86.

5. McCulloch RA, Howgate D, Gibbs VN, Palmer A, Taylor AH, Kendrick B. Assessing the performance and learning curve of orthopaedic surgical trainees in primary total hip arthroplasty. *Annals of the Royal College of Surgeons of England* 2021; **103**(7): 514-9.

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8. McNally S, Phizacklea EC, Gibbs VN, Brown R, Wilcocks KV, O'Brien S, Burton HK, Evans S, Vella-Baldacchino M, Khader A, Afzal I, Mehdian R, Power KM. Lean pathways in orthopaedics: multiple wins for sustainability. *Orthopaedics and Trauma* 2022; **36**(5): 265-73.

Papers submitted:

1) A systematic review of clinical prediction models for blood transfusion in patients undergoing elective surgery" has been successfully submitted online and is presently being given full consideration for publication in BMJ. *Dhiman P,* Gibbs VN, Rampotas

A, Kamal H, Arshad SS, Kirtley S, Doree C, Murphy MF, Collins GS, Palmer AJR.Your manuscript ID is BMJ-2022-070963.

2) Concomitant acetabular component revision at the time of femoral revision for peri-prosthetic fracture is not associated with increased blood transfusion or mortality." *Buckle C, Gibbs VN, McCulloch R, Palmer AJR, Taylor A, Kendrick B.* Journal of Arthroplasty

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Appendix figures

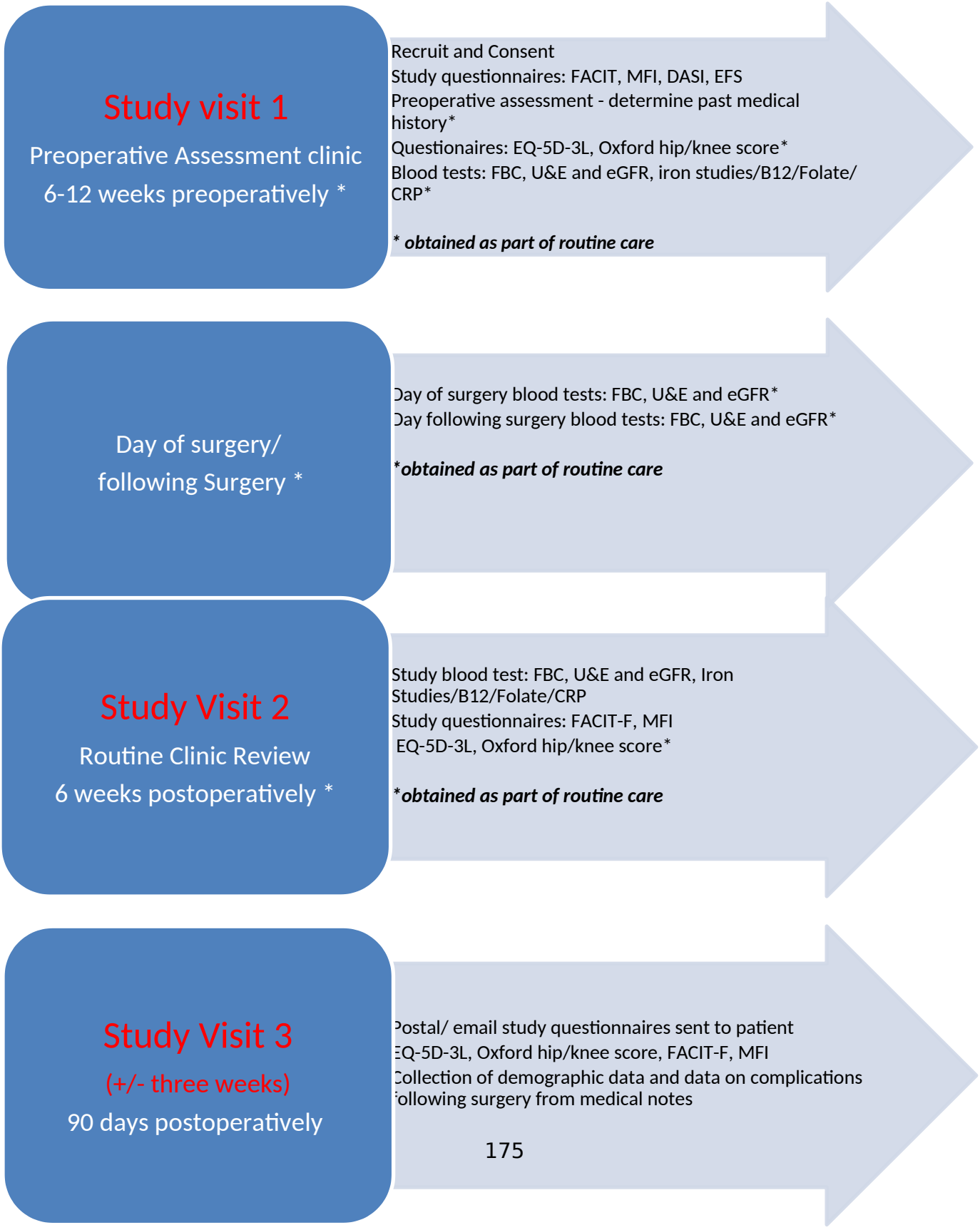
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A.1.1 Patient flow diagram



A.1.2 Original sample size calculation

The study was originally powered on the reliability of the predicted probabilities for patients who do not restore their Hb levels to within 10g/L of their preoperative value six weeks postoperatively using a prediction model. For such analyses, a minimum of 10 events per variable were considered to provide reliable predictions, reducing the risk of developing an over-fitted prediction model.

The plan was to develop a prediction model using six candidate predictors to identify which patients do not recover their Hb levels at six weeks post-surgery, and so required a sample with 60 events (patients with unrecovered Hb). Candidate variables for the prediction model included age, sex, preoperative transferrin saturation, day following surgery Hb, BMI, DASI Score (functional capacity), preoperative CRP, preoperative B12, preoperative folate.

A clinically significant fall from baseline at six weeks was considered 10g/L, which equated to the approximate increase in Hb achieved with the transfusion of a single unit of allogeneic packed red cells. Based on previous literature, the estimated incidence of not recovering Hb levels 6 weeks post-surgery was 25%[88], therefore the sample size calculation was for 240 patients (60/0.25) to attain 60 events.

A.1.3 Prediction model logistic regression

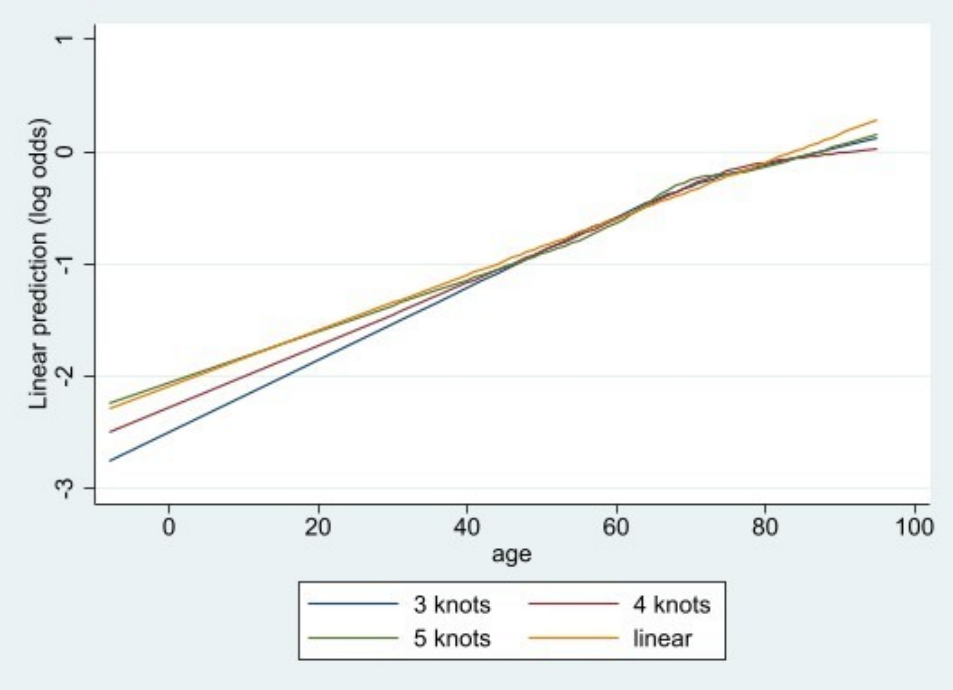
The primary objective was to predict whether a person would ‘recover’ to within 10g/l of preoperative Hb levels versus ‘not recover’ to within 10g/l of preoperative Hb levels. Therefore, a logistic regression prediction

model was developed with the outcome recovered or not recovered explored. However, through the process of model checking and internal validation, the model did not appear to predict well and therefore the main analysis presented is through the development of a linear regression prediction model. Included here is the process by which this conclusion was drawn.

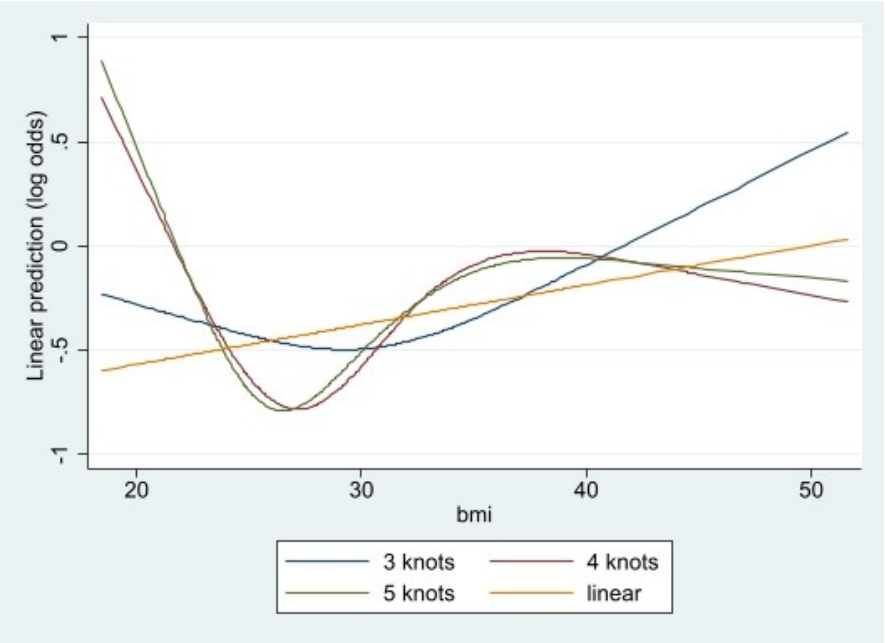
A.1.3.1 Exploration of linear and non-linear relationships

There are methods for increased flexibility in modelling non-linear functions which include restricted cubic splines and fractional polynomials. These were used to explore linear and non-linear relationships.

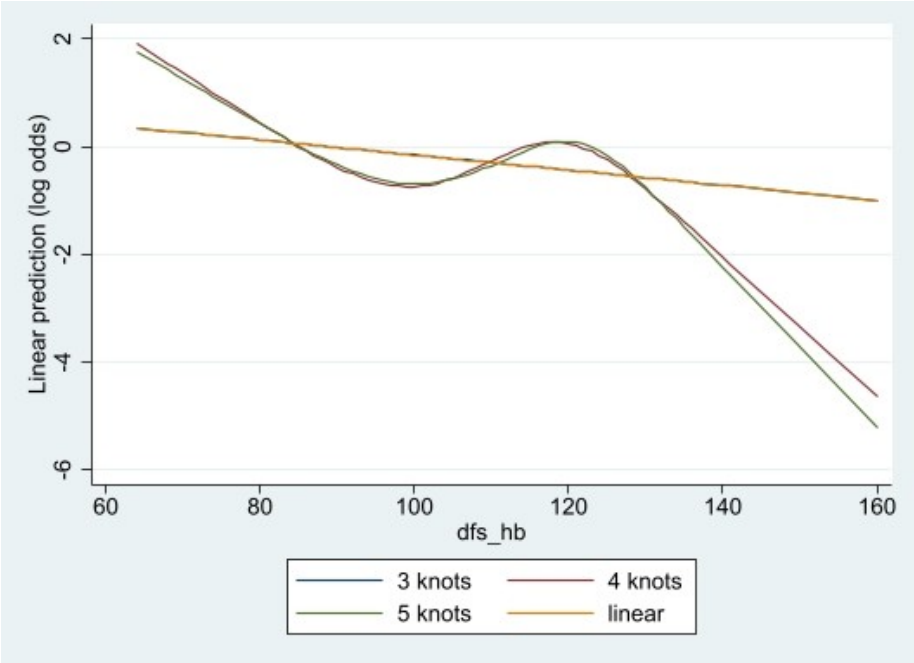
A.1.3.2 Restricted cubic splines



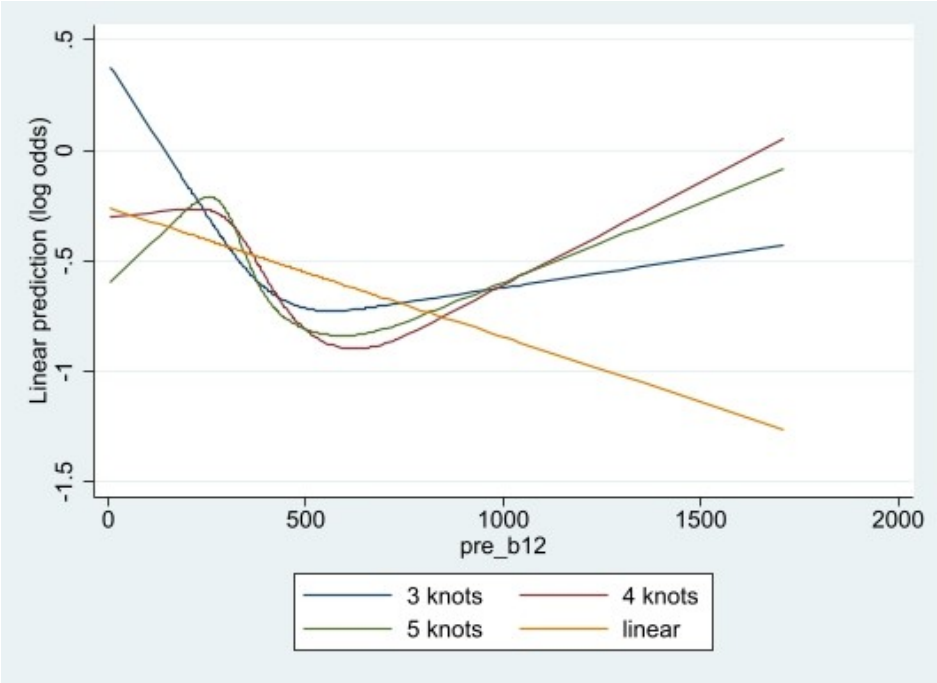
Appendix figure a Age restricted cubic splines graph



Appendix figure b BMI restricted splines graph

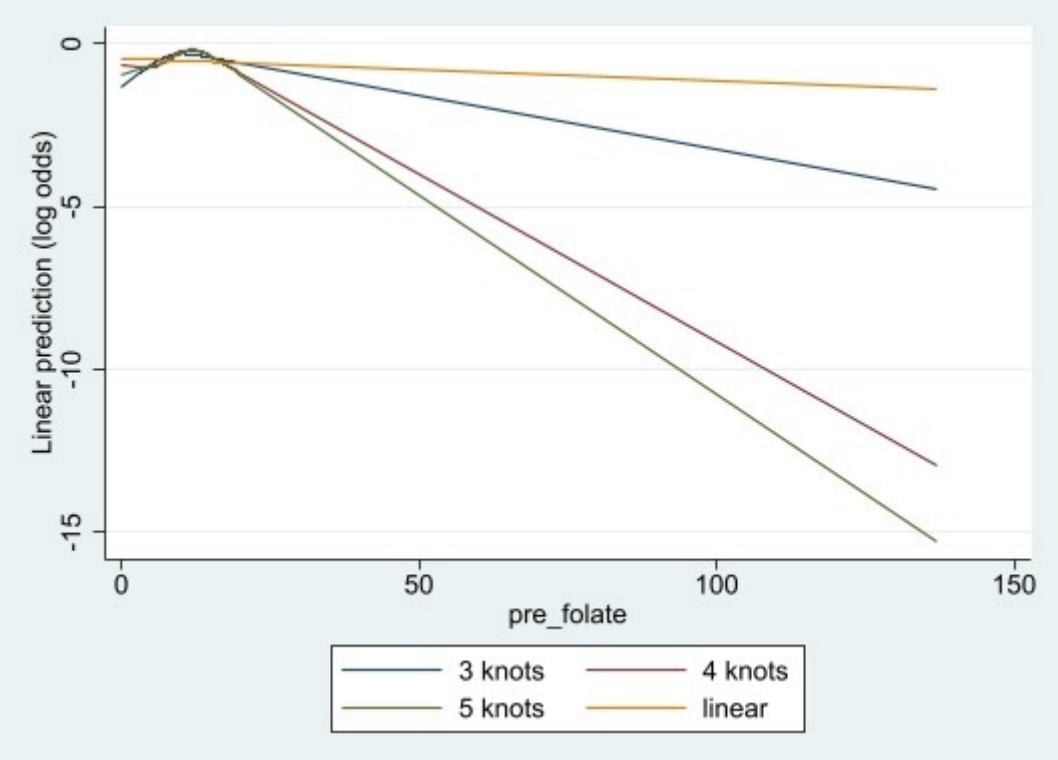


Appendix figure c Day following haemoglobin level restricted splines graph

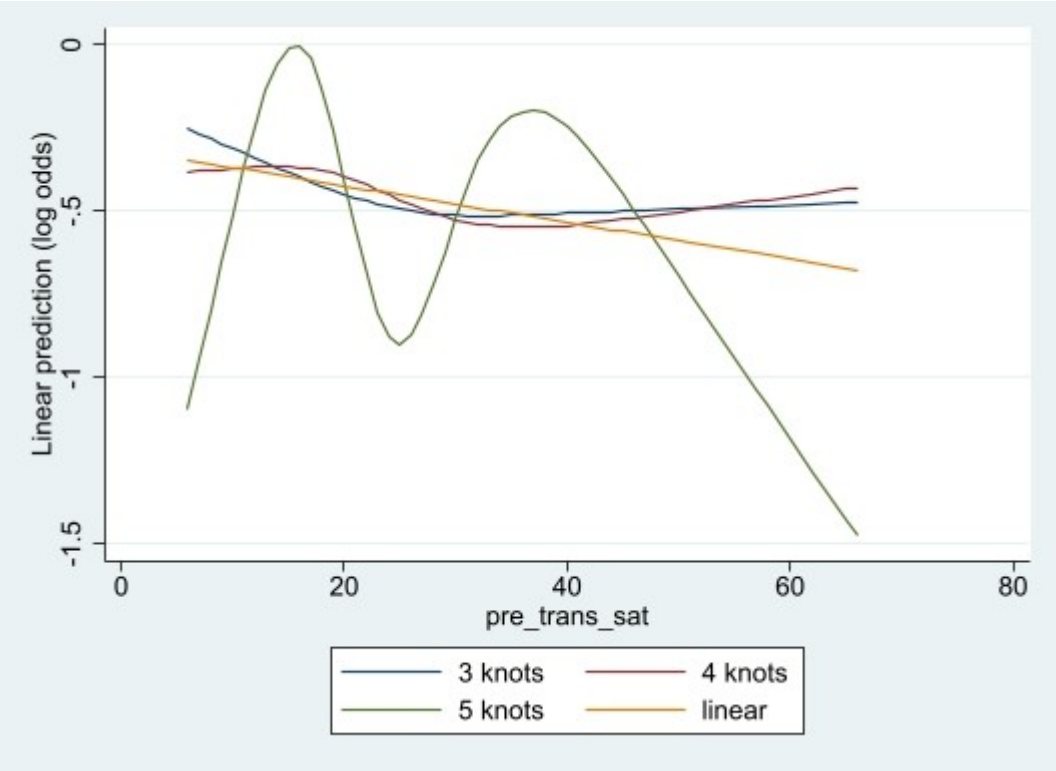


Appendix figure d Preoperative B12 level restricted splines graph

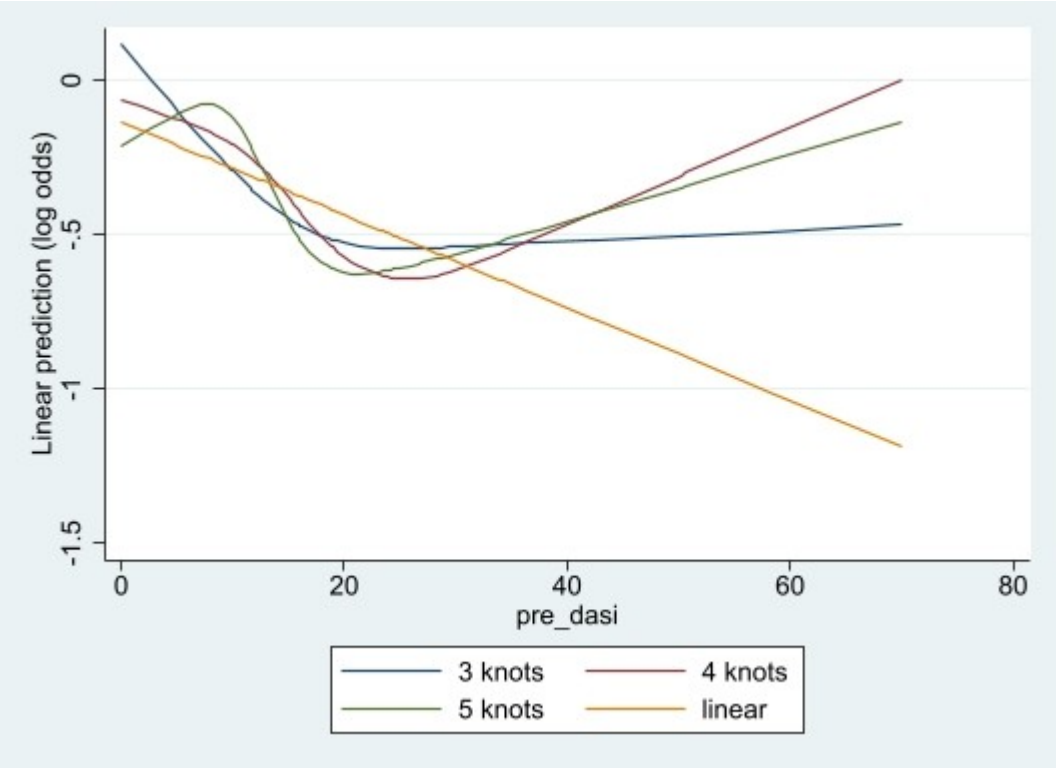
Appendix figure e Preoperative CRP level restricted splines graph



Appendix figure f Preoperative folate level restricted splines graph

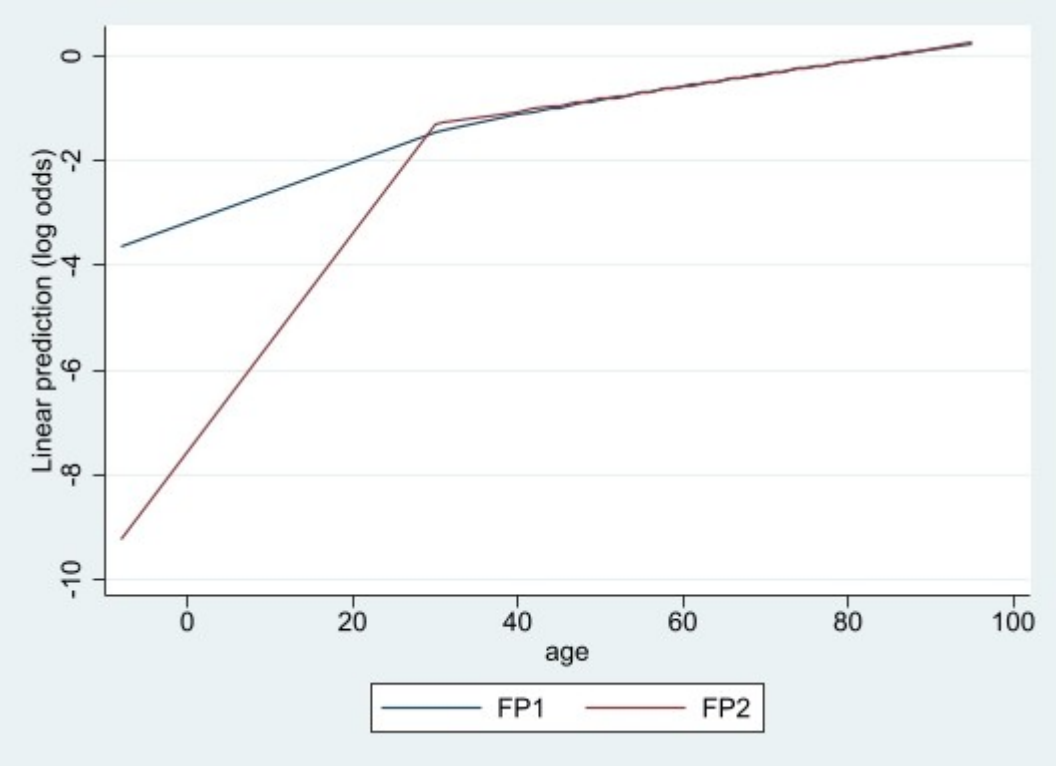


Appendix figure g Preoperative transferrin saturation restricted cubic spline graph

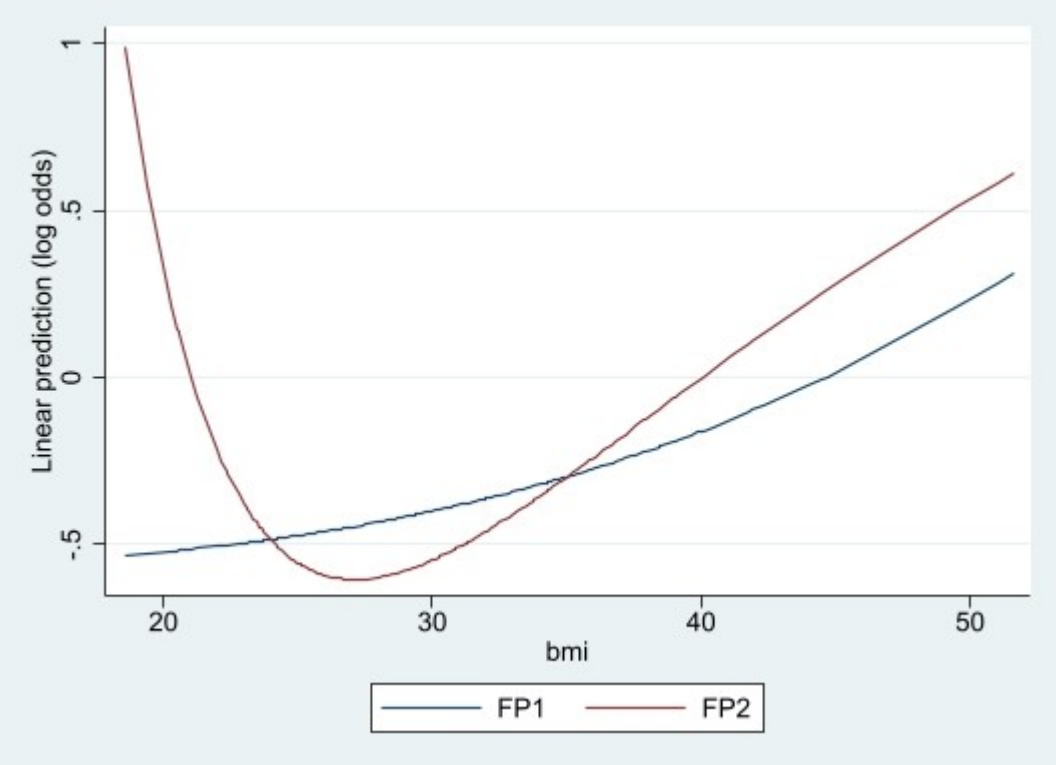


Appendix figure h Preoperative DASI score restricted cubic spline graph

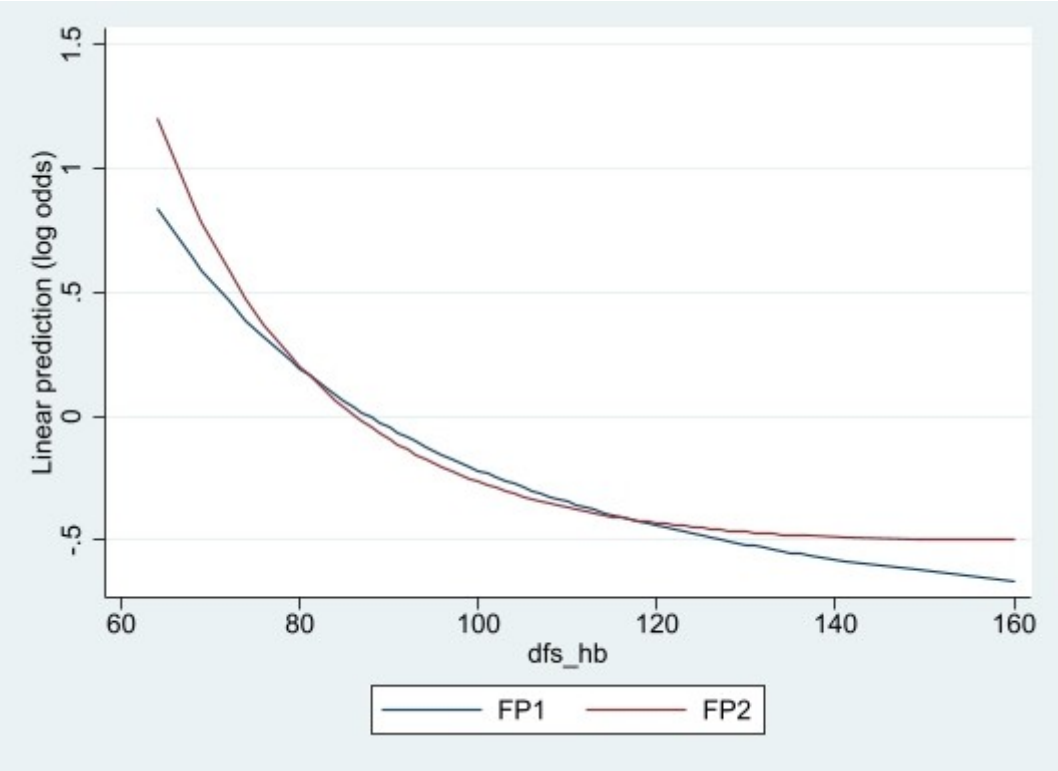
A.1.3.3 Fractional polynomials



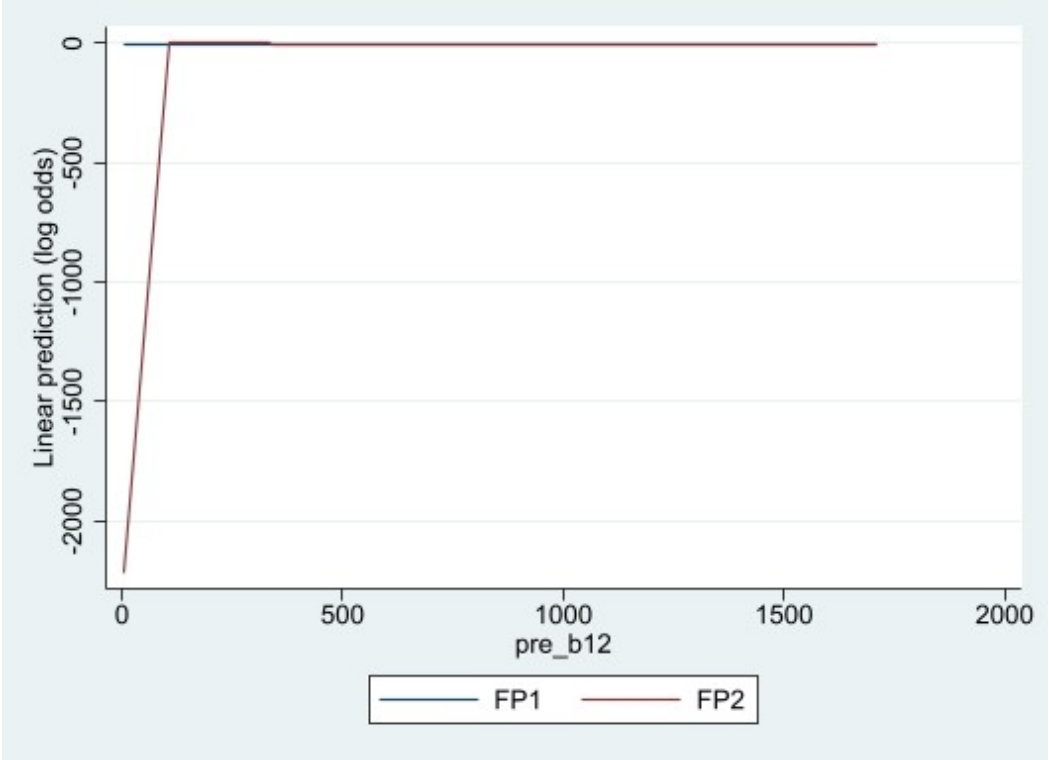
Appendix figure i Age fractional polynomial graph



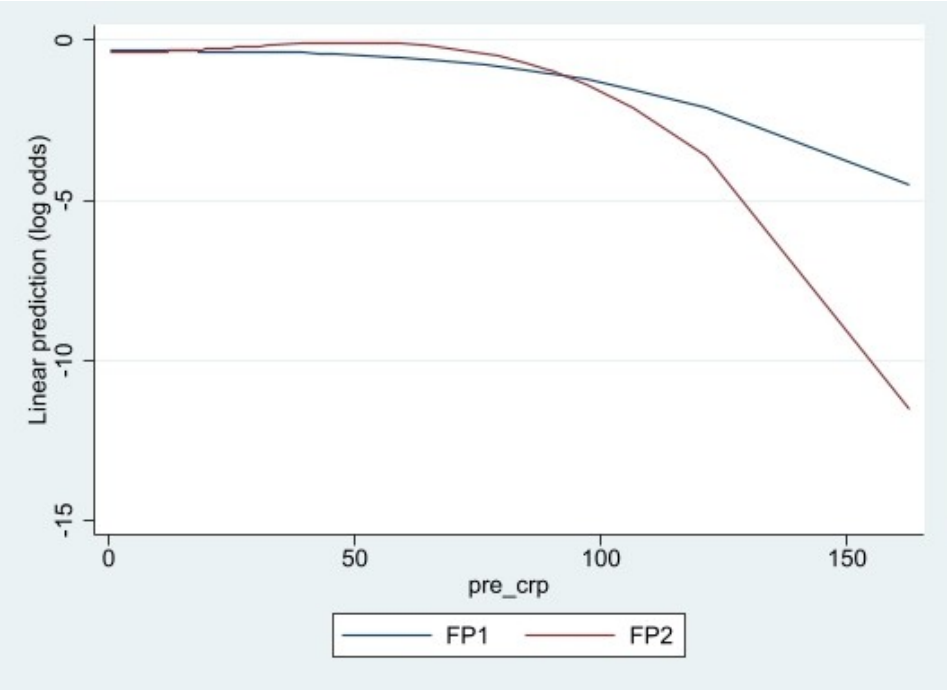
Appendix figure j BMI fractional polynomial graph



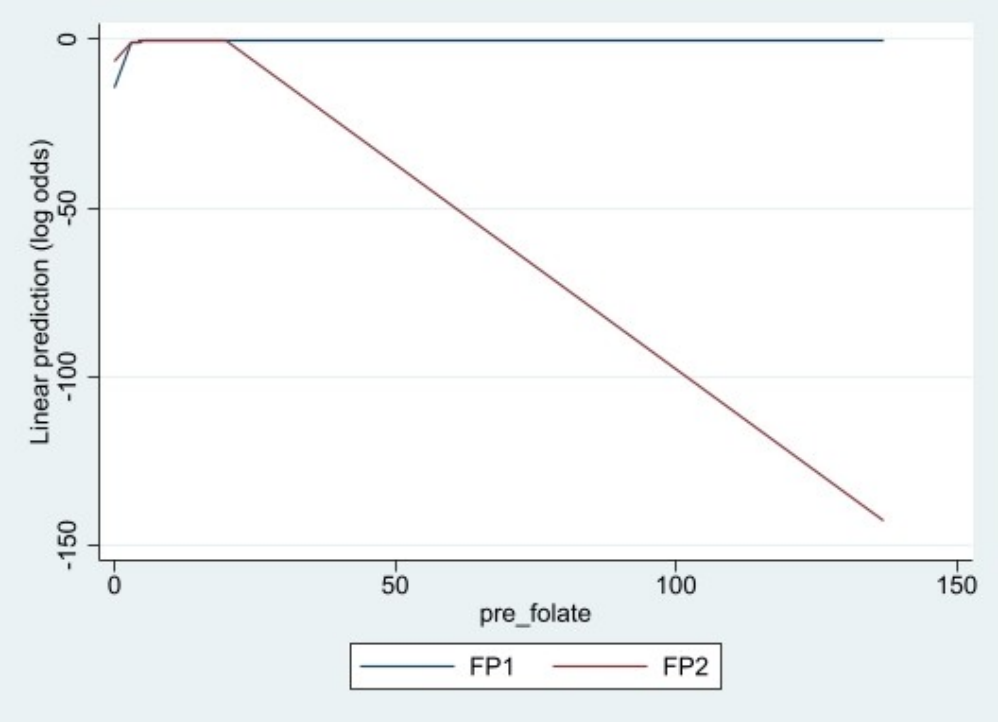
Appendix figure k Day following surgery Hb fractional polynomial graph



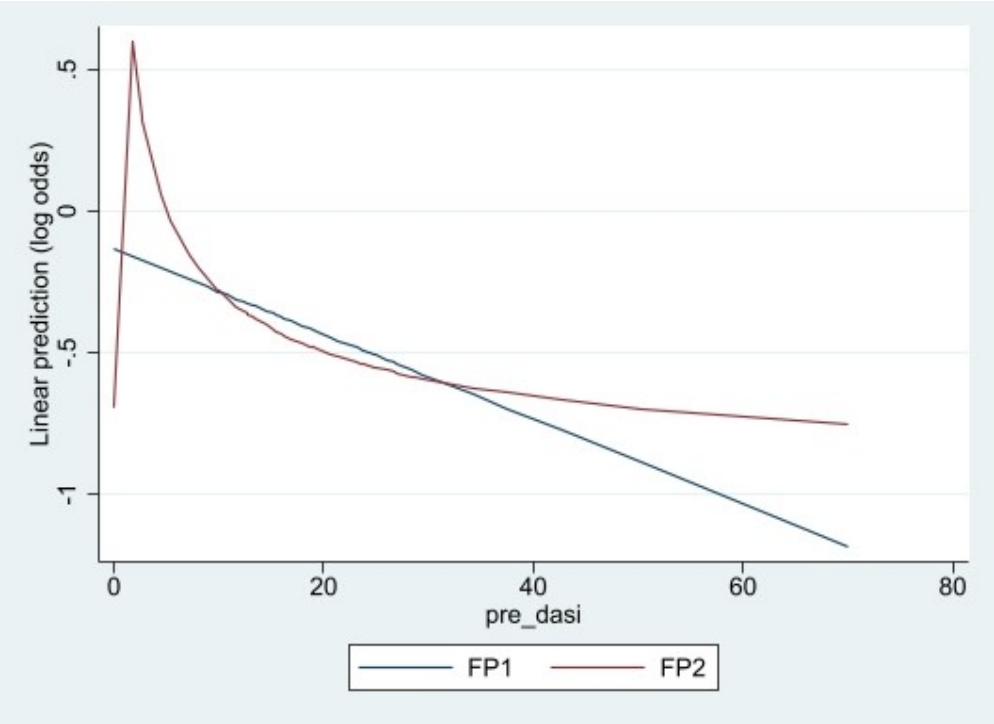
Appendix figure l Preoperative B12 fractional polynomial graph



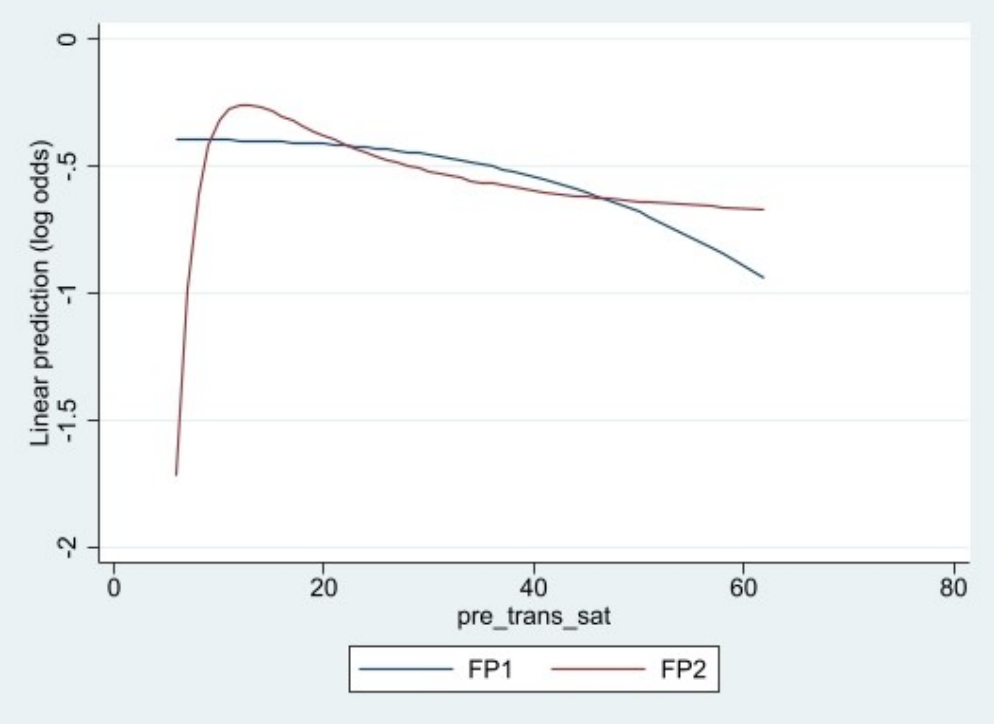
Appendix figure m Preoperative CRP fractional polynomial graph



Appendix figure n Preoperative folate fractional polynomial graph



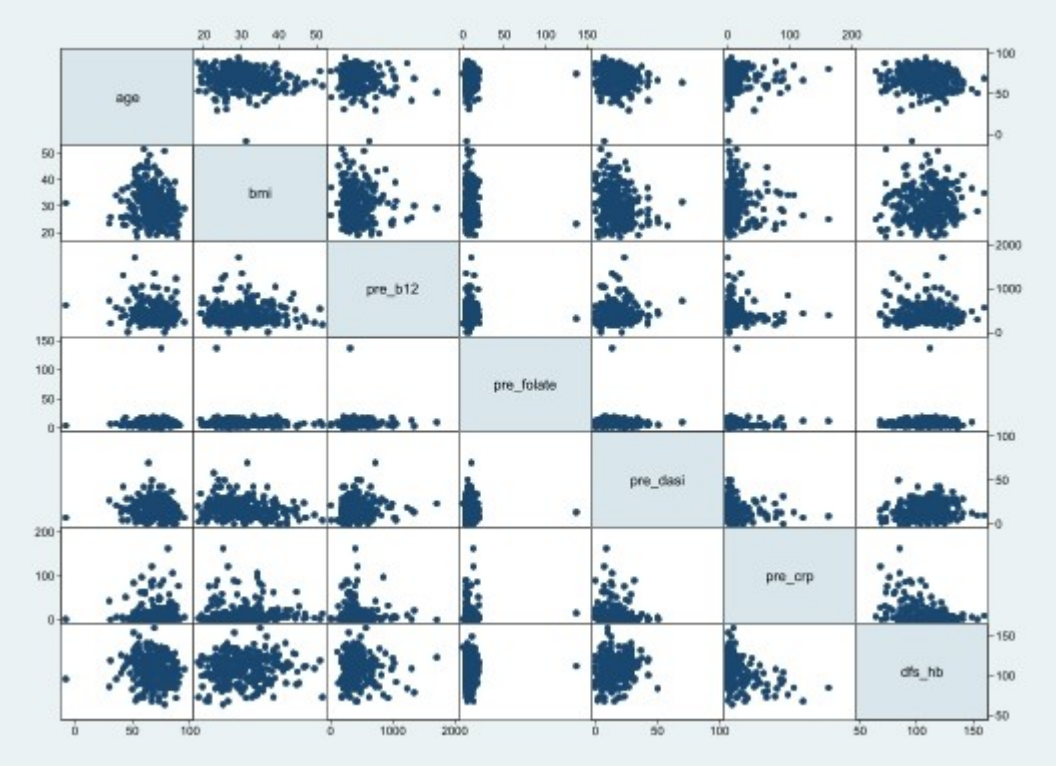
Appendix figure o Preoperative DASI fractional polynomial graph



Appendix figure p Preoperative transferrin saturation

A.1.3.4 Collinearity

A scatter graph was created to look for potential relationships between continuous candidate predictors and calculating correlation coefficients. There were no predictors that appeared to be correlated (Appendix figure q, Appendix table a).



Appendix figure q Scatter plot between continuous predictors

Appendix table a Correlation coefficients between continuous predictors

	age	bmi	Preop B12	Preop folate	Preop DASI	Preop CRP	Day following surgery Hb
age	1						
bmi	-0.18	1					
Preop B12	-0.13	-0.04	1				
Preop folate	0.04	-0.1	0.03	1			
Preop DASI	-0.11	-0.23	0.07	-0.01	1		
Preop CRP	0.05	0.01	-0.04	-0.01	-0.17	1	
Day following surgery Hb	-0.11	0.13	-0.08	0.01	0.18	-0.4	1

A.1.3.5 Model development and internal validation

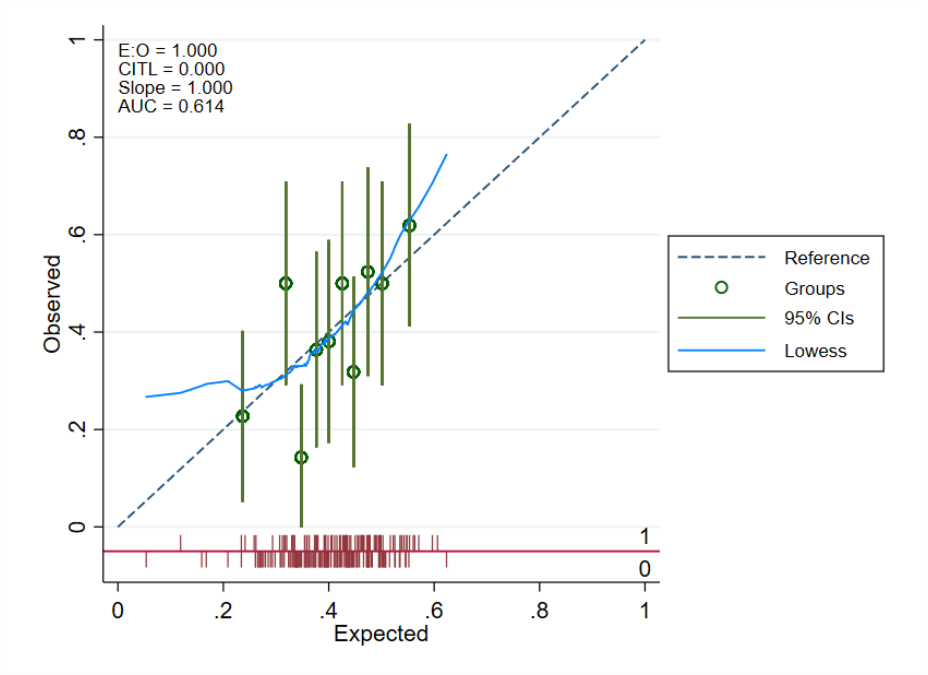
Using backward elimination and the “mfp” command in STATA (considers fractional polynomial terms for the continuous predictors), age, bmi and pre-crp were selected as model predictors. Then the predicted probabilities and the value of the linear predictor for each individual was calculated using the “predict” command.

Appendix table b Summary of the distribution of the linear predictor

Variable	Obs	Mean	Std. dev.	Min	Max
Linear predictor	284	-0.389	0.412	-2.868	0.504

The C-statistic was used to evaluate the apparent discrimination performance of the model (0.61 95% CI 0.54-0.69) and a visual plot created (Appendix figure r). The Brier score was calculated at 0.23 (range 0-0.25 where a lower score is better).

The optimism in the model was assessed by calculating the shrinkage required to adjust the regression coefficients. Bootstrap validation was used to adjust performance statistics such as the C-statistic for optimism and reduce the risk of overfitting. The optimism adjusted performance was calculated using the original model apparent performance minus the original model test performance in the bootstrap samples.



Appendix figure r visual assessment of calibration by risk groups

The optimism adjusted C-statistic was 0.54, the optimism adjusted calibration-in-the-large was 0.008 and the optimism adjusted c-slope was 0.83.

Unfortunately, this model did not perform well and therefore the decision to proceed with a linear model was made and presented as the main analysis.

A.1.4 Rubins rules for pooling performance measures

Equations:

To calculate the pooled mean differences the following formula was used:

$$\bar{\theta} = \frac{1}{m}\left(\sum_{i=1}^{m}\theta_i\right)$$

Where “m” is the number of imputed datasets, theta is the pooled estimate and theta “i” is the parameter estimate in each imputed dataset.

To calculate within imputation variance the following formula was used:

$$V_W = \frac{1}{m}\sum_{i=1}^{m} SE_i^2$$

Where SE^2i is the sum of the squared standard error, estimated in each imputed dataset.

To calculate between imputation variance the following formula was used:

$$V_B = \frac{\sum_{i=1}^{m}(\theta_i - \bar{\theta})^2}{m-1}$$

V total was then calculated and the square root of the pooled standard error gives the pooled standard error:

$$V_{Total} = V_W + V_B + \frac{V_B}{m}$$

$$SE_{Pooled} = \sqrt{V_{Total}}$$

Appendix table c Table of calculations r^2

Imputed dataset	Final r^2	theta	Final r^2 – theta	r^2 Standard Error	SE squared
1	0.596824	0.6062812	8.9439E-05	0.0017188	2.95427E-06
2	0.618224	0.6062812	1.4263E-04	0.0017153	2.94225E-06
3	0.61068	0.6062812	1.9349E-05	0.0016974	2.88117E-06
4	0.613372	0.6062812	5.0279E-05	0.0017062	2.91112E-06
5	0.605912	0.6062812	1.3631E-07	0.0016937	2.86862E-06
6	0.606236	0.6062812	2.0430E-09	0.0016936	2.86828E-06
7	0.586394	0.6062812	3.9550E-04	0.001916	3.67106E-06
8	0.59301	0.6062812	1.7612E-04	0.0017092	2.92136E-06
9	0.62083	0.6062812	2.1167E-04	0.0017217	2.96425E-06
10	0.61133	0.6062812	2.5490E-05	0.0017519	3.06915E-06
Pooled estimate	0.6062812		0.00012340220		3.00515E-06
V total	0.000138748				
SE pooled	0.011779116				
lower CI	0.583194133				
higher CI	0.629368267				

Appendix table d Table of calculations r^2

Imputed dataset	Final r^2a	theta	Final r^2a – theta	R^2a Standard Error	SE squared
1	0.590262	0.5998508	9.19451E-05	0.0017508	3.0653E-06
2	0.611684	0.5998508	0.000140025	0.0017436	3.04014E-06
3	0.604148	0.5998508	1.84659E-05	0.0017253	2.97666E-06
4	0.60687	0.5998508	4.92692E-05	0.0017364	3.01508E-06
5	0.599374	0.5998508	2.27338E-07	0.0017223	2.96632E-06
6	0.59974	0.5998508	1.22766E-08	0.0017237	2.97114E-06
7	0.579766	0.5998508	0.000403399	0.0019495	3.80055E-06
8	0.586532	0.5998508	0.00017739	0.0017383	3.02169E-06
9	0.615292	0.599850	0.000238431	0.0017494	3.0604E-06

		8			
10	0.60484	0.5998508	2.48921E-05	0.0017785	3.16306E-06
Pooled estimate	0.5998508		0.000127117		3.10803E-06
Vtotal	0.000142937				
SE pooled	0.011955635				
lower CI	0.576417756				
higher CI	0.623283844				

Appendix table e Table of calculations cslope

Imputed dataset	Final cslope	theta	Final cslope-theta	cslope Standard Error	Final cslope
1	0.999568	1.0239546	0.000594706	0.0023904	0.999568
2	1.02716	1.0239546	1.02746E-05	0.0022632	1.02716
3	1.006742	1.0239546	0.000296274	0.0023036	1.006742
4	1.025926	1.0239546	3.88642E-06	0.0023299	1.025926
5	1.015354	1.0239546	7.39703E-05	0.0024645	1.015354
6	1.003902	1.0239546	0.000402107	0.0024282	1.003902
7	1.056948	1.0239546	0.001088564	0.0028837	1.056948
8	1.069668	1.0239546	0.002089715	0.0023433	1.069668
9	0.99346	1.0239546	0.000929921	0.0022676	0.99346
10	1.040818	1.0239546	0.000284374	0.0023272	1.040818
Pooled estimate	1.0239546		0.000641532		1.0239546
Vtotal	0.000711476				
SE pooled	0.026673513				
lower CI	0.971674515				
higher CI	1.076234685				

Appendix table f Table of calculations Calibration in the Large (CITL)

Imputed dataset	Final CITL	theta		CITL Standard Error	
1	0.028904	0.1561528 1	0.01619226	0.0315907	0.000998
2	-0.010018	0.1561528 1	0.027612738	0.0303952	0.000924
3	-0.001806	0.1561528 1	0.024950986	0.031347	0.000983
4	0.6989586	0.1561528 1	0.294638126	0.0312584	0.000977
5	0.011542	0.1561528 1	0.020912286	0.0313958	0.000986
6	0.012626	0.1561528 1	0.020599945	0.0314761	0.000991
7	0.080592	0.1561528 1	0.005709436	0.0313251	0.000981
8	0.03012	0.1561528 1	0.015884269	0.0310416	0.000964
9	0.6803715	0.1561528 1	0.274805235	0.0304271	0.000926
10	0.030238	0.1561528 1	0.015854539	0.0303467	0.000921
Pooled estimate	0.15615281		0.079684424		0.000965
Vtotal	0.088617825				
SE pooled	0.297687461				
lower CI	-0.427314614				
higher CI	0.739620234				

B.1.1 Cochrane Electronic Search Strategy

CENTRAL (The Cochrane Library)

#1 MeSH descriptor: [Arthroplasty, Replacement, Hip] this term only#2 MeSH descriptor: [Hip] this term only and with qualifier(s): [surgery - SU]#3 MeSH descriptor: [Osteoarthritis, Hip] explode all trees and with qualifier(s): [surgery - SU]#4 MeSH descriptor: [Arthroplasty, Replacement, Knee] this term only#5 MeSH descriptor: [Knee Injuries] explode all trees and with qualifier(s): [surgery -

SU]#6 MeSH descriptor: [Knee] explode all trees and with qualifier(s): [surgery - SU]#7 MeSH descriptor: [Osteoarthritis, Knee] explode all trees and with qualifier(s): [surgery - SU]#8 ((hip* or knee* or femur or femoral) near/10 (replac* or operat* or surg* or arthroplast* or reconstruct* or repair* or osteotom* or alloplast* or plast* or resurfac* or implant* or prosthes*))#9 (acetabuloplast* or acetabulum arthroplast*)#10 (THA or THR or TKA or TKR or UKA or UKR)#11 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10#12 MeSH descriptor: [Antifibrinolytic Agents] this term only#13 MeSH descriptor: [Tranexamic Acid] this term only#14 MeSH descriptor: [Aminocaproic Acid] explode all trees#15 antifibrinolytic* or anti-fibrinolytic* or antifibrinolysin* or antiplasmin* or plasmin inhibitor* or tranexamic or tranhexamic or cyclohexanecarboxylic acid* or amcha or t-amcha or amca or transamin or amchafibrin or anvitoff or spotof or cyklokapron or femstrual or ugurol#16 AMCHA or amchafibrin or amikapron or amstat or antivoff or caprilon or cl65336 or cyclocapron or cyclokapron or cyklocapron or cyklokapron or exacyl or frenolyse or fibrinon or hemostan or hexacapron#17 hexakapron or kalnex or lysteda or rikaparin or ronex or theranex or tranexam or tranexanic or tranexic or "trans achma" or transexamic or trenaxin or TXA#18 (fibrinolysis near/2 inhibitor*)#19 (Agretax or Bio-Stat or Capiloc or Capitrax or Clip Inj or Clot-XL or Clotawin-T or Coastat or Cuti or Cymin or Dubatran or Espercil or Examic or Existat or Extam or Fibran or Gynae-Pil or Hemstate or Kapron or Menogia or Monitex or Nestran or Nexamic or Nexi-500 or Nexmeff or Nicolda or Nixa-500 or Pause or Rheonex or Sylstep TX or Synostat or T-nex or T Stat or T Stat or Tanmic or Temsyl-T or Texakind or Texanis or Texapar or Texid or Thams or Tonopan or Traklot or Tramic or Tramix or Tranarest or Trance Inj or Tranecid or Tranee or Tranemic or Tranex or Tranexa or Tranfib or Tranlok or Transtat or Transys or Transcam or Tranxi or Trapic or Traxage or Traxamic or Traxyl or

Trenaxa or Trexamic or Trim Inj or Tx-1000 or Tx 500 or Wistran or X-Tran or Xamic)#20 ecapron or ekaprol or epsamon or epsicaprom or epsicapron or epsilcapramin or epsilon amino caproate or epsilon aminocaproate or epsilonaminocaproic or epsilonaminocapronsav or ethaaminocaproic or ethaaminocaproich or emocaprol or hepin or ipsilon or neocaprol or resplamin or tachostyptan#21 lederle or acikaprin or afibrin or amicar or caprocid or capracid or capramol or caprogel or caprolest or caprolisin* or caprolysin* or capromol or epsikapron or hemocaprol or caproamin or EACA or caprolest or capralense or hexalense or hamostat or hemocid#22 aminohexanoic or aminocaproic or aminohexanoic or amino caproic or amino-caproic or amino-n-hexanoic#23 #12 or #13 or #14 or #15 or #16 or #17 or #18 or #19 or #20 or #21 or #22#24 MeSH descriptor: [Aprotinin] this term only#25 (antagosan or antilysin* or aprotimbin or apronitin* or aprotinin* or bayer a128 or contrical or contrycal or contrykal or dilmintal or frey inhibitor or kontrycal or Kunitz inhibitor or gordox or haemoprot or kallikrein-trypsin inactivator or iniprol or kontrikal or kontrykal or kunitz pancreatic trypsin inhibitor or midran or pulmin or tracylol or trascolan or trasilol or tra?ylol or traskolan or zymofren or pancreas antitrypsin or protinin or riker 52g or Rivilina zymofren)#26 #24 or #25#27 MeSH descriptor: [Factor VIIa] this term only#28 (factor viia or factor 7a or rfviia or fviia or novoseven* or novo seven* or aryoseven or acset or eptacog* or proconvertin)#29 (activated near/1 (factor seven or factor vii or rfvii or fvii))#30 (factor seven or factor vii or factor 7):ti#31 #27 or #28 or #29 or #30#32 MeSH descriptor: [Fibrinogen] this term only#33 ("fibrinogen concentrate" or "factor I" or Haemocomplettan* or Riastap* or Fibryga* or Fibryna*)#34 #32 or #33#35 MeSH descriptor: [Deamino Arginine Vasopressin] this term only#36 (desmopressin* or vasopressin deamino or D amino D arginine vasopressin or deamino 8 d arginine vasopressin or vasopressin desamino 8 arginine or desmotabs or DDAVP or desmogalen or adin

or adiuretin or concentraid or d void or dav ritter or deamino 8 dextro arginine vasopressin or deamino 8d arginine vasopressin or deamino dextro arginine vasopressin or deaminovasopressin or defirin or defirin melt or desmirin pr desmomelt or desmopresina or desmospray or desmotab* or desurin or emosint or enupresol or minirin or minirinette or minirinmelt or minrin or minurin or miram or nictur or noctisson or nocturin or nocutil or nordurine or novidin or nucotil or octim or octostim or presinex or stimate or wetirin)#37 #35 or #36#38 MeSH descriptor: [Factor XIII] explode all trees#39 (factor xiii or fxiii or fibrin stabili?ing factor* or Tretten* or Catridecacog)#40 #38 or #39#41 MeSH descriptor: [Tissue Adhesives] explode all trees#42 MeSH descriptor: [Collagen] explode all trees and with qualifier(s): [therapeutic use - TU]#43 MeSH descriptor: [Thrombin] explode all trees and with qualifier(s): [therapeutic use - TU]#44 MeSH descriptor: [Gelatin] explode all trees and with qualifier(s): [therapeutic use - TU]#45 MeSH descriptor: [Gelatin Sponge, Absorbable] this term only#46 ((fibrin* or collagen or cellulose or gelatin or gel or thrombin* or albumin or hemostatic* or haemostatic*) next (glu* or seal* or adhesive* or topical* or local* or matrix or matrices or spong* or fleece* or foam* or scaffold* or patch* or sheet* or bandag* or aerosol* or dressing* or paste or powder*))#47 ((nonfibrin* or non-fibrin* or synthetic* or non-biological* or nonbiological* or biological*) near/3 (glue* or seal* or adhesive*))#48 (surgical* near/3 (glue* or sealant* or adhesive*))#49 ((fibrin* or collagen or cellulose or gelatin or thrombin) near/3 (hemosta* or haemosta*))#50 (8Y or Aafact or Actif-VIII or Advate or Artiss or Bioglue or Biocol or Collaseal or Omrixil or Transglutine or Raplixa or Evarrest or Aleviate or Alphanate or Amofil or Beriate or Beriplast or Biostate or Bolheal or Cluvot or Conco-Eight-HT or Crosseel or Crosseal or Crosseight or Emoclot or Evarrest or Evicel or Factane or Fanhdi or Fibrogammin P or Green VIII or Green VIII Factor or Greengene or Greenmono or Greenplast or

Haemate or Haemate P or Haemate P or Haemate P500 or Haemate-P or Haemoctin or Haemoctin SDH or Haemoctin-SDH or Hemaseel or Hemaseal or Hemofil M or Hemoraas or Humaclot or Humafactor-8 or Humate-P or Immunate or Innovate or Koate or Koate-DVI or Kogenate Bayer or Kogenate FS or Monoclate-P or NovoThirteen or Octafil or Octanate or Octanate or Optivate or Quixil or Talate or Tisseel or Tisseal or Tissel or Tissucol or Tricos or Vivostat or Voncento or Wilate or Wilnativ or Wilstart or Xyntha)#51 (Glubran or Gluetiss or Ifabond or Indermil or LiquiBand or TissuGlu or Evithrom or Floseal or Hemopatch or Gel-Flow or Gelfoam or Gelfilm or Recothrom or Surgifoam or Surgiflo* or "rh Thrombin" or Thrombi-Gel or Thrombi-Pad or Thrombin-JMI or Thrombinar or Thrombogen or Thrombostat)#52 (porcine gelatin or bovine collagen or bovine gelatin or nu-knit or arista or hemostase or vita sure or thrombin-jmi or thrombinjmi or avicel or vivagel or lyostypt or tabotamp or arterx or omnex or veriset)#53 (polysaccharide next (sphere* or hemostatic powder))#54 MeSH descriptor: [Chitosan] this term only#55 MeSH descriptor: [Polyethylene Glycols] this term only and with qualifier(s): [therapeutic use - TU]#56 MeSH descriptor: [Hydrogel, Polyethylene Glycol Dimethacrylate] explode all trees and with qualifier(s): [therapeutic use - TU]#57 MeSH descriptor: [Polyurethanes] explode all trees and with qualifier(s): [pharmacology - PD, adverse effects - AE, toxicity - TO, administration & dosage - AD, therapeutic use - TU]#58 ((polymer-derived elastic* or polymer tissue adhesive* or elastic hydrogel* or glutaraldehyde or PEG-based or polyurethane-based tissue or polyethylene glycol* or polyvinyl alcohol-based tissue or PVA-based tissue or natural biopolymer* or polypeptide-based or protein-based or polysaccharide-based or chitosan or poliglusam or cyanoacrylic or cyanoacrylate or cyacrin or dextran-based or chondroitin sulfate-based or mussel-inspired elastic* or glycol hydrogel or polymer-based) next (glu* or seal* or adhesive* or topical* or local* or matrix or matrices or spong* or

fleece* or foam* or scaffold* or patch* or sheet* or bandag* or aerosol* or dressing* or paste* or powder*))#59 MeSH descriptor: [Cellulose, Oxidized] this term only#60 (absorbable cellulose or resorbable cellulose or oxidi?ed cellulose or carboxycellulose or oxycellulose or cellulosic acid or oxycel or oxidi?ed regenerated cellulose)#61 (BioGlue or Progel or Duraseal or Coseal or FocalSeal or ADAL-1 or AdvaSeal or Pleuraseal or Angio-Seal or Avitene or Instat or Helitene or Helistat or TDM-621 or Dermabond or Tissueseal or PolyStat or Raplixa or Spongostan or Surgicel or Surgilux or Tachosil or Traumstem)#62 (collagen-thrombin or thrombin-collagen or gelatin-fibrinogen or fibrinogen-gelatin or gelatin-thrombin or thrombin-gelatin or fibrinogen-thrombin or thrombin-fibrinogen or collagen-fibrinogen or fibrinogen-collagen or microfibrillar collagen or CoStasis or "GRF Glue" or GR-Dial or Algosterile or TraumaStat or HemCon or ChitoFlex or Celox or QuikClot or WoundStat or Vitagel or TachSeal or TachoComb or Cryoseal)#63 #41 or #42 or #43 or #44 or #45 or #46 or #47 or #48 or #49 or #50 or #51 or #52 or #53 or #54 or #55 or #56 or #57 or #58 or #59 or #60 or #61 or #62#64 MeSH descriptor: [Waxes] explode all trees#65 (bonewax* or bone wax* or bone putty or hemasorb or ostene)#66 #64 or #65#67 (((haemosta* or hemosta* or antihaemorrhag* or antihemorrhag* or anti haemorrhag* or anti-hemorrhag*) next (drug* or agent* or treat* or therap*)) or ((coagulat* or clotting) next factor*))#68 #23 or #26 or #31 or #34 or #37 or #40 or #63 or #66 or #67#69 #11 and #68

MEDLINE (Ovid)

1. Arthroplasty, Replacement, Hip/2. Hip/su3. Osteoarthritis, Hip/su4. Arthroplasty, Replacement, Knee/5. exp Knee Injuries/su6. Knee/su7. Osteoarthritis, Knee/su8. ((hip* or knee* or femur or femoral) adj10 (replac* or

operat* or surg* or arthroplast* or reconstruct* or repair* or osteotom* or alloplast* or plast* or resurfac* or implant* or prosthes*)).tw,kf.9. (acetabuloplast* or acetabulum arthroplast*).tw,kf.10. (THA or THR or TKA or TKR or UKA or UKR).tw.11. or/1-1012. Antifibrinolytic Agents/13. Tranexamic Acid/14. Aminocaproic Acid/15. (antifibrinolytic* or anti-fibrinolytic* or antifibrinolysin* or antiplasmin* or plasmin inhibitor* or tranexamic or tranhexamic or cyclohexanecarboxylic acid* or amcha or trans-4-aminomethyl-cyclohexanecarboxylic acid* or t-amcha or amca or "kabi 2161" or transamin or amchafibrin or anvitoff or spotof or cyklokapron or cyclo-F or femstrual or ugurol or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or AMCHA or amchafibrin or amikapron or aminomethyl cyclohexane carboxylic acid or aminomethyl cyclohexanecarboxylic acid or aminomethylcyclohexane carbonic acid or aminomethylcyclohexane carboxylic acid or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or aminomethylcyclohexanocarboxylic acid or aminomethylcyclohexanoic acid or amstat or antivoff or caprilon or cl? 65336 or cl65336 or cyclocapron or cyclokapron or cyklocapron or cyklokapron or exacyl or frenolyse or fibrinon or hemostan or hexacapron or hexakapron or kalnex or lysteda or rikaparin or ronex or theranex or tranexam or tranexanic or tranexic or trans achma or transexamic or trenaxin or TXA or (fibrinolysis adj2 inhibitor*)).tw,kf.16. (Agretax or Bio-Stat or Capiloc or Capitrax or Clip Inj or Clot-XL or Clotawin-T or Coastat or Cuti or Cymin or Dubatran or Espercil or Examic or Existat or Extam or Fibran or Gynae-Pil or Hemstate or Kapron or Menogia or Monitex or Nestran or Nexamic or Nexi-500 or Nexmeff or Nicolda or Nixa-500 or Pause or Rheonex or Sylstep TX or Synostat or T-nex or T Stat or T Stat or Tanmic or Temsyl-T or Texakind or Texanis or Texapar or Texid or Thams or Tonopan or Traklot or Tramic or Tramix or Tranarest or Trance Inj or Tranecid or

Tranee or Tranemic or Tranex or Tranexa or Tranfib or Tranlok or Transtat or Transys or Transcam or Tranxi or Trapic or Traxage or Traxamic or Traxyl or Trenaxa or Trexamic or Trim Inj or Tx-1000 or Tx 500 or Wistran or X-Tran or Xamic).tw,kf.17. (6-aminohexanoic or amino?caproic or amino?hexanoic or amino caproic or amino-caproic or amino-n-hexanoic or cy-116 or cy116 or lederle or acikaprin or afibrin or amicar or caprocid or capracid or capramol or caprogel or caprolest or caprolisin* or caprolysin* or capromol or epsikapron or hemocaprol or caproamin or EACA or caprolest or capralense or hexalense or hamostat or hemocid or cl 10304 or cl10304 or ecapron or ekaprol or epsamon or epsicaprom or epsicapron or epsilcapramin or epsilon amino caproate or epsilon aminocaproate or epsilonaminocaproic or epsilonaminocapronsav or etha?aminocaproic or ethaaminocaproich or emocaprol or hepin or ipsilon or jd?177or neocaprol or nsc?26154 or resplamin or tachostyptan).tw,kf.18. or/12-1719. Aprotinin/20. (antagosan or antilysin* or aprotimbin or apronitin* or aprotinin* or bayer a128 or contrical or contrycal or contrykal or dilmintal or frey inhibitor or kontrycal or Kunitz inhibitor or gordox or haemoprot or kallikrein-trypsin inactivator).tw,kf.21. (iniprol or kontrikal or kontrykal or kunitz pancreatic trypsin inhibitor or midran or pulmin or tracylol or trascolan or trasilol or tra?ylol or traskolan or zymofren or pancreas antitrypsin or protinin or riker 52g or Rivilina zymofren).tw,kf.22. or/19-2123. Factor VIIa/24. (factor viia or factor 7a or rfviia or fviia or novoseven* or novo seven* or aryoseven or acset or eptacog* or proconvertin).tw,kf.25. ((activated adj2 factor seven) or (activated adj2 factor vii) or (activated adj3 rfvii) or (activated adj2 fvii)).tw,kf.26. (factor seven or factor vii or factor 7).ti.27. 23 or 24 or 25 or 2628. Fibrinogen/ad, ae, de, sd, tu, th, to29. *Fibrinogen/30. (fibrinogen concentrate* or factor I or Haemocomplettan* or Riastap* or Fibryga* or Fibryna*).tw,kf.31. 28 or 29 or 3032. Deamino Arginine Vasopressin/33. (desmopressin* or vasopressin deamino or D-amino D-arginine

vasopressin or deamino-8-d-arginine vasopressin or vasopressin 1-desamino-8-arginine or desmotabs or DDAVP or desmogalen or adin or adiuretin or concentraid or d-void or dav ritter or deamino 8 dextro arginine vasopressin or deamino 8d arginine vasopressin or deamino dextro arginine vasopressin or deaminovasopressin or defirin or defirin melt or desmirin or desmomelt or desmopresina or desmospray or desmotab* or desurin or emosint or enupresol or minirin or minirinette or minirinmelt or minrin or minurin or miram or nictur or noctisson or nocturin or nocutil or nordurine or novidin or nucotil or octim or octostim or presinex or stimate or wetirin).tw,kf.34. 32 or 3335. exp Factor XIII/36. (factor XIII or fXIII or fibrin stabili?ing factor* or Tretten* or Catridecacog).tw,kf.37. 35 or 3638. exp Tissue Adhesives/39. *Adhesives/40. Collagen/tu41. Thrombin/tu42. Gelatin/tu43. Gelatin Sponge, Absorbable/44. ((fibrin* or collagen or cellulose or gelatin or gel or thrombin* or albumin or hemostatic* or haemostatic*) adj3 (glu* or seal* or adhesive* or topical* or local* or matrix or matrices or spong* or fleece* or foam* or scaffold* or patch* or sheet* or bandag* or aerosol* or dressing* or paste or powder*)).tw,kf.45. ((nonfibrin* or non-fibrin* or synthetic* or non-biological* or nonbiological* or biological*) adj3 (glue* or seal* or adhesive*)).tw,kf.46. (surgical* adj3 (glue* or sealant* or adhesive*)).tw,kf.47. ((fibrin* or collagen or cellulose or gelatin or thrombin) adj3 (hemosta* or haemosta*)).tw,kf.48. (8Y or Aafact or Actif-VIII or Advate or Artiss or Bioglue or Biocol or Collaseal or Omrixil or Transglutine or Raplixa or Evarrest or Aleviate or Alphanate or Amofil or Beriate or Beriplast or Biostate or Bolheal or Cluvot or Conco-Eight-HT or Crosseel or Crosseal or Crosseight or Emoclot or Evarrest or Evicel or Factane or Fanhdi or Fibrogammin P or Green VIII or Green VIII Factor or Greengene or Greenmono or Greenplast or Haemate or Haemate P or Haemate P or Haemate P500 or Haemate-P or Haemoctin or Haemoctin SDH or Haemoctin-SDH or Hemaseel or Hemaseal or

Hemofil M or Hemoraas or Humaclot or Humafactor-8 or Humate-P or Immunate or Innovate or Koate or Koate-DVI or Kogenate Bayer or Kogenate FS or Monoclate-P or NovoThirteen or Octafil or Octanate or Octanate or Optivate or Quixil or Talate or Tisseel or Tisseal or Tissel or Tissucol or Tricos or Vivostat or Voncento or Wilate or Wilnativ or Wilstart or Xyntha).tw,kf.49. (Glubran or Gluetiss or Ifabond or Indermil or LiquiBand or TissuGlu).tw,kf.50. (Evithrom or Floseal or Hemopatch or Gel-Flow or Gelfoam or Gelfilm or Recothrom or Surgifoam or Surgiflo* or "rh Thrombin" or Thrombi-Gel or Thrombi-Pad or Thrombin-JMI or Thrombinar or Thrombogen or Thrombostat).tw,kf.51. (porcine gelatin or bovine collagen or bovine gelatin or nu-knit or arista or hemostase or vita sure or thrombin-jmi or thrombinjmi or avicel or vivagel or lyostypt or tabotamp or arterx or omnex or veriset).tw,kf.52. (polysaccharide adj (sphere* or hemostatic powder)).tw,kf.53. *Chitosan/54. *Polyethylene Glycols/55. *Hydrogel, Polyethylene Glycol Dimethacrylate/56. Polyurethanes/ad, ae, pd, tu, to57. ((polymer-derived elastic* or polymer tissue adhesive* or elastic hydrogel* or glutaraldehyde or PEG-based or polyurethane-based tissue or polyethylene glycol* or polyvinyl alcohol-based tissue or PVA-based tissue or natural biopolymer* or polypeptide-based or protein-based or polysaccharide-based or chitosan or poliglusam or cyanoacrylic or cyanoacrylate or cyacrin or dextran-based or chondroitin sulfate-based or mussel-inspired elastic* or glycol hydrogel or polymer-based) adj3 (glu* or seal* or adhesive* or topical* or local* or matrix or matrices or spong* or fleece* or foam* or scaffold* or patch* or sheet* or bandag* or aerosol* or dressing* or paste* or powder*)).tw,kf.58. Cellulose, Oxidized/59. (absorbable cellulose or resorbable cellulose or oxidi?ed cellulose or carboxycellulose or oxycellulose or cellulosic acid or oxycel or oxidi?ed regenerated cellulose).tw,kf.60. (BioGlue or Progel or Duraseal or Coseal or FocalSeal or ADAL-1 or AdvaSeal or Pleuraseal or Angio-Seal or Avitene or Instat

or Helitene or Helistat or TDM-621 or Dermabond or Tissueseal or PolyStat or Raplixa or Spongostan or Surgicel or Surgilux or Tachosil or Traumstem).tw,kf.61. (collagen-thrombin or thrombin-collagen or gelatin-fibrinogen or fibrinogen-gelatin or gelatin-thrombin or thrombin-gelatin or fibrinogen-thrombin or thrombin-fibrinogen or collagen-fibrinogen or fibrinogen-collagen or microfibrillar collagen or CoStasis or "GRF Glue" or GR-Dial or Algosterile or TraumaStat or HemCon or ChitoFlex or Celox or QuikClot or WoundStat or Vitagel or TachSeal or TachoComb or Cryoseal).tw,kf.62. or/38-6163. exp Waxes/64. (bonewax* or bone wax* or bone putty or hemasorb or ostene).tw,kf.65. 63 or 6466. (((haemosta* or hemosta* or antihaemorrhag* or antihemorrhag* or anti haemorrhag* or anti-hemorrhag*) adj5 (drug* or agent* or treat* or therap*)) or ((coagulat* or clotting) adj factor*)).tw,kf.67. 18 or 22 or 27 or 31 or 34 or 37 or 62 or 65 or 6668. 11 and 6769. Meta-Analysis.pt.70. ((meta analy* or metaanaly*) and (trials or studies)).ab.71. (meta analy* or metaanaly* or evidence-based).ti.72. ((systematic* or evidence-based) adj2 (review* or overview*)).tw,kf.73. (evidence synthes* or cochrane or medline or pubmed or embase or cinahl or cinhal or lilacs or "web of science" or science citation index or scopus or search terms or literature search or electronic search* or comprehensive search* or systematic search* or published articles or search strateg* or reference list* or bibliograph* or handsearch* or hand search* or manual* search*).ab.74. Cochrane Database of systematic reviews.jn.75. (additional adj (papers or articles or sources)).ab.76. ((electronic* or online) adj (sources or resources or databases)).ab.77. (relevant adj (journals or articles)).ab.78. or/69-7779. Review.pt.80. exp Randomized Controlled Trials as Topic/81. selection criteria.ab. or critical appraisal.tw.82. (data adj (abstract* or extract* or analys*)).ab.83. exp Randomized Controlled Trial/84. or/80-8385. 79 and 8486. 78 or 8587. Randomized Controlled Trial.pt.88. Controlled Clinical Trial.pt.89. (placebo or

randomly or groups).ab.90. (randomi* or trial).tw,kf.91. exp Clinical Trial as Topic/92. 86 or 87 or 88 or 89 or 90 or 9193. exp animals/ not humans/94. 92 not 9395. 68 and 94

Embase (Ovid)

1. exp Hip Surgery/2. exp Hip Disease/su3. exp Knee Surgery/4. exp Knee Disease/su5. ((hip* or knee* or femur or femoral) adj10 (replac* or operat* or surg* or arthroplast* or reconstruct* or repair* or osteotom* or alloplast* or plast* or resurfac* or implant* or prosthes*)).tw.6. (acetabuloplast* or acetabulum arthroplast*).tw.7. or/1-68. Antifibrinolytic Agent/9. Tranexamic Acid/ 10. Aminocaproic Acid/11. (antifibrinolytic* or anti-fibrinolytic* or antifibrinolysin* or antiplasmin* or plasmin inhibitor* or tranexamic or tranhexamic or cyclohexanecarboxylic acid* or amcha or trans-4-aminomethyl-cyclohexanecarboxylic acid* or t-amcha or amca or "kabi 2161" or transamin or amchafibrin or anvitoff or spotof or cyklokapron or cyclo-F or femstrual or ugurol or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or AMCHA or amchafibrin or amikapron or aminomethyl cyclohexane carboxylic acid or aminomethyl cyclohexanecarboxylic acid or aminomethylcyclohexane carbonic acid or aminomethylcyclohexane carboxylic acid or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or aminomethylcyclohexanocarboxylic acid or aminomethylcyclohexanoic acid or amstat or antivoff or caprilon or cl? 65336 or cl65336 or cyclocapron or cyclokapron or cyklocapron or cyklokapron or exacyl or frenolyse or fibrinon or hemostan or hexacapron or hexakapron or kalnex or lysteda or rikaparin or ronex or theranex or tranexam or tranexanic or tranexic or trans achma or transexamic or trenaxin or TXA or (fibrinolysis adj2 inhibitor*)).tw.12. (Agretax or Bio-Stat or Capiloc or Capitrax or Clip Inj or Clot-XL

or Clotawin-T or Coastat or Cuti or Cymin or Dubatran or Espercil or Examic or Existat or Extam or Fibran or Gynae-Pil or Hemstate or Kapron or Menogia or Monitex or Nestran or Nexamic or Nexi-500 or Nexmeff or Nicolda or Nixa-500 or Pause or Rheonex or Sylstep TX or Synostat or T-nex or T Stat or T Stat or Tanmic or Temsyl-T or Texakind or Texanis or Texapar or Texid or Thams or Tonopan or Traklot or Tramic or Tramix or Tranarest or Trance Inj or Tranecid or Tranee or Tranemic or Tranex or Tranexa or Tranfib or Tranlok or Transtat or Transys or Transcam or Tranxi or Trapic or Traxage or Traxamic or Traxyl or Trenaxa or Trexamic or Trim Inj or Tx-1000 or Tx 500 or Wistran or X-Tran or Xamic).tw.13. (6-aminohexanoic or amino?caproic or amino?hexanoic or amino caproic or amino-caproic or amino-n-hexanoic or cy-116 or cy116 or lederle or acikaprin or afibrin or amicar or caprocid or capracid or capramol or caprogel or caprolest or caprolisin* or caprolysin* or capromol or epsikapron or hemocaprol or caproamin or EACA or caprolest or capralense or hexalense or hamostat or hemocid or cl 10304 or cl10304 or ecapron or ekaprol or epsamon or epsicaprom or epsicapron or epsilcapramin or epsilon amino caproate or epsilon aminocaproate or epsilonaminocaproic or epsilonaminocapronsav or etha? aminocaproic or ethaaminocaproich or emocaprol or hepin or ipsilon or jd?177or neocaprol or nsc?26154 or resplamin or tachostyptan).tw.14. or/8-1315. Aprotinin/16. (antagosan or antilysin* or aprotimbin or apronitin* or aprotinin* or bayer a128 or contrical or contrycal or contrykal or dilmintal or frey inhibitor or kontrycal or Kunitz inhibitor or gordox or haemoprot or kallikrein-trypsin inactivator).tw.17. (iniprol or kontrikal or kontrykal or kunitz pancreatic trypsin inhibitor or midran or pulmin or tracylol or trascolan or trasilol or tra?ylol or traskolan or zymofren or pancreas antitrypsin or protinin or riker 52g or Rivilina zymofren).tw.18. or/15-1719. Blood Clotting Factor 7a/20. (factor viia or factor 7a or rfviia or fviia or novoseven* or novo seven* or aryoseven or acset or eptacog*

or proconvertin).tw.21. ((activated adj2 factor seven) or (activated adj2 factor vii) or (activated adj3 rfvii) or (activated adj2 fvii)).tw.22. (factor seven or factor vii or factor 7).ti.23. 19 or 20 or 21 or 2224. Fibrinogen Concentrate/25. (fibrinogen concentrate* or factor I or Haemocomplettan* or Riastap* or Fibryga* or Fibryna*).tw.26. 24 or 2527. Desmopressin/28. (desmopressin* or vasopressin deamino or D-amino D-arginine vasopressin or deamino-8-d-arginine vasopressin or vasopressin 1-desamino-8-arginine or desmotabs or DDAVP or desmogalen or adin or adiuretin or concentraid or d-void or dav ritter or deamino 8 dextro arginine vasopressin or deamino 8d arginine vasopressin or deamino dextro arginine vasopressin or deaminovasopressin or defirin or defirin melt or desmirin or desmomelt or desmopresina or desmospray or desmotab* or desurin or emosint or enupresol or minirin or minirinette or minirinmelt or minrin or minurin or miram or nictur or noctisson or nocturin or nocutil or nordurine or novidin or nucotil or octim or octostim or presinex or stimate or wetirin).tw.29. 27 or 2830. Blood Clotting Factor 13/31. (factor xiii or fxiii or fibrin stabili?ing factor* or Tretten* or Catridecacog).tw.32. 30 or 3133. exp Tissue Adhesive/34. *Adhesive Agent/35. *Hemostatic Agent/36. ((fibrin* or collagen or cellulose or gelatin or gel or thrombin* or albumin or hemostatic* or haemostatic*) adj3 (glu* or seal* or adhesive* or topical* or local* or matrix or matrices or spong* or fleece* or foam* or scaffold* or patch* or sheet* or bandag* or aerosol* or dressing* or paste or powder*)).tw.37. ((nonfibrin* or non-fibrin* or synthetic* or non-biological* or nonbiological* or biological*) adj3 (glue* or seal* or adhesive*)).tw.38. (surgical* adj3 (glue* or sealant* or adhesive*)).tw.39. ((fibrin* or collagen or cellulose or gelatin or thrombin) adj3 (hemosta* or haemosta*)).tw.40. (8Y or Aafact or Actif-VIII or Advate or Artiss or Raplixa or Evarrest or Aleviate or Alphanate or Amofil or Beriate or Beriplast or Biostate or Bolheal or Cluvot or Conco-Eight-HT or Crosseel or Crosseal or Crosseight or

Emoclot or Evarrest or Evicel or Factane or Fanhdi or Fibrogammin P or Green VIII or Green VIII Factor or Greengene or Greenmono or Greenplast or Haemate or Haemate P or Haemate P or Haemate P500 or Haemate-P or Haemoctin or Haemoctin SDH or Haemoctin-SDH or Hemaseel or Hemaseal or Hemofil M or Hemoraas or Humaclot or Humafactor-8 or Humate-P or Immunate or Innovate or Koate or Koate-DVI or Kogenate Bayer or Kogenate FS or Monoclate-P or NovoThirteen or Octafil or Octanate or Octanate or Optivate or Quixil or Talate or Tisseel or Tisseal or Tissel or Tissucol or Tricos or Vivostat or Voncento or Wilate or Wilnativ or Wilstart or Xyntha).tw.41. (Glubran or Gluetiss or Ifabond or Indermil or LiquiBand or TissuGlu).tw.42. Collagen Sponge/ or Collagen Dressing/ 43. Gelatin Sponge/ or Gelfoam/44. (Evithrom or Floseal or Hemopatch or Gel-Flow or Gelfoam or Gelfilm or Recothrom or Surgifoam or Surgiflo* or "rh Thrombin" or Thrombi-Gel or Thrombi-Pad or Thrombin-JMI or Thrombinar or Thrombogen or Thrombostat).tw.45. *Chitosan/46. Hydrogel Dressing/47. Fibrinogen plus Thrombin/48. Polyvinyl Alcohol Sponge/49. (porcine gelatin or bovine collagen or bovine gelatin or nu-knit or arista or hemostase or vita sure or thrombin-jmi or thrombinjmi or avicel or vivagel or lyostypt or tabotamp or arterx or omnex or veriset).tw.50. (polysaccharide adj (sphere* or hemostatic powder)).tw.51. ((polymer-derived elastic* or polymer tissue adhesive* or elastic hydrogel* or glutaraldehyde or PEG-based or polyurethane-based tissue or polyethylene glycol* or polyvinyl alcohol-based tissue or PVA-based tissue or natural biopolymer* or polypeptide-based or protein-based or polysaccharide-based or chitosan or poliglusam or cyanoacrylic or cyanoacrylate or cyacrin or dextran-based or chondroitin sulfate-based or mussel-inspired elastic* or glycol hydrogel or polymer-based) adj3 (glu* or seal* or adhesive* or topical* or local* or matrix or matrices or spong* or fleece* or foam* or scaffold* or patch* or sheet* or bandag* or aerosol* or dressing* or paste* or powder*)).tw.52.

Oxidized Cellulose/53. Oxidized Regenerated Cellulose/54. Recombinant Thrombin/55. Tachocomb/56. (absorbable cellulose or resorbable cellulose or oxidi?ed cellulose or carboxycellulose or oxycellulose or cellulosic acid or oxycel or oxidi?ed regenerated cellulose).tw.57. (BioGlue or Progel or Duraseal or Coseal or FocalSeal or ADAL-1 or AdvaSeal or Pleuraseal or Angio-Seal or Avitene or Instat or Helitene or Helistat or TDM-621 or Dermabond or Tissueseal or PolyStat or Raplixa or Spongostan or Surgicel).tw.58. (Tachosil or Traumstem or CoStasis or "GRF Glue" or GR-Dial or Algosterile or TraumaStat or HemCon or ChitoFlex or Celox or QuikClot or WoundStat or Vitagel or TachSeal or TachoComb or Cryoseal).tw.59. (collagen-thrombin or thrombin-collagen or gelatin-fibrinogen or fibrinogen-gelatin or gelatin-thrombin or thrombin-gelatin or fibrinogen-thrombin or thrombin-fibrinogen or collagen-fibrinogen or fibrinogen-collagen or microfibrillar collagen).tw.60. or/33-5961. Bone Wax/62. (bonewax* or bone wax* or bone putty or hemasorb or ostene).tw.63. or/61-6264. (((haemosta* or hemosta* or antihaemorrhag* or antihemorrhag* or anti haemorrhag* or anti-hemorrhag*) adj5 (drug* or agent* or treat* or therap*)) or ((coagulat* or clotting) adj factor*)).tw.65. 14 or 18 or 23 or 26 or 29 or 32 or 60 or 63 or 6466. 7 and 6567. Meta Analysis/68. (meta analy* or metaanaly* or evidence-based).ti.69. ((meta analy* or metaanaly*) and (trials or studies)).ab.70. Systematic Review/71. ((systematic* or evidence-based) adj2 (review* or overview*)).tw.72. (evidence synthes* or cochrane or medline or pubmed or embase or cinahl or cinhal or lilacs or "web of science" or science citation index or scopus or search terms or literature search or electronic search* or comprehensive search* or systematic search* or published articles or search strateg* or reference list* or bibliograph* or handsearch* or hand search* or manual* search*).ab.73. ((electronic* or online) adj (sources or resources or databases)).ab.74. ((additional adj (papers or articles or sources)) or (relevant

adj (journals or articles))).ab.75. or/67-7476. Review.pt.77. (data extraction or selection criteria).ab.78. 76 and 7779. 75 or 7880. Editorial.pt.81. 79 not 8082. crossover-procedure/ or double-blind procedure/ or randomized controlled trial/ or single-blind procedure/83. (random* or factorial* or crossover* or cross over* or cross-over* or placebo* or doubl* blind* or singl* blind* or assign* or allocat* or volunteer*).mp.84. 82 or 8385. 81 or 8486. 66 and 85

Emcare (Ovid)

1. exp Hip Surgery/2. exp Knee Surgery/3. ((hip* or knee* or femur or femoral) adj10 (replac* or operat* or surg* or arthroplast* or reconstruct* or repair* or osteotom* or alloplast* or plast* or resurfac* or implant* or prosthes*)).tw.4. (acetabuloplast* or acetabulum arthroplast*).tw.5. 1 or 2 or 3 or 46. Antifibrinolytic Agent/7. Tranexamic Acid/8. Aminocaproic Acid/9. (antifibrinolytic* or anti-fibrinolytic* or antifibrinolysin* or antiplasmin* or plasmin inhibitor* or tranexamic or tranhexamic or cyclohexanecarboxylic acid* or amcha or trans-4-aminomethyl-cyclohexanecarboxylic acid* or t-amcha or amca or "kabi 2161" or transamin or amchafibrin or anvitoff or spotof or cyklokapron or cyclo-F or femstrual or ugurol or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or AMCHA or amchafibrin or amikapron or aminomethyl cyclohexane carboxylic acid or aminomethyl cyclohexanecarboxylic acid or aminomethylcyclohexane carbonic acid or aminomethylcyclohexane carboxylic acid or aminomethylcyclohexanecarbonic acid or aminomethylcyclohexanecarboxylic acid or aminomethylcyclohexanocarboxylic acid or aminomethylcyclohexanoic acid or amstat or antivoff or caprilon or cl?65336 or cl65336 or cyclocapron or cyclokapron or cyklocapron or cyklokapron or exacyl or frenolyse or fibrinon or

hemostan or hexacapron or hexakapron or kalnex or lysteda or rikaparin or ronex or theranex or tranexam or tranexanic or tranexic or trans achma or transexamic or trenaxin or TXA or (fibrinolysis adj2 inhibitor*)).tw.10. (Agretax or Bio-Stat or Capiloc or Capitrax or Clip Inj or Clot-XL or Clotawin-T or Coastat or Cuti or Cymin or Dubatran or Espercil or Examic or Existat or Extam or Fibran or Gynae-Pil or Hemstate or Kapron or Menogia or Monitex or Nestran or Nexamic or Nexi-500 or Nexmeff or Nicolda or Nixa-500 or Pause or Rheonex or Sylstep TX or Synostat or T-nex or T Stat or T Stat or Tanmic or Temsyl-T or Texakind or Texanis or Texapar or Texid or Thams or Tonopan or Traklot or Tramic or Tramix or Tranarest or Trance Inj or Tranecid or Tranee or Tranemic or Tranex or Tranexa or Tranfib or Tranlok or Transtat or Transys or Transcam or Tranxi or Trapic or Traxage or Traxamic or Traxyl or Trenaxa or Trexamic or Trim Inj or Tx-1000 or Tx 500 or Wistran or X-Tran or Xamic).tw.11. (6-aminohexanoic or amino?caproic or amino?hexanoic or amino caproic or amino-caproic or amino-n-hexanoic or cy-116 or cy116 or lederle or acikaprin or afibrin or amicar or caprocid or capracid or capramol or caprogel or caprolest or caprolisin* or caprolysin* or capromol or epsikapron or hemocaprol or caproamin or EACA or caprolest or capralense or hexalense or hamostat or hemocid or cl 10304 or cl10304 or ecapron or ekaprol or epsamon or epsicaprom or epsicapron or epsilcapramin or epsilon amino caproate or epsilon aminocaproate or epsilonaminocaproic or epsilonaminocapronsav or etha?aminocaproic or ethaaminocaproich or emocaprol or hepin or ipsilon or jd?177or neocaprol or nsc?26154 or resplamin or tachostyptan).tw.12. or/6-1113. Aprotinin/14. (antagosan or antilysin* or aprotimbin or apronitin* or aprotinin* or bayer a128 or contrical or contrycal or contrykal or dilmintal or frey inhibitor or kontrycal or Kunitz inhibitor or gordox or haemoprot or kallikrein-trypsin inactivator).tw.15. (iniprol or kontrikal or kontrykal or kunitz pancreatic trypsin inhibitor or midran or

pulmin or tracylol or trascolan or trasilol or tra?ylol or traskolan or zymofren or pancreas antitrypsin or protinin or riker 52g or Rivilina zymofren).tw.16. or/13-1517. Blood Clotting Factor 7a/18. (factor viia or factor 7a or rfviia or fviia or novoseven* or novo seven* or aryoseven or acset or eptacog* or proconvertin).tw.19. ((activated adj2 factor seven) or (activated adj2 factor vii) or (activated adj3 rfvii) or (activated adj2 fvii)).tw.20. (factor seven or factor vii or factor 7).ti.21. 17 or 18 or 19 or 2022. Fibrinogen Concentrate/23. (fibrinogen concentrate* or factor I or Haemocomplettan* or Riastap* or Fibryga* or Fibryna*).tw.24. 22 or 2325. Desmopressin/26. (desmopressin* or vasopressin deamino or D-amino D-arginine vasopressin or deamino-8-d-arginine vasopressin or vasopressin 1-desamino-8-arginine or desmotabs or DDAVP or desmogalen or adin or adiuretin or concentraid or d-void or dav ritter or deamino 8 dextro arginine vasopressin or deamino 8d arginine vasopressin or deamino dextro arginine vasopressin or deaminovasopressin or defirin or defirin melt or desmirin or desmomelt or desmopresina or desmospray or desmotab* or desurin or emosint or enupresol or minirin or minirinette or minirinmelt or minrin or minurin or miram or nictur or noctisson or nocturin or nocutil or nordurine or novidin or nucotil or octim or octostim or presinex or stimate or wetirin).tw.27. 25 or 2628. Blood Clotting Factor 13/29. (factor xiii or fxiii or fibrin stabili?ing factor* or Tretten* or Catridecacog).tw.30. 28 or 2931. exp Tissue Adhesive/32. *Adhesive Agent/33. *Hemostatic Agent/34. ((fibrin* or collagen or cellulose or gelatin or gel or thrombin* or albumin or hemostatic* or haemostatic*) adj3 (glu* or seal* or adhesive* or topical* or local* or matrix or matrices or spong* or fleece* or foam* or scaffold* or patch* or sheet* or bandag* or aerosol* or dressing* or paste or powder*)).tw.35. ((nonfibrin* or non-fibrin* or synthetic* or non-biological* or nonbiological* or biological*) adj3 (glue* or seal* or adhesive*)).tw.36. (surgical* adj3 (glue* or sealant* or adhesive*)).tw.37.

((fibrin* or collagen or cellulose or gelatin or thrombin) adj3 (hemosta* or haemosta*)).tw.38. (8Y or Aafact or Actif-VIII or Advate or Artiss or Raplixa or Evarrest or Aleviate or Alphanate or Amofil or Beriate or Beriplast or Biostate or Bolheal or Cluvot or Conco-Eight-HT or Crosseel or Crosseal or Crosseight or Emoclot or Evarrest or Evicel or Factane or Fanhdi or Fibrogammin P or Green VIII or Green VIII Factor or Greengene or Greenmono or Greenplast or Haemate or Haemate P or Haemate P or Haemate P500 or Haemate-P or Haemoctin or Haemoctin SDH or Haemoctin-SDH or Hemaseel or Hemaseal or Hemofil M or Hemoraas or Humaclot or Humafactor-8 or Humate-P or Immunate or Innovate or Koate or Koate-DVI or Kogenate Bayer or Kogenate FS or Monoclate-P or NovoThirteen or Octafil or Octanate or Octanate or Optivate or Quixil or Talate or Tisseel or Tisseal or Tissel or Tissucol or Tricos or Vivostat or Voncento or Wilate or Wilnativ or Wilstart or Xyntha).tw.39. (Glubran or Gluetiss or Ifabond or Indermil or LiquiBand or TissuGlu).tw.40. Collagen Sponge/ or Collagen Dressing/ 41. Gelatin Sponge/ or Gelfoam/42. (Evithrom or Floseal or Hemopatch or Gel-Flow or Gelfoam or Gelfilm or Recothrom or Surgifoam or Surgiflo* or "rh Thrombin" or Thrombi-Gel or Thrombi-Pad or Thrombin-JMI or Thrombinar or Thrombogen or Thrombostat).tw.43. *Chitosan/44. Hydrogel Dressing/45. Fibrinogen plus Thrombin/46. Polyvinyl Alcohol Sponge/47. (porcine gelatin or bovine collagen or bovine gelatin or nu-knit or arista or hemostase or vita sure or thrombin-jmi or thrombinjmi or avicel or vivagel or lyostypt or tabotamp or arterx or omnex or veriset).tw.48. (polysaccharide adj (sphere* or hemostatic powder)).tw.49. ((polymer-derived elastic* or polymer tissue adhesive* or elastic hydrogel* or glutaraldehyde or PEG-based or polyurethane-based tissue or polyethylene glycol* or polyvinyl alcohol-based tissue or PVA-based tissue or natural biopolymer* or polypeptide-based or protein-based or polysaccharide-based or chitosan or poliglusam or cyanoacrylic or cyanoacrylate or cyacrin or

dextran-based or chondroitin sulfate-based or mussel-inspired elastic* or glycol hydrogel or polymer-based) adj3 (glu* or seal* or adhesive* or topical* or local* or matrix or matrices or spong* or fleece* or foam* or scaffold* or patch* or sheet* or bandag* or aerosol* or dressing* or paste* or powder*)).tw.50. Oxidized Cellulose/51. Oxidized Regenerated Cellulose/52. Recombinant Thrombin/53. Tachocomb/54. (absorbable cellulose or resorbable cellulose or oxidi?ed cellulose or carboxycellulose or oxycellulose or cellulosic acid or oxycel or oxidi?ed regenerated cellulose).tw.55. (BioGlue or Progel or Duraseal or Coseal or FocalSeal or ADAL-1 or AdvaSeal or Pleuraseal or Angio-Seal or Avitene or Instat or Helitene or Helistat or TDM-621 or Dermabond or Tissueseal or PolyStat or Raplixa or Spongostan or Surgicel).tw.56. (Tachosil or Traumstem or CoStasis or "GRF Glue" or GR-Dial or Algosterile or TraumaStat or HemCon or ChitoFlex or Celox or QuikClot or WoundStat or Vitagel or TachSeal or TachoComb or Cryoseal).tw.57. (collagen-thrombin or thrombin-collagen or gelatin-fibrinogen or fibrinogen-gelatin or gelatin-thrombin or thrombin-gelatin or fibrinogen-thrombin or thrombin-fibrinogen or collagen-fibrinogen or fibrinogen-collagen or microfibrillar collagen).tw.58. or/31-5759. Bone Wax/60. (bonewax* or bone wax* or bone putty or hemasorb or ostene).tw.61. or/59-6062. (((haemosta* or hemosta* or antihaemorrhag* or antihemorrhag* or anti haemorrhag* or anti-hemorrhag*) adj5 (drug* or agent* or treat* or therap*)) or ((coagulat* or clotting) adj factor*)).tw.63. 12 or 16 or 21 or 24 or 27 or 30 or 58 or 61 or 6264. 5 and 6365. Meta Analysis/66. (meta analy* or metaanaly* or evidence-based).ti.67. ((meta analy* or metaanaly*) and (trials or studies)).ab.68. Systematic Review/69. ((systematic* or evidence-based) adj2 (review* or overview*)).tw.70. (evidence synthes* or cochrane or medline or pubmed or embase or cinahl or cinhal or lilacs or "web of science" or science citation index or scopus or search terms or literature search or electronic search*

or comprehensive search* or systematic search* or published articles or search strateg* or reference list* or bibliograph* or handsearch* or hand search* or manual* search*).ab.71. ((electronic* or online) adj (sources or resources or databases)).ab.72. ((additional adj (papers or articles or sources)) or (relevant adj (journals or articles))).ab.73. or/65-7274. Review.pt.75. (data extraction or selection criteria).ab.76. 74 and 7577. 73 or 7678. Editorial.pt.79. 77 not 7880. crossover-procedure/ or double-blind procedure/ or randomized controlled trial/ or single-blind procedure/81. (random* or factorial* or crossover* or cross over* or cross-over* or placebo* or doubl* blind* or singl* blind* or assign* or allocat* or volunteer*).mp.82. 80 or 8183. 79 or 8284. 64 and 83

TRANSFUSION EVIDENCE LIBRARY Clinical Specialty: Orthopaedic SurgeryANDSubject Areas: Alternatives to Blood/Antifibrinolytics OR Alternatives to Blood/Fractionated Blood Proucts OR Alternatives to Blood/Recombinant Coagulation Factors

ClinicalTrials.gov1.

Other Terms: (hip surgery OR knee surgery OR arthroplasty OR hip replacement OR femoral replacement OR knee replacement OR knee injury OR osteoarthritis OR THA OR TKA) AND (randomized or randomised OR randomly OR random) ANDIntervention: hemostatic OR antifibrinolytic OR tranexamic OR EACA OR aminocaproic OR aprotinin OR desmopressin OR DDAVP OR factor viia OR novoseven OR aryoseven OR fibrinogen OR haemocomplettan OR Riastap OR Fibryna OR Fibryga OR factor XIII OR Tretten2. Other Terms: (hip surgery OR knee surgery OR arthroplasty OR hip replacement OR femoral replacement OR knee replacement OR knee injury OR osteoarthritis OR THA OR TKA) AND (randomized or randomised OR randomly OR random) ANDIntervention: sealant

OR adhesive OR collagen OR cellulose OR gelatin OR glue OR matrix OR sponge OR fleece OR foam OR scaffold OR patch OR sheet OR gelfoam OR chitosan OR hydrogel OR polyethylene glycol OR tachocomb OR BioGlue OR Surgicel OR Veriset3. Other Terms: (hip surgery OR knee surgery OR arthroplasty OR hip replacement OR femoral replacement OR knee replacement OR knee injury OR osteoarthritis OR THA OR TKA) AND (randomized or randomised OR randomly OR random) ANDIntervention: Evithrom OR Floseal OR Tachosil OR Cryoseal OR Hemopatch OR Progel OR Duraseal OR Coseal OR FocalSeal OR Algosterile OR TraumaStat OR HemCon OR ChitoFlex OR Celox OR QuikClot OR WoundStat OR Vitagel OR TachSeal OR bonewax OR hemasorb OR ostene4. Other Terms: (hip surgery OR knee surgery OR arthroplasty OR hip replacement OR femoral replacement OR knee replacement OR knee injury OR osteoarthritis OR THA OR TKA) AND (randomized or randomised OR randomly OR random) ANDIntervention: iniprol or kontrikal OR CloSys OR Glubran OR Gluetiss OR Ifabond OR Indermil OR LiquiBand OR Octafil OR Octanate OR Optivate OR Quixil OR Tisseel OR Tissucol OR TissuGlu OR Thrombi-Gel OR Vivostat OR Voncento OR Wilate OR Wilnativ OR Wilstart5. Other Terms: (hip surgery OR knee surgery OR arthroplasty OR hip replacement OR femoral replacement OR knee replacement OR knee injury OR osteoarthritis OR THA OR TKA) AND (randomized or randomised OR randomly OR random) ANDTitle: hemostasis OR hemostatic OR antifibrinolytic OR factor OR fibrinogen OR thrombin OR collagen OR gelatin OR cellulose6. Other Terms: (hip surgery OR knee surgery OR arthroplasty OR hip replacement OR femoral replacement OR knee replacement OR knee injury OR osteoarthritis OR THA OR TKA) AND (randomized or randomised OR randomly OR random) ANDCondition: bleeding OR hemorrhage OR blood loss OR bloodloss7. 1 OR 2 OR 3 OR 4 OR 5 OR 6 [N.B. combined and de-duplicated in EndNote]

WHO ICTRP1.

Title OR Condition: hip surgery OR knee surgery OR arthroplasty OR hip replacement OR femoral replacement OR knee replacement OR knee injury OR osteoarthritis OR TKA OR THAIntervention: hemostatic OR antifibrinolytic OR tranexamic OR EACA OR aminocaproic OR aprotinin OR desmopressin OR DDAVP OR factor viia OR novoseven OR aryoseven OR fibrinogen OR haemocomplettan OR Riastap OR Fibryna OR Fibryga OR factor XIII OR Tretten

2. Title OR Condition: hip surgery OR knee surgery OR arthroplasty OR hip replacement OR femoral replacement OR knee replacement OR knee injury OR osteoarthritis OR TKA OR THAIntervention: sealant OR adhesive OR collagen OR cellulose OR gelatin OR glue OR matrix OR sponge OR fleece OR foam OR scaffold OR patch OR sheet OR gelfoam OR chitosan OR hydrogel OR polyethylene glycol OR tachocomb OR BioGlue OR Surgicel OR Veriset

3. Title OR Condition: hip surgery OR knee surgery OR arthroplasty OR hip replacement OR femoral replacement OR knee replacement OR knee injury OR osteoarthritis OR TKA OR THAIntervention: Evithrom OR Floseal OR Tachosil OR Cryoseal OR Hemopatch OR Progel OR Duraseal OR Coseal OR FocalSeal OR Algosterile OR TraumaStat OR HemCon OR ChitoFlex OR Celox OR QuikClot OR WoundStat OR Vitagel OR TachSeal OR bonewax OR hemasorb OR ostene

4. Title OR Condition: hip surgery OR knee surgery OR arthroplasty OR hip replacement OR femoral replacement OR knee replacement OR knee injury OR osteoarthritis OR TKA OR THAIntervention: iniprol or kontrikal OR CloSys OR

Glubran OR Gluetiss OR Ifabond OR Indermil OR LiquiBand OR Octafil OR Octanate OR Optivate OR Quixil OR Tisseel OR Tissucol OR TissuGlu OR Thrombi-Gel OR Vivostat OR Voncento OR Wilate OR Wilnativ OR Wilstart

5. Title OR Condition: hip surgery OR knee surgery OR arthroplasty OR hip replacement OR femoral replacement OR knee replacement OR knee injury OR osteoarthritis OR TKA OR THAIntervention OR Title: hemostasis OR hemostatic OR antifibrinolytic OR factor OR fibrinogen OR thrombin OR collagen OR gelatin OR cellulose

6. 1 OR 2 OR 3 OR 4 OR 5 [N.B. combined and de-duplicated in EndNote]

B.1.2 Data extraction form

Study Identification
Sponsorship source
Country
Setting
Comments
Authors name
Institution
Email
Address
Native language of paper
Reference type
Trial registration number
Was it translated for this review?
Methods
Design
Group
Intention to treat analysis
Length of duration of study
Power calculation reached?
Transfusion strategy?
Was the trial stopped early?
Population

Inclusion criteria
Exclusion criteria
Group differences
If TKR, is tourniquet used?
Indication for surgery
Type of anaesthetic
Type of surgery
Age (years) (mean SD)
Ethnicity
Gender (males, females)
Length of surgery (minutes)
Proportion of participants on anticoagulants prior to surgery? (n, %)
Incidence of preoperative anaemia?
Co-morbidities
ASA 1 (n, %)
ASA 2 (n, %)
ASA 3 (n, %)
ASA 4 (n, %)
Number of participants randomised
Number of participants receiving treatment
Number of participants analysed
Dropout rate
Interventions
Cut and paste
Short description
Outcomes
All-cause mortality up to 30 days post-surgery
Red cell transfusions up to 30 days post-surgery
Proportion of participants receiving any allogenic blood product
Proportion of participants undergoing reoperation for bleeding up to 7 days post-surgery
Proportion of participants experiencing an MI up to 30 days post-surgery
Proportion of participants experiencing a CVA up to 30 days post-surgery
Proportion of participants experiencing a DVT up to 30 days post-surgery
Proportion of participants experiencing a PE up to 30 days post-surgery
Proportion of participants experiencing transfusion reaction within 24 hours post-surgery
Proportion of participants experiencing suspected serious drug reactions within 30 days of surgery
Length of Hospital stay
Other
Health related quality of life up to 30 days post-surgery using validated measures
Cost data

B.1.3 Information Given to Expert Blinded Panel

Meeting 23rd April 2020 pre-meeting information & agenda

Thank you for agreeing to participate in the expert panel for the review "Pharmacological interventions for preventing bleeding in people requiring elective hip or knee surgery: a systematic review and network meta-analysis"

We have now completed data extraction and as per the protocol (attached to the email) we are now looking towards how to put the network meta-analysis together.

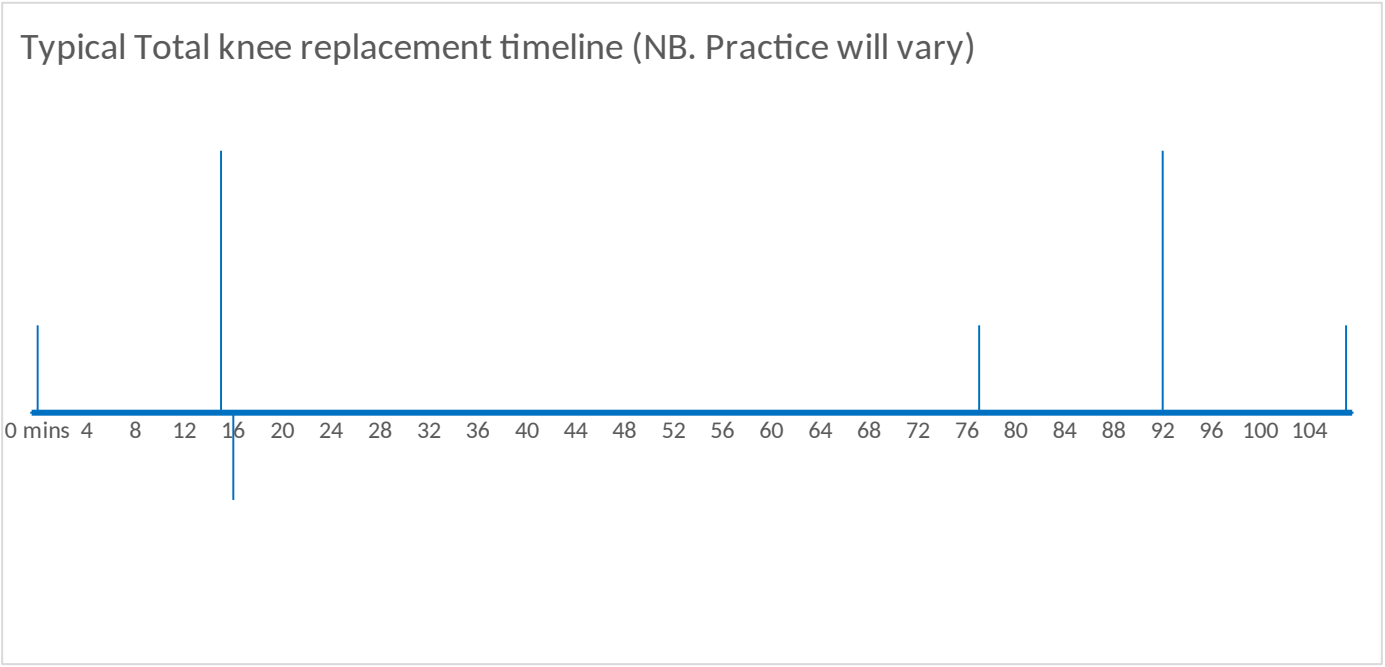
Background on network meta-analysis:

Network meta-analysis (NMA) allows the comparison of more than two treatments. The evidence on each comparison is represented by networks. Each treatment is represented by a node (vertex), a line then connects the two treatments being compared. In a network, there will be a mix of solid and blank lines – solid lines represent 'direct' comparisons where the treatments in question have been compared in clinical trials. However, blank or absent lines represent 'indirect' comparisons, meaning there are no clinical trials on this comparison. NMA utilises clinical trial data from the 'direct' comparisons to 'indirectly' infer and estimate the effects of the missing comparisons. By doing this, NMA can be used to bridge gaps in the evidence by combining data from direct comparisons in clinical trials with missing comparison information in the network structure.

Aim of the meeting:

- To establish different nodes suitable for analysis that are clinically helpful to the end user

General information to consider:



- Average total hip replacement duration from induction to end ~2.5 hours +/- 30 mins
- Cementing may or may not take place in hip replacement surgery

For trials involving EACA versus active intervention

1) The range of doses used in trials for EACA is 13.11g-15g. Would you consider 13.11g and 15g similar enough a dose to be combined in the analysis as a single node?

For trials involving TXA versus active intervention

General information to consider:

- The half-life of TXA is 3 hours

1) What doses would you consider similar enough to group as nodes in the analysis?

2) Would you consider oral TXA 2 hours prior to surgery equivalent to IV at induction?

3) Interventions are given in terms of hours and surgical events. How would you group timing of interventions with the available information?

> 3a) would you consider TXA administration prior to incision and at tourniquet inflation equivalent?
> 3b) would you consider TXA administration between tourniquet inflation to deflation equivalent?
> 3c) would you consider an intervention delivered 'x' hours post op, the same as 'x' hours after 1st dose similar enough to analyse together?
> 3d) would you consider immediately after anaesthesia the same as at anaesthesia?

For trials involving Aprotinin versus active intervention

1) What doses would you consider similar enough to group as nodes in the analysis?

2) _Would you group all trials involving Aprotinin as one or would you separate them out e.g. those with just a bolus?

For trials involving Desmopressin versus active intervention

1) The range of doses used in trials for Desmopressin is 17.31mgg-24.21mcg. Would you consider 17.31mcg and 24.21mcg similar enough a dose to be combined in the analysis as a single node?

General questions:

1) Some studies are extreme outliers (highlighted in red in the excel form). Should these be included in a group or analysed separately?

2) How should studies analysing bilateral procedures simultaneously be considered?

B.1.4 Characteristics of included studies

B.1.4.1 Alvarez 2008

Methods	**Study design:** Single centre, 2-arm, RCT **Country:** Spain **Length of duration of study:** 13 months **Power calculation reached:** No **Transfusion strategy:** Not reported **Was the trial stopped early:** No
Participants	**Baseline Characteristics** Placebo arm *Age (years) (mean SD)*: 72 (7) *Ethnicity*: Not reported *Gender (males, females)*: 10, 39 *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: 0/ 55, 0% *Incidence of preoperative anaemia:* Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N, %)*: 3/ 49, 6.12% *ASA 2 (n/ N, %)*: 39/ 49, 79.59% *ASA 3 (n/ N, %)*: 7/ 49, 14.29% *ASA 4 (n/ N, %)*: Not reported *Number of participants randomised*: 55 *Number of participants receiving treatment*: 50 *Number of participants analysed*: 49 *Dropout rate*: 6/55 (10.91%) TXA arm *Age (years) (mean SD)*: 71 (9)

	Ethnicity: Not reported *Gender (males, females)*: 7, 39 *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: 0/ 55, 0% *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N, %)*: 1/ 46, 2.17% *ASA 2 (n/ N, %)*: 39/ 46, 84.78% *ASA 3 (n/ N, %)*: 5/ 46, 10.87% *ASA 4 (n/ N, %)*: Not reported *Number of participants randomised*: 55 *Number of participants receiving treatment*: 46 *Number of participants analysed*: 46 *Dropout rate*: 9/ 55 (16.36%) **Included criteria:** 1) Patients scheduled for total knee replacement surgery, 2) Diagnosed with osteoarthrosis **Excluded criteria:** 1) Known allergy to tranexamic acid, 2) ASA-IV physical status or higher, 3) Severe ischemia and/or heart valve disease, 4) History of thromboembolic episodes, 5) Known coagulopathy, 6) Renal dysfunction (serum creatinine concentration >1.5 mg/dL) **Tourniquet use:** Yes **Indication for surgery:** Osteoarthrosis **Type of anaesthetic:** Spinal **Type of surgery:** Primary TKR
Interventions	**Intervention Characteristics** Placebo arm Placebo bolus (physiologic saline), administered by the research anaesthetist 30 minutes before deflation of the tourniquet followed by an infusion of 1 mg per kg per hour starting at the end of the operation and continuing during the first 6 postoperative hour TXA arm TXA bolus of 10mg per kg tranexamic acid, administered by the research anaesthetist 30 minutes before deflation of the tourniquet followed by an infusion of 1 mg per kg per hour starting at the end of the operation and

	continuing during the first 6 postoperative hours
Outcomes	*Primary outcome* Transfusion rate *Secondary outcome* Postoperative blood loss
Notes	**Sponsorship source:** Not reported **Country**: Spain **Setting**: Not reported **Comments**: None **Authors name:** J.C. Alvarez **Institution:** University Hospital of Mar-Esperança **Email:** 94188@imas.imim.es **Address:** Department of Anaesthesiology, University Hospital of Mar-Esperança, Passeig Marítim 25, 08003 Barcelona, Spain **Native language of paper:** English **Reference type:** Full text (1) **Trial registration number:** Not applicable, but when checked trial registration number not found **Was it translated for this review:** No

B.1.4.2 Alvarez 2019 hips

Methods	**Study design:** RCT **Length of duration of study:** Recruitment period not stated but follow-up was 1yr **Power calculation reached:** Yes **Transfusion strategy:** If haemoglobin (Hb) levels fell to below 8 g/dL or the patient showed signs of anaemia, the protocol permitted the transfusion of red blood cells **Was the trial stopped early:** No
Participants	**Baseline Characteristics** Placebo, IV *Age (years) (mean SD)*: 70 (12.4) *Ethnicity*: Not reported

	Gender (Male, female): 4/ 11, 36.4% (M); 7/ 11, 63.6% (F) *Length of surgery (minutes) (mean SD)*: 59 (30) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: BMI 30.2 (6.2) *ASA 1 (n/ N, %)*: Not reported *ASA 2 (n/ N, %)*: 8/ 11, 72.7% *ASA 3 (n/ N, %)*: 3/ 11, 27.3% *ASA 4 (n/ N, %)*: 0/ 11, 0% *Number of participants randomised*: 11 *Number of participants receiving treatment*: 11 *Number of participants analysed*: 11 *Dropout rate (%)*: 0/ 11, 0% TXA, IV *Age (years) (mean SD)*: 68.4 (9.4) *Ethnicity*: Not reported *Gender (Male, female)*: 3/ 11, 27.3% (M); 8/ 11, 72.7% (F) *Length of surgery (minutes) (mean SD)*: 71 (30) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N, %)*: Not reported *ASA 2 (n/ N, %)*: 8/ 11, 72.7% *ASA 3 (n/ N, %)*: 3/ 11, 27.3% *ASA 4 (n/ N, %)*: 0/ 11, 0% *Number of participants randomised*: 11 *Number of participants receiving treatment*: 11 *Number of participants analysed*: 11 *Dropout rate (%)*: 0/ 11, 0% Overall *Age (years) (median range)*: Not reported *Ethnicity*: Not reported *Gender (Male, female)*: Not reported

	Length of surgery (minutes) (mean SD): Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N, %)*: Not reported *ASA 2 (n/ N, %)*: Not reported *ASA 3 (n/ N, %)*: Not reported *ASA 4 (n/ N, %)*: Not reported *Number of participants randomised*: 22 *Number of participants receiving treatment*: 22 *Number of participants analysed*: 22 *Dropout rate (%)*: 0/ 22, 0% **Included criteria:** Patients scheduled for TKA and THA were considered eligible for the study **Excluded criteria:** Exclusion criteria were: allergy to TXA or radiological contrast media, history of thromboembolism (to avoid exposing patients with previously undetected thrombophilia to TXA), coagulopathy, and kidney failure with glomerular filtration <60 mL/min/m2. **Tourniquet use:** Yes (tourniquet was inflated to 350 mmHg during surgery) **Indication for surgery:** Not reported **Type of anaesthetic:** The anaesthesia protocol prioritised the use of spinal anaesthesia, but general anaesthesia was also permitted. **Type of surgery:** Primary TKA
Interventions	**Intervention Characteristics** Placebo, IV An independent anaesthetist prepared 2 vials containing 10 mg/kg TXA (Amchafibrin, Agenzia-Ecopharma Laboratories) or placebo (saline solution). Following the double-blind protocol, the researcher administered the medication in 2 infusions: 30 min before and 3 h after the incision. TXA, IV TXA, IV, 10mg/ kg, pre-op + 10mg/ kg, post-op
Outcomes	*Primary outcome:*

	Percentage of patients requiring transfusion. Secondary outcome: Postoperative bleeding Incidence of DVT and PE. Clotting and fibrinolysis parameters
Notes	**Sponsorship source:** Non-pharmaceutical (This study was funded by an FIS grant from the Carlos III Institute, Madrid (FIS 2006/1227). **Country:** Spain **Setting:** Single-centre **Comments**: 1. This paper gives data for both Knees and Hips, we will be extracting KNEES on this form 2. Red blood cell divided by TXA/ Placebo not by operation as well **Authors name:** J. Alvarez **Institution:** Institut Hospital del Mar d'Investigacions Mèdiques (IMIM), Universitat Autònoma de Barcelona (UAB) **Email:** J. Alvarez: 94188@hospitaldelmar.cat **Address:** J. Alvarez: 94188@hospitaldelmar.cat **Native language of paper:** English **Reference type:** Full text (1) **Trial registration number:** EudraCT2007-000193-22 **Was it translated for this review:** No

B.1.4.3 Alvarez 2019 knees

Methods	**Study design:** RCT **Length of duration of study:** Recruitment period not stated but follow-up was 1yr **Power calculation reached:** Yes **Transfusion strategy:** If haemoglobin (Hb) levels fell to below 8 g/dL or the patient showed signs of anaemia, the protocol permitted the transfusion of red blood cells **Was the trial stopped early:** No
Participants	**Baseline Characteristics** Placebo, IV *Age (years) (mean SD)*: 72.4 (7.1)

	Ethnicity: Not reported *Gender (Male, female)*: 2/ 11, 18.2% (M); 9/ 11, 81.8% (F) *Length of surgery (minutes) (mean SD)*: 84 (14) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: BMI: 34.6 (8.9) *ASA 1 (n/ N, %)*: Not reported *ASA 2 (n/ N, %)*: 5/ 11, 45.5% *ASA 3 (n/ N, %)*: 6/ 11, 54.5% *ASA 4 (n/ N,%)*: 0/ 11, 0% *Number of participants randomised*: 11 *Number of participants receiving treatment*: 11 *Number of participants analysed*: 11D*ropoutt rate (%)*: 0/ 11, 0% TXA, IV *Age (years) (mean SD)*: 70 (7.5) *Ethnicity*: Not reported *Gender (Male, female)*: 3/ 11, 27.3% (M); 8/ 11, 72.7% (F) *Length of surgery (minutes) (mean SD)*: 85 (22) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: BMI 34.1 (7) *ASA 1 (n/ N, %)*: Not reported *ASA 2 (n/ N, %)*: 6/ 11, 54.5% *ASA 3 (n/ N, %)*: 4/ 11, 36.4% *ASA 4 (n/ N,%)*: 1/ 11, 9.1% *Number of participants randomised*: 11 *Number of participants receiving treatment*: 11 *Number of participants analysed*: 11 *Dropout rate (%)*: 0/ 11, 0% Overall *Age (years) (median range)*: Not reported *Ethnicity*: Not reported

	Gender (Male, female): Not reported *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N, %)*: Not reported *ASA 2 (n/ N, %)*: Not reported *ASA 3 (n/ N, %)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 22 *Number of participants receiving treatment*: 22 *Number of participants analysed*: 22 *Dropout rate (%)*: 0/ 22, 0% **Included criteria:** Patients scheduled for TKA and THA were considered eligible for the study **Excluded criteria:** Exclusion criteria were: allergy to TXA or radiological contrast media, history of thromboembolism (to avoid exposing patients with previously undetected thrombophilia to TXA), coagulopathy, and kidney failure with glomerular filtration <60 mL/min/m2. **Tourniquet use:** Yes (tourniquet was inflated to 350 mmHg during surgery) **Indication for surgery:** Not reported **Type of anaesthetic:** The anaesthesia protocol prioritised the use of spinal anaesthesia, but general anaesthesia was also permitted. **Type of surgery:** Primary TKA
Interventions	**Intervention Characteristics** Placebo, IV An independent anaesthetist prepared 2 vials containing 10 mg/kg TXA (Amchafibrin, Agenzia-Ecopharma Laboratories) or placebo (saline solution). Following the double-blind protocol, the researcher administered the medication in 2 infusions: 30 min before and 3 h after the incision. TXA, IV TXA, IV, 10mg/ kg, pre-op + 10mg/ kg, post-op

Outcomes	*Primary outcome:* Percentage of patients requiring transfusion. Secondary outcome: Postoperative bleeding Incidence of DVT and PE. Clotting and fibrinolysis parameters
Notes	**Sponsorship source:** Non-pharmaceutical (This study was funded by an FIS grant from the Carlos III Institute, Madrid (FIS 2006/1227). **Country:** Spain **Setting:** Single-centre **Comments**: 1. This paper gives data for both Knees and Hips, we will be extracting KNEES on this form 2. Red blood cell divided by TXA/ Placebo not by operation as well **Authors name:** J. Alvarez **Institution:** Institut Hospital del Mar d'Investigacions Mèdiques (IMIM), Universitat Autònoma de Barcelona (UAB) **Email:** J. Alvarez: 94188@hospitaldelmar.cat **Address:** J. Alvarez: 94188@hospitaldelmar.cat **Native language of paper:** English **Reference type:** Full text (1) **Trial registration number:** EudraCT2007-000193-22 **Was it translated for this review:** No

B.1.4.4 Benoni 1996

Methods	**Study design:** 2-arm, RCT **Country:** Sweden **Length of duration of study:** Not reported **Power calculation reached:** No **Transfusion strategy:** No specific value for Hb concentration or haematocrit levels, each transfusion prescribed with regard to the patient's cardiovascular history, present status, fall in Hb level, rate of blood loss and age. As a rule of thumb, they considered blood transfusion indicated at a Hb concentration of below 85 to 100 g/l. **Was the trial stopped early:** No

	Registration: No trial registration
Participants	**Baseline Characteristics** Placebo *Age (years) (mean SD)*: 74 (7) *Ethnicity*: Not reported *Gender (males, females)*: 10, 33 *Length of surgery (minutes) (mean SD)*: 96 (18) *Proportion of participants on anticoagulants prior to surgery (n/ N, %) (within one week)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 48 *Number of participants receiving treatment*: Not reported *Number of participants analysed*: 43 *Dropout rate*: 5/43 (11.6%) TXA *Age (years) (mean SD)*: 76 (7) *Ethnicity*: Not reported *Gender (males, females)*: 13, 30 *Length of surgery (minutes) (mean SD)*: 96 (18) *Proportion of participants on anticoagulants prior to surgery (n/ N, %) (within one week)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 48 *Number of participants receiving treatment*: Not reported

	Number of participants analysed: 43 *Dropout rate*: 5/43 (11.6%) **Included criteria:** 1) No history of bleeding disorders or warfarin medication, 2) Diagnosis of osteoarthritis or aseptic bone necrosis, 3) Primary, unilateral, bicompartmental knee arthroplasty, 4) Either both or no components cemented, 5) Continuous epidural anaesthesia, 6) Use of only balanced electrolyte solutions and/or albumin for plasma volume restitution **Excluded criteria:** Rheumatoid arthritis **Tourniquet use:** Yes **Indication for surgery:** Osteoarthritis or aseptic bone necrosis **Type of anaesthetic:** Epidural **Type of surgery:** Primary TKR
Interventions	**Intervention Characteristics** Placebo Placebo given as a slow intravenous injection towards the end of the operation at a median time of 12 minutes (1 to 40) before deflation of the tourniquet. This dose was repeated after three hours from the other ampoule of the pair provided in an envelope TXA Tranexamic acid of 10 mg/kg body-weight, maximum 1 g = 10 ml was given as a slow intravenous injection towards the end of the operation at a median time of 12 minutes (1 to 40) before deflation of the tourniquet. This dose was repeated after three hours from the other ampoule of the pair provided in an envelope
Outcomes	*Primary outcome* Blood loss *Secondary outcome* Need for blood transfusion Knee circumference Wound complications Range of motion Thromboembolic complications
Notes	**Sponsorship source:** Non-pharmaceutical

	Country: Sweden **Setting**: Not reported **Comments**: None **Authors name:** G. Benoni **Institution:** Malmö University Hospital **Email:** Not reported **Address:** Malmö University Hospital, S-205 02 Malmö, Sweden **Native language of paper:** English **Reference type:** Full text (1) **Trial registration number:** Not applicable, but when checked trial registration number not found **Was it translated for this review:** No

B.1.4.5 Benoni 2000

Methods	**Study design:** 2-arm, RCT **Country:** Sweden **Length of duration of study:** Not reported **Power calculation reached:** Yes **Transfusion strategy:** According to patients' clinical need, with individual regard to age, cardiovascular status and present clinical condition **Was the trial stopped early:** No **Registration:** No trial registration
Participants	**Baseline Characteristics** Placebo *Age (years) (mean SD)*: 68 (10) *Ethnicity*: Not reported *Gender (males, females)*: 11,8 *Length of surgery (minutes, mean SD)*: 105 (17) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported

	ASA 2 (n/ N,%): Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 20 *Number of participants receiving treatment*: 19 *Number of participants analysed*: 19 *Dropout rate*: 1/20 (5%) TXA *Age (years) (mean SD)*: 69.5 (10) *Ethnicity*: Not reported *Gender (males, females)*: 6,14 *Length of surgery (minutes, mean SD)*: 107 (25) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 20 *Number of participants receiving treatment*: 20 *Number of participants analysed*: 20 *Dropout rate*: 0/20 (0%) **Included criteria:** 1) Osteoarthrosis, 2) Idiopathic femoral head necrosis undergoing THR **Excluded criteria:** 1) Previously operated hip **Tourniquet use:** Not applicable **Indication for surgery:** Osteoarthrosis or idiopathic femoral head necrosis **Type of anaesthetic:** Mixed (continuous epidural, spinal, spinal/epidural, general, general and epidural) **Type of surgery:** primary THR
Interventions	**Intervention Characteristics** Placebo

	Placebo given intravenously at the end of the operation and the administration was repeated 3 hours later TXA Tranexamic acid 10 mg/kg body weight intravenously at the end of the operation and the administration was repeated 3 hours later
Outcomes	*Primary outcome* Postoperative blood loss Need for blood transfusion Deep venous thrombosis
Notes	**Sponsorship source:** Non-pharmaceutical **Country**: Sweden **Setting**: Not reported **Comments**: None **Authors name:** G. Benoni **Institution:** Malmö University Hospital, Sweden. **Email:** Not reported **Address:** Departments of Orthopedics, Malmö University Hospital, SE-205 02 Malmö, Sweden **Native language of paper:** English **Reference type:** Full paper (1) **Trial registration number:** Not applicable, but when checked trial registration number not found **Was it translated for this review:** No

B.1.4.6 Benoni 2001

Methods	**Study design:** Multi-centre, 2-arm, RCT **Country:** Sweden **Length of duration of study:** Not reported **Power calculation reached:** Yes **Transfusion strategy:** Transfusions were given on a case-by-case basis with regard to age, cardiovascular status, hemoglobin concentration and blood loss. Most patients who had blood transfusions received these at a hemoglobin concentration between 80 and 100 g/L. **Was the trial stopped early:** No

	Registration: No trial registration
Participants	**Baseline Characteristics** Placebo *Age (years) (mean SD)*: 68 (9.4) *Ethnicity*: Not reported *Gender (males, females)*: 10,10 *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 20 *Number of participants receiving treatment*: 20 *Number of participants analysed*: 20 *Dropout rate*: 0/20, (0%) TXA *Age (years) (mean SD)*: 66 (9.5) *Ethnicity*: Not reported *Gender (males, females)*: 9, 9 *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 20 *Number of participants receiving treatment*: 20

	Number of participants analysed: 18 *Dropout rate*: 2/20 (10%) **Included criteria:** 1) Patients scheduled for a unilateral, primary total hip replacement for osteoarthrosis or osteonecrosis **Excluded criteria:** 1) Rheumatoid arthritis, 2) Patients who were to undergo bone grafting, 3) Bleeding disorders, 4) Signs of renal insufficiency. **Pre-treatment:** No **Tourniquet use:** Not applicable **Indication for surgery:** Osteoarthrosis or osteonecrosis **Type of anaesthetic:** Mixed (general, spinal and epidural) **Type of surgery:** Primary THR
Interventions	**Intervention Characteristics** Placebo saline was given as a slow (5–10 minutes) intravenous injection immediately before the operation started TXA tranexamic acid 100 mg/mL, 10 mg/kg body weight (maximum 1 g), in a slow (5–10 minutes) intravenous injection immediately before the operation started
Outcomes	*Primary outcome* Blood loss Need for transfusion Hemoglobin concentration Clinical events
Notes	**Sponsorship source:** Mixed pharmaceutical and non-pharmaceutical **Country**: Sweden **Setting**: Not reported **Comments**: None **Authors name:** G. Benoni **Institution:** Malmö University Hospita **Email:** goran.benoni@skane.se **Address:** Departments of Orthopaedics and Diagnostic Radiology, Malmö University Hospital, SE-205 02 Malmö,

	Sweden **Native language of paper:** English **Reference type:** Full text (1) **Trial registration number:** Not applicable, but when checked trial registration number not found **Was it translated for this review:** No

B.1.4.7 Boese 2017

Methods	**Study design:** Single centre, 2-arm RCT **Country:** USA **Length of duration of study:** 23 months **Power calculation reached:** No **Transfusion strategy:** Standard transfusion protocol was utilized, dictating that a transfusion be performed only when the Hgb level dropped below 7 g/dL, or below 10 g/dL if there were clinical symptoms related to anemia **Was the trial stopped early:** Yes **Registration:** Trial prospectively registered
Participants	**Baseline Characteristics** TXA *Age (years) (mean SD)*: 64.97 (9.59) *Ethnicity*: Not reported *Gender (males, females)*: 29, 69 *Length of surgery (minutes) (mean SD)*: 76.67 (25.27) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: 98/98, (100%) *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: 1/98, (1%) *ASA 2 (n/ N,%)*: 37/98, (37.8%) *ASA 3 (n/ N,%)*: 55/98, (56.1%) *ASA 4 (n/ N,%)*: 5/98, (5.1%) *Number of participants randomised*: 98 *Number of participants receiving treatment*: Not reported *Number of participants analysed*: Not reported

	Dropout rate: Not reported EACA *Age (years) (mean SD)*: 66.12 (9.73) *Ethnicity*: Not reported *Gender (males, females)*: 25, 71 *Length of surgery (minutes) (mean SD)*: 73.78 (12.71) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: 96/96, (100%) *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: 2/96, (2.1%) *ASA 2 (n/ N,%)*: 38/96, (39.6%) *ASA 3 (n/ N,%)*: 53/ 96, (55.2%) *ASA 4 (n/ N,%)*: 3/96, (3.1%) *Number of participants randomised*: 96 *Number of participants receiving treatment*: Not reported *Number of participants analysed*: Not reported *Dropout rate*: Not reported Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males, females)*: Not reported *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: Not reported *Number of participants receiving treatment*: Not reported *Number of participants analysed*: Not reported *Dropout rate*: Not reported

	Included criteria: 1) Patients between the ages of 18 and 90 years who were scheduled to be treated with a unilateral total knee replacement by 1 of 3 surgeons from the same orthopaedic practice were eligible for inclusion. **Excluded criteria:** 1) History of coagulopathy, 2) History of deep vein thrombosis or pulmonary embolism 1 year prior to surgery, 3) Treatment with a coronary stent 1 year prior to surgery, 4) Preoperative autologous blood donation, 5) Being unwilling or unable to take an anticoagulant for prophylaxis against deep vein thrombosis, 6) Nonsteroidal anti-inflammatory drug (NSAID) or platelet antiaggregant treatment 5 days prior to surgery, 7) A recorded preoperative creatinine level of >1.5 mg/dL, 8) An inability to speak English. **Pre-treatment:** No **Tourniquet use:** Yes **Indication for surgery:** Not reported **Type of anaesthetic:** Mixed (General, Spinal and Epidural) **Type of surgery:** Primary TKR
Interventions	**Intervention Characteristics** TXA Tranexamic acid was given 1g in 250 mL of saline solution over 30 minutes prior to inflating the tourniquet and making the initial incision. A second 1g in 250mL of saline solution was infused over 30 minutes beginning at the time of wound closure EACA EACA was given 7g in 250 mL of saline solution over 30 minutes just prior to inflating the tourniquet and making the initial incision. A second 7g of EACA in 250 mL of saline solution was infused over 30 minutes beginning at the time of wound closure
Outcomes	*Primary outcome* Transfusions Estimated blood loss Drop in the hemoglobin (Hgb) level *Secondary outcome* Change in the serum creatinine level Postoperative complications Length of hospital stay

Notes	**Sponsorship source:** Non-pharmaceutical **Country:** USA **Setting**: Not reported **Comments**: None **Authors name:** R.W Walters **Institution:** Creighton University **Email:** ryanwalters@creighton.edu **Address:** Department of Medicine, Creighton University, Omaha, Nebraska **Native language of paper:** English **Reference type:** Full text (1) Trial registration (1) **Trial registration number:** NCT01873768 **Was it translated for this review:** No

B.1.4.8 Bradley 2019a

Methods	**Study design:** RCT **Country:** USA **Length of duration of study:** 34 months + 3 months follow-up **Power calculation reached:** No (study enrolment stopped early therefore unable to reach target sample size) **Transfusion strategy:** Patients received a transfusion based on the institutional protocol of Hgb < 7.0 g/dl or Hgb < 10.0 g/dl with associated symptoms. **Was the trial stopped early:** No (enrolment stopped early - but not trial. Enrolment on to study terminated early due to national lack of EACA) **Registration:** Prospectively registered
Participants	**Baseline Characteristics** TXA *Age (years) (median IQR)*: 61.3 (55.8 to 69.3) *Ethnicity (N, %)*: Caucasian 38 (82.6), African American 7 (15.2), Other 1 (2.2) *Gender (females) (N, %)*: 27 (58.7) *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to*

	surgery (n/ N, %): Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%) or ASA 2 (n/ N,%)*: 30 (65.2%) *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: Not reported *Number of participants receiving treatment*: 46 *Number of participants analysed*: 46 *Dropout rate*: Not reported EACA *Age (years) (median IQR)*: 59.2 (50.2 to 68.0) *Ethnicity (N, %)*: Caucasian 36 (81.8), African American 6 (13.6) , Other 2 (4.6) *Gender (females) (N, %)*: 21 (47.7) *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%) or ASA 2 (n/ N,%)*: 24 (54.6) *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: Not reported *Number of participants receiving treatment*: 44 *Number of participants analysed*: 44 *Dropout rate*: Not reported Overall *Age (years) (median IQR)*: Not reported *Ethnicity (N, %)*: Not reported *Gender (females) (N, %)*: 48/90 *Length of surgery (minutes) (mean IQR)*: 98 minutes (86 to 110)

	Proportion of participants on anticoagulants prior to surgery (n/ N, %): Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%) or ASA 2 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 94 *Number of participants receiving treatment*: 90 *Number of participants analysed*: 90 *Dropout rate*: 4/90, 4.4% **Included criteria:** All patients aged 18 years and over who were to undergo primary THA or TKA were considered for inclusion in the study. **Excluded criteria:** Patients were excluded if they had a history of cardiac stents, myocardial infarction (MI), cerebrovascular accident or stroke, deep venous thrombosis (DVT), pulmonary embolism (PE), late-onset colour blindness, or any known hypercoagulable state **Tourniquet use:** Not applicable **Indication for surgery:** Not reported **Type of anaesthetic:** Spinal **Type of surgery:** THA
Interventions	**Intervention Characteristics** TXA TXA was given as 1 g intravenously in two doses. The dosage was determined on the recommendation of the cardiac anaesthesiology team at our hospital, noting that TXA binds to plasminogen six to ten times more than EACA TXA IV 1g pre-incision, 1g wound closure EACA Antifibrinolytics were given twice perioperatively. The first dose was given immediately before making the incision and a second dose was given during wound closure. EACA was given as a 5 g dose in 250 ml of normal saline EACA IV 5g pre-incision, 5g wound closure
Outcomes	Primary outcome:

	Change in haemoglobin level and blood volume Postoperative drainage Rate of transfusion. Secondary outcome: Postoperative complications Cost Length of stay (LOS)
Notes	**Sponsorship source:** Hospital funded **Country:** USA **Setting**: Single-centre **Comments**: None **Authors name:** K.E. Bradley **Institution:** Duke University Medical Center **Email:** kendall.bradley@duke.edu **Address:** Duke University Medical Center, Durham North Carolina, United States **Native language of paper:** English **Reference type:** Full text (1), trial registration (1) **Trial registration number:** NCT02030821 **Was it translated for this review:** No

B.1.4.9 Bradley 2019b

Methods	**Study design:** RCT **Country:** USA **Length of duration of study:** 34 months + 3 months follow-up **Power calculation reached:** No (study enrolment stopped early therefore unable to reach target sample size) **Transfusion strategy:** Patients received a transfusion based on the institutional protocol of Hgb < 7.0 g/dl or Hgb < 10.0 g/dl with associated symptoms. **Was the trial stopped early:** No (enrolment stopped early - but not trial) **Registration:** Prospectively registered
Participants	**Baseline Characteristics**

	TXA *Age (years) (median IQR)*: 64.7 (60.7 to 69.6) *Ethnicity (N, %)*: Caucasian 57 (78.1) African American 15 (20.5) Other 1 (1.4) *Gender (males, females) (N)*: 23, 50 *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%) or ASA 2 (n/ N,%)*: 34 (46.6) *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: Not reported *Number of participants receiving treatment*: Not reported *Number of participants analysed*: 73 *Dropout rate*: Not reported EACA *Age (years) (median IQR)*: 65.6 (58.8 to 69.4) *Ethnicity (N, %)*: Caucasian 52 (72.2) African American 18 (25.0) Other 2 (2.8) *Gender (males, females) (N)*: 30, 42 *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%) or ASA 2 (n/ N,%)*: 33 (45.8) *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: Not reported *Number of participants receiving treatment*: Not reported *Number of participants analysed*: 72

	Dropout rate: Not reported Overall *Age (years) (median IQR)*: Not reported *Ethnicity (N, %)*: Not reported *Gender (males, females) (N)*: Not reported *Length of surgery (minutes) (mean SD)*: 104 minutes (IQR 90 to 120) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%) or ASA 2 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 152 *Number of participants receiving treatment*: 145 *Number of participants analysed*: 145 *Dropout rate*: Not reported **Included criteria:** All patients aged 18 years and over who were to undergo primary THA or TKA were considered for inclusion in the study. **Excluded criteria:** 1) History of cardiac stents 2) myocardial infarction (MI) 3) cerebrovascular accident or stroke 4) deep venous thrombosis (DVT) 5) pulmonary embolism (PE) 6) late-onset col-our blindness 7) any known hypercoagulable state **Tourniquet use:** Yes **Indication for surgery:** Not reported **Type of anaesthetic:** For TKA, patients had an adductor canal block and sedation **Type of surgery:** Primary TKR
Interventions	**Intervention Characteristics** TXA Antifibrinolytics were given twice perioperatively. The first dose was given immediately before making the incision and a second dose was given during wound closure. EACA was given as a 5 g dose in 250 ml of normal saline, while

	TXA was given as 1 g intravenously in two doses. TXA, IV, 1g, intraop incision and TXA, IV, 1g, intraop wound closure EACA EACA was given as a 5 g dose in 250 ml of normal saline EACA, IV, 1g, intraop incision and EACA, IV, 1g, intraop wound closure
Outcomes	Primary outcome: Change in haemoglobin level and blood volume Postoperative drainage Rate of transfusion. Secondary outcome: Postoperative complications Cost Length of stay (LOS)
Notes	**Sponsorship source:** Non-pharmaceutical **Country:** USA **Setting**: Single-centre **Comments**: 1. Extraction done for KNEES 2. Check if complications in table 4 are classed as 'serious drug reactions' or 'transfusion reaction', if so add to outcomes table 3. Enrolment on to study terminated early due to national lack of EACA. **Authors name:** K.E. Bradley **Institution:** Duke University Medical Center **Email:** kendall.bradley@duke.edu **Address:** Duke University Medical Center, Durham North Carolina, United States **Native language of paper:** English **Reference type:** Full text (1), trial registration (1) **Trial registration number:** NCT02030821 **Was it translated for this review:** No

B.1.4.10 Camarasa 2006

Methods	**Study design:** 3-arm, RCT, unclear whether single-centre

	or multi-centre **Length of duration of study:** 15 months **Power calculation reached:** Yes **Transfusion strategy:** A haemoglobin level of less than 8 g/dl was considered a transfusion trigger except in patients who could have poor tolerance to these levels because of associated conditions such as myocardial ischaemia chronic obstructive pulmonary disease (COPD), cerebral arterial insufficiency, or patients who presented signs, symptoms, or both of hypoxia such as tachycardia, dyspnoea, or syncope. The transfusion trigger was placed at less than 10 g/dl for these patients. **Was the trial stopped early:** No
Participants	**Baseline Characteristics** Placebo *Age (years) (median range)*: 72 (52–85) *Ethnicity*: Not reported *Gender (Male, female)*: 12, 48 *Length of surgery (minutes) (mean SD)*: 102 (19) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N, %)*: 3/ 60 (5%) *ASA 2 (n/ N, %)*: 44/ 60 (73.3%) *ASA 3 (n/ N, %)*: 13/ 60 (21.7%) *ASA 4 (n/ N,%)*: 0/ 60 (0%) *Number of participants randomised*: 60 *Number of participants receiving treatment*: 60 *Number of participants analysed*: 60 *Dropout rate (%)*: 0/ 60 (0%) TXA *Age (years) (median range)*: 73 (61-84) *Ethnicity*: Not reported *Gender (Male, female)*: 9, 26 *Length of surgery (minutes) (mean SD)*: 97 (22) *Proportion of participants on anticoagulants prior to*

	surgery (n/ N, %): Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N, %)*: 2/ 35 (5.7%) *ASA 2 (n/ N, %)*: 24/ 35 (68.6%) *ASA 3 (n/ N, %)*: 9/ 35 (25.7%) *ASA 4 (n/ N,%)*: 0/ 60 (0%) *Number of participants randomised* : 35 *Number of participants receiving treatment*: 35 *Number of participants analysed* : 35 *Dropout rate (%)*: 0/ 35 (0%) EACA *Age (years) (median range)*: 73 (59-80) *Ethnicity*: Not reported *Gender (Male, female)*: 4, 28 *Length of surgery (minutes) (mean SD)*: 102 (20) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N, %)*: 0/ 32 (0%) *ASA 2 (n/ N, %)*: 28/ 32 (87.5%) *ASA 3 (n/ N, %)*: 4/ 32 (12.5%) *ASA 4 (n/ N,%)*: 0/ 60 (0%) *Number of participants randomised*: 33 *Number of participants receiving treatment*: 33 *Number of participants analysed*: 32 *Dropout rate (%)*: 1/ 32 (3.1%) **Included criteria:** 1) All patients who needed unilateral, bicompartmental, primary, cemented TKR because of osteoarthritis or rheumatoid arthritis, 2) Anaesthetic risk groups ASA I–III **Excluded criteria:** 1) History of coagulopathy or thrombosis, embolism, or both, 2) Had received acenocoumarol, aspirin or platelet antiaggregant treatment in the week before surgery, or nonsteroidal anti-inflammatory agents in the 2 days before surgery, 3)

	Preoperative plasma creatinine greater than 130 mmol/litre, 4) History of myocardial infarction or chronic arteriopathy, 5) Unstable angina in the previous 12 months, 6) Mental states prevented them from understanding the study proposal **Tourniquet use:** Yes **Indication for surgery:** Osteoarthritis or rheumatoid arthritis **Type of anaesthetic:** Spinal anaesthetic **Type of surgery:** Primary TKR
Interventions	**Intervention Characteristics** Placebo Moreover, major bleeding in this type of surgery occurs in the first hours so a regimen of two doses, 3 h apart, was chosen for the effect to last over the first 6 h. With regard to EACA, the dose chosen (100 mg kg1) was mid-way between doses used in other studies and the dose recommended by the laboratory (Fides Ecopharma) and was followed by a perfusion of 1 g h1for 3 h, similar to doses used in the studies mentioned. The first dose of antifibrinolytics was administered over 30 min immediately before releasing the tourniquet which prevented the agent from reaching the lower limb. Placebo, IV, intraop bolus (before tourniquet deflation) AND Placebo, IV, intraop infusion AND Placebo, IV, 3 hours later bolus TXA Patients in the study group received tranexamic acid 10 mg kg1 i.v. just before the tourniquet was deflated and 3 h later, or epsilon-aminocaproic acid 100 mg kg1 before tourniquet deflation followed by continuous perfusion (1 g h1) during3 h. TXA, IV, 10mg/kg, intraop bolus (before tourniquet deflation) AND Placebo, IV, intraop infusion AND TXA, IV, 10mg/kg 3 hours later bolus EACA Moreover, major bleeding in this type of surgery occurs in the first hours so a regimen of two doses, 3 h apart, was chosen for the effect to last over the first 6 h. With regard to EACA, the dose chosen (100 mg kg1) was mid-way between doses used in other studies and the dose recommended by the laboratory (Fides Ecopharma) and was followed by a perfusion of 1 g h1for 3 h, similar to doses used in the studies mentioned. The first dose of antifibrinolytics was administered over 30 min immediately

	before releasing the tourniquet which prevented the agent from reaching the lower limb. EACA, IV, 100mg/kg, intraop bolus (before tourniquet deflation) AND EACA, IV, 100mg/kg intraop infusion AND Placebo, IV, 3 hours later bolus
Outcomes	*Primary outcome* Reduction in perioperative bleeding
Notes	**Sponsorship source:** Non-pharmaceutical **Country:** Spain **Setting:** Not reported **Comments**: None **Authors name:** M.A. Camarasa **Institution:** Hospital de Mataro **Email:** 12517mcg@comb.es **Address:** C/ Maria Vidal 202 A, 3-1a, 08340 Vilassar de Mar, Barcelona, Spain. **Native language of paper:** English **Reference type:** Full Text (1) **Trial registration number:** Not applicable, but when checked trial registration number not found **Was it translated for this review:** No

B.1.4.11 Cao 2018

Methods	**Study design:** RCT **Intention to treat analysis:** Yes **Length of duration of study:** 8 months **Power calculation reached:** Yes **Transfusion strategy:** Transfusions were applied if the Hb level was <70 or 70– 100 g/L with symptoms of anaemia (defined as bad mental status, palpitation, or shortness of breath not due to other causes) according to the guidelines by the National Ministry of Health. **Was the trial stopped early:** No
Participants	**Baseline Characteristics** TXA + Placebo repeated dose

	Age (years) (mean SD): 64.6 (12.8) *Ethnicity*: Not reported *Gender (males, females)*: 27, 24 *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 51 *Number of participants receiving treatment*: 51 *Number of participants analysed*: 51 *Dropout rate*: 0/51, (0%) TXA repeated dose + Placebo repeated dose *Age (years) (mean SD)*: 64.2 (10.1) *Ethnicity*: Not reported *Gender (males, females)*: 20, 31 *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities:* Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 51 *Number of participants receiving treatment*: 51 *Number of participants analysed*: 51 *Dropout rate*: 0/51, (0%) TXA repeated dose *Age (years) (mean SD)*: 64.9 (11.9)

	Ethnicity: Not reported *Gender (males, females)*: 22, 28 *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 50 *Number of participants receiving treatment*: 50 *Number of participants analysed*: 50 *Dropout rate*: 0/50, (0%) Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males, females)*: Not reported *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: Not reported *Number of participants receiving treatment*: Not reported *Number of participants analysed*: Not reported *Dropout rate*: Not reported **Included criteria:** All patients undergoing primary unilateral THA for osteoarthritis, osteonecrosis of the femoral head, and developmental dysplasia of hip (Crowe I/II)

	Excluded criteria: 1) Patients with anemia (< 120 g/L for female, < 130 g/L for male), 2) History of deep venous thrombosis (DVT) or pulmonary embolism (PE), 3) Cardiovascular problems, 4) Congenital or acquired clotting disorders, 5) Known allergy to TXA, 6) Renal insufficiency **Pre-treatment:** No **If TKR, is tourniquet used:** Not applicable **Indication for surgery:** Osteoarthritis, osteonecrosis of the femoral head, and developmental dysplasia of hip **Type of anaesthetic:** General **Type of surgery:** Primary THR
Interventions	**Intervention Characteristics** TXA + Placebo repeated dose Group A: patients received 2 g of oral TXA using four tablets of 500 mg two hours pre-operatively and four placebo tablets, identical in appearance with no active ingredient, four, ten, and 16 hours post-operatively. TXA, 2g, oral, 2 hours preop AND Placebo, oral, 4, 10, 16 hours post op TXA repeated dose + Placebo repeated dose Group B: patients received 2 g of oral TXA two hours pre-operatively and four hours post-operatively along with four placebo tablets ten and 16 hours post-operatively TXA 2g, oral, 2 hours preop + 4 hours postop AND Placebo, oral, 10 and 16 hours postop. TXA repeated dose Group C: patients received 2 g of oral TXA two hours pre-operatively and then three more doses four, ten, and 16 hours post-operatively. TXA, 2g, oral, 2 hours preop + 4, 10, 16 hours postop
Outcomes	*Primary outcome* Total blood loss (TBL) hidden blood loss (HBL) Transfusion rate *Secondary outcome* Haemoglobin (Hb) and haematocrit (Hct) drop Level of fibrinolysis parameters (fibrin degradation products, D-dimer)

	Complications (thrombotic diseases, stroke, cardiac infarction, and infection)
Notes	**Sponsorship source:** Non-pharmaceutical **Country:** China **Setting:** Single-centre **Comments**: None **Authors name:** G. Cao **Institution:** West China Hospital, West China Medical School, Sichuan University **Email:** scucao@126.com **Address:** Department of Orthopaedic Surgery, West China Hospital, West China Medical School, Sichuan University, 37# Wainan Guoxue Road, Chengdu, Sichuan Province, People's Republic of China **Native language of paper:** English **Reference type:** Full text **Trial registration number:** ChiCTR-IPR-17012266 **Was it translated for this review:** No

B.1.4.12 Chin 2020

Methods	**Study design:** RCT **Intention to treat analysis:** Yes **Length of duration of study:** 6 years 11 months (from trial registration) **Power calculation reached:** No **Transfusion strategy:** A blood transfusion threshold of Hb < 80 g/dl was instated. However, patients with symptomatic anaemia with Hb in excess of 80 g/dl were also transfused on clinical reasoning **Was the trial stopped early:** Probably - target 200 and 88 achieved, long length of duration of study.
Participants	**Baseline Characteristics** Placebo *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males, females)*: Not reported

	Length of surgery (minutes) (mean SD): Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: These patients were excluded *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: Not reported *Number of participants receiving treatment*: Not reported *Number of participants analysed*: Not reported *Dropout rate*: Not reported TXA, 1g, IV *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males, females)*: Not reported *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: These patients were excluded *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: Not reported *Number of participants receiving treatment*: Not reported *Number of participants analysed*: Not reported *Dropout rate*: Not reported Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males, females)*: *Length of surgery (minutes) (mean SD)*:

	Proportion of participants on anticoagulants prior to surgery (n/ N, %): These patients were excluded *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 181 *Number of participants receiving treatment*: 181 *Number of participants analysed*: 88 *Dropout rate*: Not reported **Included criteria:** Patients undergoing elective THA for OA or osteonecrosis. **Excluded criteria:** Patients were excluded if they had contraindications for TXA (history or risk of thrombosis, active thromboembolic disease, and acquired disturbance of colour vision) or were on clopidogrel, ticagrelor, warfarin, dabigatran, or any other anticoagulant. Patients with renal failure or bleeding disorders were also excluded. Those on aspirin were asked to stop one week prior to surgery. This was recommenced on day 1 post operation. Those patients that did not receive a single-dose spinal anaesthetic were excluded. **Pre-treatment:** **If TKR, is tourniquet used:** Not applicable **Indication for surgery:** OA or osteonecrosis **Type of anaesthetic:** This RCT only included those patients that received a spinal anaesthetic (+/− general anaesthetic) as part of their procedure. **Type of surgery:** Elective THA
Interventions	**Intervention Characteristics** Placebo Placebo of IV saline prior to skin incision Placebo, IV, 1g, preop TXA, 1g, IV 1 g IV TXA prior to skin incision TXA, IV, 1g, preop

Outcomes	*Primary outcome* Intraoperative blood loss Transfusion rate *Secondary outcome* Time to discharge Functional outcome scores (Oxford Hip Score, Western Ontario and McMaster Universities Arthritis Index (WOMAC), and the High Activity Arthroplasty Score (HAAS)) Thromboembolic complications
Notes	**Sponsorship source:** Non-pharmaceutical (This research was supported by New Zealand Orthopaedic Association (grant no. NZOA JB1) **Country:** New Zealand **Setting:** single-centre **Comments**: 1. Lots of demographic data (age, gender etc) not reported, as well as denominator information being unclear particularly for outcomes **Authors name:** J. Chin **Institution:** University of Otago **Email:** kieserdavid@gmail.com **Address:** Department of Orthopaedic Surgery and Musculoskeletal Medicine, University of Otago, Christchurch, New Zealand **Native language of paper:** English **Reference type:** Full text (1) **Trial registration number:** ACTRN12610001065088 **Was it translated for this review:** No

B.1.4.13 Claeys 2007

Methods	**Study design:** RCT **Intention to treat analysis:** Yes **Length of duration of study:** Not reported **Power calculation reached:** Not reported **Transfusion strategy:** The indication for blood transfusion of packed cells was set at Hb < 8.5 g/dl or Hct < 27%. **Was the trial stopped early:** No

Participants	**Baseline Characteristics** Placebo *Age (years) (mean SD)*: 68 (11) *Ethnicity*: Not reported *Gender (males, females)*: 7, 13 *Length of surgery (minutes) (mean SD)*: 94 (15) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: 0/20 (0%) *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 20 *Number of participants receiving treatment*: 20 *Number of participants analysed*: 20 *Dropout rate*: 0/20 (0%) TXA *Age (years) (mean SD)*: 73 (8) *Ethnicity*: Not reported *Gender (males, females)*: 5, 15 *Length of surgery (minutes) (mean SD)*: 98 (18) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: 0/ 20 (0%) *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 20 *Number of participants receiving treatment*: 20 *Number of participants analysed*: 20 *Dropout rate*: 0/20 (0%)

	Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males, females)*: Not reported *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: Not reported *Number of participants receiving treatment*: Not reported *Number of participants analysed*: Not reported *Dropout rate*: Not reported **Included criteria:** 1) Scheduled for unilateral elective total hip replacement, 2) ASA I-II **Excluded criteria:** 1) Allergy to tranexamic acid, 2) Preoperative renal or hepatic dysfunction, 3) Known bleeding disorders or preoperative coagulation anomalies, 4) Anticoagulant or aspirin-like medication and long acting NSAID medication **Pre-treatment:** No **If TKR, is tourniquet used:** Not applicable **Indication for surgery:** Degenerative osteoarthrosis **Type of anaesthetic:** Spinal anaesthesia **Type of surgery:** Primary THR
Interventions	**Intervention Characteristics** Placebo The patients were randomly allocated into two groups in a double-blind fashion and received either tranexamic acid (15 mg/kg) or an equal volume of saline in a slow infusion 15 minutes before surgery. Placebo, IV, preop (15 mins before surgery) TXA

	The patients were randomly allocated into two groups in a double-blind fashion and received either tranexamic acid (15 mg/kg) or an equal volume of saline in a slow infusion 15 minutes before surgery. TXA, IV, 15mg/kg, preop (15 mins before surgery)
Outcomes	*Primary outcome* Blood loss *Secondary outcome* Need for blood transfusion Incidence of DVT
Notes	**Sponsorship source:** Not reported **Country:** Belgium **Setting:** Not reported **Comments:** Unable to work out SD for mean transfusions from text. **Authors name:** M.A. Claeys **Institution:** Universitair Ziekenhuis Brussel **Email:** MarieAnne.Claeys@uzbrussel.be **Address:** Department of Anaesthesiology, Universitair Ziekenhuis, Brussel, Laarbeeklaan 101B-1090 Brussel, Belgium **Native language of paper:** English **Reference type:** Full text (1) **Trial registration number:** Not applicable, but when checked trial registration number not found **Was it translated for this review:** No

B.1.4.14 Clave 2019

Methods	**Study design:** RCT **Intention to treat analysis:** Patients were analysed by both ITT and per protocol **Length of duration of study:** 22 months (19 months + 3 months (FU)) **Power calculation reached:** Yes **Transfusion strategy:** Transfusions were undertaken in accordance with the French guidelines (Société Française d'Anesthésie Réanimation):15 autologous packed red blood

	cell (PRBC) transfusions were given when the level of Hb fell to < 7 g/dl in patients with no relevant history; to between 8 g/dl and 9 g/dl in those with a cardiovascular history; and to < 10 g/dl in those clinically intolerant of lower Hb levels, or with coronary heart disease or proven cardiac insufficiency. **Was the trial stopped early:** No
Participants	**Baseline Characteristics** Placebo *Age (years) (mean SD)*: 64.4 (11.64) *Ethnicity*: Not reported *Gender (males, females)*: 33 M, 42 F *Length of surgery (minutes) (mean SD)*: 78.9 (19.80) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: 3 (4.1) *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 75 *Number of participants receiving treatment*: 75 *Number of participants analysed*: 70 *Dropout rate*: 5/ 75, 6.67% Short TXA, IV *Age (years) (mean SD)*: 65.0 (11.99) *Ethnicity*: Not reported *Gender (males, females)*: 31 M, 45 F *Length of surgery (minutes) (mean SD)*: 78.3 (20.23) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: 7 (9.5) *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported

	ASA 4 (n/ N,%): Not reported *Number of participants randomised*: 76 *Number of participants receiving treatment*: 76 *Number of participants analysed*: 74 *Dropout rate*: 2/ 76, 2.63% Long TXA, IV *Age (years) (mean SD)*: 67.1 (10.59) *Ethnicity*: Not reported *Gender (males, females)*: 34 M, 44 F *Length of surgery (minutes) (mean SD)*: 75.7 (18.83) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: 4 (5.3) *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 78 *Number of participants receiving treatment*: 78 *Number of participants analysed*: 74 *Dropout rate*: 4/ 78, 5.13% Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males, females)*: Not reported *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N%)*: Not reported *ASA 4 (n/ N,%)*: Not reported

	Number of participants randomised: 229 *Number of participants receiving treatment*: Not reported *Number of participants analysed*: Not reported *Dropout rate*: Not reported **Included criteria:** 1) over 18 years of age; 2) awaiting primary elective THA; 3) scheduled for antithrombotic prophylaxis with rivaroxaban; 4) provided informed consent; and 5) registered in the national social security system **Excluded criteria:** 1) rapidly destructive osteoarthritis of the hip; 2) previous ipsilateral hip surgery; 3) major contraindications for treatment with TXA, such as epilepsy and renal failure (renal clearance < 30 ml/min); 4) patients already receiving antiplatelet agents (aspirin > 160 mg/j) or anticoagulants; 5) ischaemic arterial disease (myocardial infarction, stroke); 6) previous venous thromboembolism (VTE); 7) contraindication to treatment with rivaroxaban and 8) Child B-stage cirrhosis with coagulopathy. **If TKR, is tourniquet used:** Not applicable **Indication for surgery:** Not reported **Type of anaesthetic:** General or spinal **Type of surgery:** Primary THR
Interventions	**Intervention Characteristics** Placebo 1 g placebo IV at hour 0 followed by 1 g IV at postoperative hours 3, 7, and 11 Short TXA, IV Short-TXA group: 1 g TXA IV at hour 0 followed by 1 g IV at postoperative hour 3, and 1 g of placebo IV at postoperative hours 7 and 11 Long TXA, IV Long-TXA group: 1g TXA IV at hour 0 (the time of incision), followed by 1 g IV at postoperative hours 3, 7, and 11.
Outcomes	*Primary outcome* Difference in perioperative Real Blood Loss (RBL) between the baseline level and the level on day 3 (D3) postoperatively *Secondary outcome* Haemostatic effects of TXA on the levels of Hb and Ht Need for transfusion

	Major bleeding was defined as clinically overt bleeding accompanied by one or more of the following: a decrease in the Hb level of > 2g/dl over a 24-hour period, transfusion of two or more units of PRBCs, bleeding at a critical site (intracranial, intraspinal, intraocular, pericardial, intra-articular, intra-muscular with compartment syndrome, or retroperitoneal), or fatal bleeding. Symptomatic thromboembolic events Adjudicated cardiovascular mortality Need for revision surgery All-cause mortality
Notes	**Sponsorship source:** Pharmaceutical **Country:** France **Setting:** Multi-centre **Comments:** 1. 4 medical centres; 2. Reoperation reported but not clear if it was for bleeding **Authors name:** A. Clave **Institution:** Brest University Hospital **Email:** arnaud.clave@orange.fr **Address:** Department of Orthopedics and Traumatology, Brest University Hospital, Brest, France **Native language of paper:** English **Reference type:** Full text (1), trial registration (1) **Trial registration number:** NCT02403596 **Was it translated for this review:** No

B.1.4.15 Colwell 2007

Methods	**Study design:** RCT **Intention to treat analysis:** No **Length of duration of study:** Not reported **Power calculation reached:** No **Transfusion strategy:** The only transfusion criteria specified by the study was a haematocrit less than 18% at any time after randomization when the patient was given whole blood or packed red blood cells (RBCs). No other transfusion criteria were specified; however, even when the haematocrit was greater than 18%, whole blood or packed RBCs were given if deemed necessary based on the

	patient's clinical condition and the judgment of the investigator. **Was the trial stopped early:** No
Participants	**Baseline Characteristics** Placebo *Age (at enrolment) (years) (mean SD)*: 64.4 (12.7) *Ethnicity (white) (n/ N,%)*: 170/ 177 (96%) *Gender (males, females) (%)*: 81, 96 *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: 0/ 177 (0%) *Incidence of preoperative anaemia (n/ N, %)* : 29/ 177, (16%) *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: 6/ 177 (3.39%) *ASA 2 (n/ N,%)*: 62/ 177 (35.02%) *ASA 3 (n/ N,%)*: 31/ 177 (17.51%) *ASA 4 (n/ N,%)*: 2/ 177 (1.13%) *Number of participants randomised*: 179 *Number of participants receiving treatment*: 177 *Number of participants analysed*: 175 *Dropout rate*: 4/ 179 (2.23%) Aprotinin *Age (at enrolment) (years) (mean SD)*: 63.4 (12.1) *Ethnicity (white) (n/ N,%)*: 164/175 (94%) *Gender (males, females) (%)*: 91, 84 (48%) *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: 0/ 175 (0%) *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: 10/ 175 (5.71%) *ASA 2 (n/ N,%)*: 56/ 175 (32%) *ASA 3 (n/ N,%)*: 33/ 175 (18.86%) *ASA 4 (n/ N,%)*: 1/ 175 (0.57%)

	Number of participants randomised: 180 *Number of participants receiving treatment*: 176 *Number of participants analysed*: 175 *Dropout rate*: 4/180 (2.22%) Overall *Age (at enrolment) (years) (mean SD)*: Not reported *Ethnicity (white) (n/ N,%)*: Not reported *Gender (males, females) (%)*: Not reported *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Issue - placebo numbers do not add up to 100% *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: Not reported *Number of participants receiving treatment*: Not reported *Number of participants analysed*: Not reported *Dropout rate*: Not reported **Included criteria:** 1) At least 18 years of age, 2) Elective, unilateral, primary THR **Excluded criteria:** 1) Both hips replaced during the same operation, 2) Undergone cardiac surgery using aprotinin within the previous 6 months, 3) Known or suspected allergy to aprotinin, 4) Impaired renal function (serum creatinine greater than 3.5 mg/dL or 309 mol/L), 5) A history of bleeding diathesis, 6) A known coagulation factor deficiency, 7) A history of deep vein thrombosis (DVT) or pulmonary embolism (PE), 8) A known major organ system failure including renal, or any active noteworthy medical illness that in the opinion of the investigator was likely to affect the patient's ability to complete the study, 9) Refused to receive allogeneic blood products or had low preoperative red blood cell volume (haematocrit less than 22% or hemoglobin values less than 8 g/dL), 10) Concomitant chronic treatment with warfarin, 11) Planned use of other antifibrinolytic agents such as tranexamic acid, 12) Patients chronically treated with clopidogrel were

	included if treatment was discontinued at least 7 days before surgery, 13) Pregnant or breastfeeding women, 14) Participation in an investigational drug study within the past 30 days **Pre-treatment:** No **If TKR, is tourniquet used:** Not applicable **Indication for surgery:** Not reported **Type of anaesthetic:** Mixed (epidural or general) **Type of surgery:** Primary THR
Interventions	**Intervention Characteristics** Placebo Treatment with either aprotinin (loading dose of 2 million KIU followed by 0.5 million KIU per hour until the end of surgery)or matching placebo. All patients received a 1-mL (10,000 KIU) test dose of the study drug or placebo to assess the potential for allergic reactions before full study drug administration. Placebo, IV, intraop, loading dose + infusion until end of surgery. Aprotinin Treatment with either aprotinin (loading dose of 2 million KIU followed by 0.5 million KIU per hour until the end of surgery)or matching placebo. All patients received a 1-mL (10,000 KIU) test dose of the study drug or placebo to assess the potential for allergic reactions before full study drug administration. Aprotinin, IV, intraop, 2 million KIU loading dose + 0.5 million KIU infusion until end of surgery.
Outcomes	*Primary outcome* percentage of patients requiring a blood transfusion (whole blood or packed RBCs, autologous or allogeneic) any time during the intraoperative or postoperative period up to the earlier of 7 days or discharge. *Secondary outcome* percentage of patients receiving an allogeneic transfusion of blood or packed RBCs during surgery and up to the earlier of day 7 or discharge the number of units of whole blood or packed RBCs transfused the number of units of blood or packed RBCs transfused per patient requiring transfusion

	estimated blood loss during surgery, drainage from the operative site during the first 6 hours postoperatively, and total drainage until removal of drains
Notes	**Sponsorship source:** Pharmaceutical **Country:** USA **Setting:** multi-centre (eight centres in Canada and 20 centres in the United States) **Comments**: None **Authors name:** C.W. Clifford **Institution:** Scripps Clinic **Email:** colwell@scripps.edu; hardwick.mary@scrippshealth.org **Address:** Shiley Center for Orthopaedic Research and Education at Scripps Clinic, 11025 North Torrey Pines Road, Suite 140, La Jolla, CA 92037. **Native language of paper:** English **Reference type:** Full Text (1) Abstract (2) **Trial registration number:** Not applicable, but when checked trial registration number not found **Was it translated for this review:** No

B.1.4.16 Compostella 1997

Methods	**Study design:** RCT **Intention to treat analysis:** Unclear **Length of duration of study:** Not reported **Power calculation reached:** Not reported **Transfusion strategy:** The patients were transfused if the Ht value was less than 27% postoperatively. **Was the trial stopped early:** No
Participants	**Baseline Characteristics** Placebo *Age (years) (median)*: 67 *Ethnicity*: Not reported *Gender (males)*: Not reported *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to*

	surgery (n/ N, %): Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 50 *Number of participants receiving treatment*: Not reported *Number of participants analysed*: Not reported *Dropout rate*: Not reported Aprotinin *Age (years) (median)*: 68 *Ethnicity*: Not reported *Gender (males)*: Not reported *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia:* Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 50 *Number of participants receiving treatment*: Not reported *Number of participants analysed*: Not reported *Dropout rate*: Not reported Overall *Age (years) (median)*: Not reported *Ethnicity*: Not reported *Gender (males)*: Not reported *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported

	Incidence of preoperative anaemia: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: Not reported *Number of participants receiving treatment*: Not reported *Number of participants analysed*: Not reported *Dropout rate*: Not reported **Included criteria:** 1) Patients undergoing elective cementless THR **Excluded criteria:** 1) Severely impaired coagulation and renal function **Pre-treatment:** Not reported **If TKR, is tourniquet used:** Not applicable **Indication for surgery:** Not reported **Type of anaesthetic:** Spinal anaesthetic **Type of surgery:** Primary THR
Interventions	**Intervention Characteristics** Placebo Saline group (infusion of saline) Placebo, IV, infusion Aprotinin Aprotinin group (loading dose of 2,000,000 KIU followed by 500,000 KIU/h) Aprotinin, IV, 2 ^6 KIU loading dose + 5^6 KIU infusion
Outcomes	*Primary outcome* Blood loss Need for transfusion
Notes	**Sponsorship source:** Not reported **Country:** Italy **Setting:** Not reported **Comments**: None

	Authors name: F.A. Compostella **Institution:** S. Camillo de Lellis Hospital **Email:** Not reported **Address:** Department of Anaesthesia, S. Camillo de Lellis Hospital, Schio, Italy **Native language of paper:** English **Reference type:** Abstract (1) **Trial registration number:** Not applicable, but when checked trial registration number not found **Was it translated for this review:** No

B.1.4.17 Cui 2019

Methods	**Study design:** RCT **Intention to treat analysis:** Unclear **Length of duration of study:** 3 months (December 2017 and March 2018) + 3 months follow-up = 6 months **Power calculation reached:** Not reported **Transfusion strategy:** Patients received blood transfusion if they had hemoglobin < 70 g/L, or hemoglobin 70 ~ 100 g/L, but with symptoms of anemia, such as dizziness, palpitation and fatigue. **Was the trial stopped early:** No
Participants	**Baseline Characteristics** TXA, IV 20mg/ kg *Age (years) (range)*: 25-75 years old, average age: 56.4 *Ethnicity*: Not reported *Gender (males, females)*: 16/ 36 M (44.4%), 20/ 36 F (55.5%) *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Patients excluded *Co-morbidities*: Hypertension 12/ 36 (33.3%), Diabetes 2/ 36 (5.6%) *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported

	ASA 3 (n/ N,%): Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 36 *Number of participants receiving treatment*: Not reported *Number of participants analysed*: Not reported *Dropout rate*: Not reported TXA, IV 40mg/ kg *Age (years) (range)*: 28-79 years old, average age: 53.9 *Ethnicity*: Not reported *Gender (males, females)*: 19/ 36 M (52.7%), 17/ 36 F (47.2%) *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Patients excluded *Co-morbidities*: Hypertension 9/ 36 (25%), Diabetes 3/ 36 (8.3%) *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: Not reported *Number of participants receiving treatment*: Not reported *Number of participants analysed*: Not reported *Dropout rate*: Not reported Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males, females)*: Not reported *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Patients excluded *Co-morbidities*: Hypertension 21/ 36 (58.3%), Diabetes 5/ 36 (13.8%) *ASA 1 (n/ N,%)*: Not reported

	ASA 2 (n/ N,%): Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: Not reported *Number of participants receiving treatment*: Not reported *Number of participants analysed*: Not reported *Dropout rate*: Not reported **Included criteria:** 1) patients anticipating unilateral THA surgery due to terminal-stage hip joint disease 2) patients who were willing to participate and provided written informed consent **Excluded criteria:** 1) patients who had inflammatory joint diseases such as rheumatoid arthritis or ankylosing spondylitis that involved hip joint 2) patients who had anemia before surgery 3) patients with coagulopathy 4) patients at high risk of thrombosis, including atrial fibrillation and status post cardiac stent or pacemaker insertion 5) patients who were allergic to TXA **If TKR, is tourniquet used:** ''No tourniquet was used during surgery'' **Indication for surgery:** Terminal-stage hip joint disease **Type of anaesthetic:** General **Type of surgery:** Primary unilateral THA
Interventions	**Intervention Characteristics** TXA, IV 20mg/ kg A single dose of 20 mg/kg TXA was administered intravenously before 5-10 minutes of operation in group A. All patients received 5 doses of 1 g TXA at 3, 6, 12, 18, and 24 hours after the first dose. TXA, IV, 20mg/ kg, preop + 1g, 3h, 6h, 12, 18, 24h after first dose TXA, IV 40mg/ kg Single dose of 40 mg/kg TXA was administered intravenously in group B at the same time point. All patients received 5 doses of 1 g TXA at 3, 6, 12, 18, and 24 hours after the first dose. TXA, IV, 40mg/ kg, preop + 1g, 3h, 6h, 12, 18, 24h after first dose
Outcomes	*Primary outcome*

	Total blood loss Hemoglobin level Fibrin(ogen)degradation products (FDP) and D-dimer levels C-reaction protein (CRP) and IL-6 Venous thrombosis Blood transfusion Pulmonary embolism *Secondary outcome* Not reported
Notes	**Sponsorship source:** Non-pharmaceutical (West China Hospital, Sichuan University) **Country:** China **Setting:** Single-centre **Comments:** None **Authors name:** D. Cui **Institution:** West China Hospital, Sichuan University **Email:** Corresponding author: F. Pei peifux@126.com **Address:** Department of Orthopedics, West China Hospital, Sichuan University, Chengdu Sichuan, 610041, P.R.China **Native language of paper:** Chinese **Reference type:** Full text (1), trial registration (1) **Trial registration number:** ChiCTR-IOR-17013861 **Was it translated for this review:** Yes

B.1.4.18 D'Ambrosio 1999

Methods	**Study design:** RCT **Intention to treat analysis:** Yes **Length of duration of study:** Not reported **Power calculation reached:** Not reported **Transfusion strategy:** Not reported **Was the trial stopped early:** No
Participants	**Baseline Characteristics** General anaesthesia + Aprotinin

	Age (years) (mean SD): 66.6 (9.2) *Ethnicity*: Not reported *Gender (males, females)* : 7, 8 *Length of surgery (minutes) (mean SD)*: 130.6 (42.8) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Nil *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised* : 15 *Number of participants receiving treatment*: 15 *Number of participants analysed* : 15 *Dropout rate*: 0 General anaesthesia + Placebo *Age (years) (mean SD)*: 60.5 (12.9) *Ethnicity*: Not reported *Gender (males, females)*: 7,8 *Length of surgery (minutes) (mean SD)*: 139.3 (39.0) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Nil *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised* : 15 *Number of participants receiving treatment*: 15 *Number of participants analysed* : 15 *Dropout rate*: 0 Overall *Age (years) (mean SD)*: Not reported

	Ethnicity: Not reported *Gender (males, females)*: Not reported *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: Not reported *Number of participants receiving treatment*: Not reported *Number of participants analysed* : Not reported *Dropout rate*: Not reported **Included criteria:** 1) Patients scheduled to undergo primary total hip arthroplasty by the same surgical and anaesthesiological team, 2) ASA groups 1-2. **Excluded criteria:** 1) Severe cardiorespiratory, 2) Coagulation diseases, 3) Therapy which could influence bleeding **Pre-treatment:** No **If TKR, is tourniquet used:** Not applicable **Indication for surgery:** Not reported **Type of anaesthetic:** General **Type of surgery:** Primary THR
Interventions	**Intervention Characteristics** General anaesthesia + Aprotinin Aprotinin was administered to groups A and C: 500,000KIU in bolus form before the surgical incision and 500,000KIU/h in drip form until the skin was sutured. Aprotinin, IV, 0.5 ^6 KIU, intraop bolus (before incision) + intraop infusion 0.5^6 until end of surgery. General anaesthesia + Placebo Groups Band D received a placebo (saline solution 0.9%) in the same way and amount as Aprotinin Placebo, IV, intraop bolus (before incision) + intraop

	infusion until end of surgery.
Outcomes	*Primary outcome* Intra and postoperative bleeding *Secondary outcome* Not reported
Notes	**Sponsorship source:** Not reported **Country:** Italy **Setting:** Single-centre **Comments:** Extracted data from groups C + D only (difference between C+D and A+B being spinal or general, not intervention type or regimen). Mean and SD worked out from paper numbers. **Authors name:** A. D'ambrosio **Institution:** Casa Sollievo Della Sofferenza Hospital **Email:** bborghi@ior.it **Address:** 1st Service of Anaesthesia and Intensive Care, I.R.C.C.S. "Casa Sollievo Della Sofferenza" Hospital, S. Giovanni Rotondo (Foggia) **Native language of paper:** English **Reference type:** Full text (1) **Trial registration number:** Not applicable, but when checked trial registration number not found **Was it translated for this review:** No

B.1.4.19 Dorji 2021

Methods	**Study design:** Randomised controlled trial **Intention to treat analysis:** Per protocol **Length of duration of study:** 15 months (June 2018 and September 2019) + 15 days (follow-up) **Power calculation reached:** Yes **Transfusion strategy:** Apart from the routine post-operative care, transfusion of blood was given to patients whose haemoglobin levels were <8.0 g/dl or to patients with haemoglobin level <9.0 g/dl with the symptoms of anaemia like increase in heart rates (tachycardia), light headedness, shortness of breath **Was the trial stopped early:** No

Participants	**Baseline Characteristics** TXA, IV + TXA, IA *Age (years) (mean SD)*: 66.28 (5.67) *Ethnicity*: Not reported *Gender (males, females)*: 11/ 14 M (78.57%), 3/ 14 F (21.43%) *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: Not reported *Number of participants receiving treatment*: 14 *Number of participants analysed*: 14 *Dropout rate*: Not reported TXA, IA *Age (years) (mean SD)*: 66.4 (5.27) *Ethnicity*: Not reported *Gender (males, females)*: 9/ 17 M (52.94%), 8/ 17 F (47.06%) *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 17 *Number of participants receiving treatment*: Not reported

	Number of participants analysed: 16 *Dropout rate*: 1/ 17, 5.9% Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males, females)*: Not reported *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 32 *Number of participants receiving treatment*: 31 *Number of participants analysed*: 31 *Dropout rate: Not reported* **Included criteria:** Subjects undergoing unilateral primary total knee replacement at the tertiary care centre were invited to participate in this study. **Excluded criteria:** Subjects were then screened for exclusion criteria: those subjects allergic to tranexamic acid, known history of thromboembolic diseases, cardiovascular diseases (myocardial infarction or angina), cerebrovascular disease (stroke), pre-operative significant renal dysfunction and pre-operative haemoglobin less than 10 g/dl. **If TKR, is tourniquet used:** Yes (Pneumatic tourniquet was used throughout the duration of the surgery in all patients.) **Indication for surgery:** Osteoarthritis, Rheumatoid arthritis **Type of anaesthetic:** Spinal **Type of surgery:** Unilateral primary TKR
Interventions	**Intervention Characteristics** TXA, IV + TXA, IA Patients in Group A (intervention group) received both

	intravenous and intra-articular tranexamic acid: Tranexamic acid 1 gm of I.V. injection 15 min before giving skin incision and Tranexamic acid 1 g intra articular application after the closure of the joint capsule TXA, IV, 1g, pre-op + IA, 1g, intraop TXA, IA Patients under Group B (control group) received only intraarticular tranexamic acid: Tranexamic acid 1 g intra-articular after joint capsule closure. TXA, IA, 1g, intraop
Outcomes	*Primary outcome* Fall in Haemoglobin level Fall in haematocrit Drain output *Secondary outcome* Amount of blood loss Need for blood transfusion Complications
Notes	**Sponsorship source:** None (This research did not receive any specific grant from any funding agencies in the public, commercial or non-profit sectors.) **Country:** India **Setting:** Single-centre **Comments:** None **Authors name:** Y. Dorji **Institution:** Maharashtra University of Health Sciences **Email:** dorjiyeshi5@gmail.com (Y. Dorji). **Address:** Department of Orthopaedics, Armed Forces Medical College, Maharashtra University of Health Sciences, Pune, Maharashtra, India **Native language of paper:** English **Reference type:** Full text (1), trial registration (1) **Trial registration number:** CTRI/2018/05/014106 **Was it translated for this review:** No

B.1.4.20 Ekback 2000

Methods	**Study design:** RCT **Intention to treat analysis:** Yes **Length of duration of study:** Not reported **Power calculation reached:** Not reported **Transfusion strategy:** Allogeneic SAGM-PRBCs was transfused if Hct < 27% after transfusion of the autologous PRBCs. **Was the trial stopped early:** No
Participants	**Baseline Characteristics** Placebo *Age (years) (mean SD)*: 65.6 (8.8) *Ethnicity*: Not reported *Gender (males, female)*: 11, 9 *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 20 *Number of participants receiving treatment*: Not reported *Number of participants analysed*: 20 *Dropout rate*: 0 TXA *Age (years) (mean SD)*: 66.4 (9.0) *Ethnicity*: Not reported *Gender (males, female)*: 9, 11 *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported

	Incidence of preoperative anaemia: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 20 *Number of participants receiving treatment*: 20 *Number of participants analysed*: 20 *Dropout rate*: 0 Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males, female)*: Not reported *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery? (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: Not reported *Number of participants receiving treatment*: Not reported *Number of participants analysed*: Not reported *Dropout rate*: Not reported **Included criteria:** 1) Patients undergoing THR **Excluded criteria:** Not reported **Pre-treatment:** No **If TKR, is tourniquet used:** Not applicable **Indication for surgery:** Not reported **Type of anaesthetic:** Spinal-epidural anaesthetic **Type of surgery:** Primary THR

Interventions	**Intervention Characteristics** Placebo Control group and got the same treatment but with a placebo drug (physiological saline). Placebo, IV, intraop (prior to surgical incision) AND Placebo, IV, infusion (for 10 hours after 1st dose) AND Placebo, IV, postop 3 hours after 1st dose. TXA First bolus dose of 10 mg/kg of TA before surgical incision. A continuous infusion of 1.0 mg/kg/h during 10 h was then started immediately after the first bolus dose. A second bolus dose of 10 mg/kg body weight was given 3 h later to counteract potential dilutive effects of IAT (intraoperative autotransfusion) on TA concentrations in blood. TXA, IV, 10mg/kg, intraop (prior to surgical incision) AND TXA, IV, 1mg/kg infusion (for 10 hours after 1st dose) AND TXA, IV, 10mg/kg, postop 3 hours after 1st dose.
Outcomes	*Primary outcome* Bleeding Postoperative drainage Deep vein thrombosis
Notes	**Sponsorship source:** Mixed, non-pharmaceutical and pharmaceutical **Country:** Sweden **Setting:** Not reported **Comments:** None **Authors name:** G. Ekback **Institution:** Orebro Medical Centre Hospital **Email:** Not reported **Address:** Department of Anaesthesiology and Intensive Care, Orebro Medical Center Hospital, S-701 85 Orebro, Sweden **Native language of paper:** English **Reference type:** Full text (1) **Trial registration number:** Not applicable, but when checked trial registration number not found **Was it translated for this review:** No

B.1.4.21 Ellis 2001

Methods	**Study design:** RCT **Intention to treat analysis:** Yes **Length of duration of study:** Not reported (3-month FU) **Power calculation reached:** Not reported **Transfusion strategy:** Throughout the postoperative period, a Hct <27 percent constituted the postoperative transfusion trigger. **Was the trial stopped early:** No
Participants	**Baseline Characteristics** TXA *Age (years) (mean SD)*: 71 (5) *Ethnicity*: Not reported *Gender (males, females)*: 8, 12 *Length of surgery (minutes) (mean SD)*: 133 (13) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: 0/20, 0% *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: 4/ 20, (20%) *ASA 2 (n/ N,%)*: 16/ 20, (80%) *ASA 3 (n/ N,%)*: 0/ 20, (0%) *ASA 4 (n/ N,%)*: 0/0, (0%) *Number of participants randomised*: 20 *Number of participants receiving treatment*: 20 *Number of participants analysed*: 20 *Dropout rate*: 0/ 20, (0%) Desmopressin *Age (years) (mean SD)*: 72 (5) *Ethnicity*: Not reported *Gender (males, females)*: 3, 17 *Length of surgery (minutes) (mean SD)*: 128 (15) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: 0/20, 0%

	Incidence of preoperative anaemia: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: 5/ 20, (25%) *ASA 2 (n/ N,%)*: 14/ 20, (70%) *ASA 3 (n/ N,%)*: 1/ 20, (5%) *ASA 4 (n/ N,%)*: 0/0 (0%) *Number of participants randomised*: 20 *Number of participants receiving treatment*: 20 *Number of participants analysed*: 20 *Dropout rate*: 0/ 20, (0%) Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males, females)*: Not reported *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: Not reported *Number of participants receiving treatment*: Not reported *Number of participants analysed*: Not reported *Dropout rate*: Not reported **Included criteria:** 1) ASA physical status I-II, 2) Patients undergoing elective TKR **Excluded criteria:** 1) History of severe ischemic heart disease (New York Heart Association grade III, IV), 2) Chronic renal failure, 3) Liver cirrhosis, 4) Bleeding disorders or those currently receiving anticoagulant therapy **Pre-treatment:** No **If TKR, is tourniquet used:** Yes **Indication for surgery:** Osteoarthritis

	Type of anaesthetic: General anaesthetic **Type of surgery:** Primary TKR
Interventions	**Intervention Characteristics** TXA In the TA group, in the 30 minutes before deflation of the limb tourniquet, an IV bolus dose of 15 mg per kg of TA was administered. Thereafter, a constant IV infusion of 10 mg per kg per hour was administered until 12 hours after final deflation of the limb tourniquet TXA, IV, 15mg/kg, intraop (30mins prior to tourniquet deflation) AND TXA, IV, 10mg/kg, intraop, infusion for 12 hours after 1st dose. Desmopressin In the desmopressin group, in the 30 minutes before deflation of the limb tourniquet, an IV bolus dose of desmopressin, 0.3 mg per kg, was infused. Thereafter, a constant IV infusion of saline was administered until 12 hours after final deflation of the limb tourniquet. Desmopressin, IV, 0.3mg/kg, intraop (30mins prior to tourniquet deflation) AND Saline, IV, intraop, infusion for 12 hours after 1st dose
Outcomes	*Primary outcome* Procoagulant and fibrinolytic systems *Secondary outcome* None reported
Notes	**Sponsorship source:** Not reported **Country:** Israel **Setting:** single-centre **Comments:** None **Authors name:** E. Zohar **Institution:** Meir Hospital **Email:** bdfgls@netvision.net.il. **Address:** Department of Anaesthesiology and Intensive Care, Meir Hospital, Kfar Saba 44281, Israel; **Native language of paper:** English **Reference type:** Full text (2) **Trial registration number:** Not applicable, but when checked trial registration number not found

	Was it translated for this review: No

B.1.4.22 Engel 2001

Methods	**Study design:** RCT **Intention to treat analysis:** Not reported **Length of duration of study:** Not reported **Power calculation reached:** No **Transfusion strategy:** If the hemoglobin concentration decreased to <10 g/dL, blood transfusions were administered. **Was the trial stopped early:** No
Participants	**Baseline Characteristics** TXA *Age (years) (mean SD)*: 71 (9) *Ethnicity*: Not reported *Gender (males, females)*: 4, 8 *Length of surgery (minutes) (mean SD)*: 107 (41) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: 0 *Incidence of preoperative anaemia (<130 g/l)*: 1/12 (8.3) *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: 0, 0 *ASA 2 (n/ N,%)*: *ASA 3 (n/ N,%)*: *ASA 4 (n/ N,%)*: *Number of participants randomised*: 12 *Number of participants receiving treatment*: 12 *Number of participants analysed*: 12 *Dropout rate*: 0 Aprotinin *Age (years) (mean SD)*: *Ethnicity*: Not reported *Gender (males, females)* : *Length of surgery (minutes) (mean SD)*:

	Proportion of participants on anticoagulants prior to surgery (n/ N, %): *Incidence of preoperative anaemia? (<130 g/l)*: *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: 1, 8.3 *ASA 2 (n/ N,%)*: 4, 33.3 *ASA 3 (n/ N,%)*: 7, 58.3 *ASA 4 (n/ N,%)*: 0, 0 *Number of participants randomised*: 12 *Number of participants receiving treatment*: 12 *Number of participants analysed*: 12 *Dropout rate*: 0 Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males, females)*: Not reported *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia (<130 g/l)*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: Not reported *Number of participants receiving treatment*: Not reported *Number of participants analysed*: Not reported *Dropout rate*: Not reported **Included criteria:** Patients undergoing total knee replacement **Excluded criteria:** Not reported **Pre-treatment:** No **If TKR, is tourniquet used:** Yes

	Indication for surgery: Not reported **Type of anaesthetic:** spinal and epidural **Type of surgery:** Primary TKR
Interventions	**Intervention Characteristics** TXA The second group received 15 mg/kg tranexamic acid, followed by a repeated dose of 10 mg/kg after 3 h. TXA, IV, 15mg/kg, intraop + 10mg/kg 3 hours post-op Aprotinin 1 million KIE aprotinin immediately before deflating the tourniquet followed by an infusion of 500,000 KIE per hour for4 h. Aprotinin, IV, 1 million KIE, intraop + 500,000 KIE infusion, 4 hours post-op
Outcomes	Primary outcome Hemoglobin concentration, Platelet count Prothrombin time Thromboplastin time Thrombin time
Notes	**Sponsorship source:** Not reported **Country:** Germany **Setting:** Not reported **Comments:** None **Authors name:** J.M. Engel **Institution:** Justus-Liebig-University, Giessen, Germany **Email:** Joerg.Engel@chiru.med.uni-giessen.de. **Address:** Department of Anaesthesiology and Intensive Care Medicine, Justus-Liebig-University, Rudolf-Buchheim-Str. 7, D-35385 Giessen, Germany. **Native language of paper:** English **Reference type:** Full text **Trial registration number:** Not applicable, but when checked trial registration number not found **Was it translated for this review:** No

B.1.4.23 Flordal 1992

Methods	**Study design:** RCT **Intention to treat analysis:** Yes **Length of duration of study:** Not reported **Power calculation reached:** Not reported **Transfusion strategy:** Not reported **Was the trial stopped early:** No
Participants	**Baseline Characteristics** Placebo *Age (years) (mean SD)*: 68 (9) *Ethnicity*: Not reported *Gender (males, females)*: 12, 13 *Length of surgery (minutes) (mean SD)*: 104 (20) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/N ,%)*: Not reported *Number of participants randomised*: 25 *Number of participants receiving treatment*: 25 *Number of participants analysed*: 25 *Dropout rate*: 0/ 25, (0%) Desmopressin *Age (years) (mean SD)*: 64 (9) *Ethnicity*: Not reported *Gender (males, females)*: 12,13 *Length of surgery (minutes) (mean SD)*: 106 (23) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported

	Co-morbidities: Not reported *ASA 1 (n/ N,%)* : Not reported *ASA 2 (n/ N,%)* : Not reported *ASA 3 (n/ N,%)* : Not reported *ASA 4 (n/ N,%)* : Not reported *Number of participants randomised*: 25 *Number of participants receiving treatment*: 25 *Number of participants analysed*: 25 *Dropout rate*: 0/ 25, (0%) Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males, females)*: Not reported *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery? (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: Not reported *Number of participants receiving treatment*: Not reported *Number of participants analysed*: N*ot reported* *Dropout rate*: Not reported **Included criteria:** 1) Scheduled for total hip replacement **Excluded criteria:** 1) Patients above the age of 80, 2) Patients with severe vascular, hepatic or renal disease **Pre-treatment:** No **If TKR, is tourniquet used:** Not applicable **Indication for surgery:** Primary and secondary arthrosis **Type of anaesthetic:** Spinal anaesthetic **Type of surgery:** Primary and revision THR

Interventions	**Intervention Characteristics** Placebo In a double-blind fashion each patient received an infusion of placebo or desmopressin (Minirin@,Femng, Sweden) 0.3 clg/kg body weight diluted in 50mL saline at the start of surgery. The same infusion was repeated six hours later, on both occasions at an infusion rate of 20-30 minutes Placebo, IV, intraop (start of surgery) + Placebo, IV, 6 hours after 1st dose Desmopressin Infusion of placebo or desmopressin (Minirin@, Femng, Sweden) 0.3 mcg/kg body weight diluted in 50 mL saline at the start of surgery. The same infusion was repeated six hours later, on both occasions at an infusion rate of 20-30 minutes. Desmopressin, IV, 0.3mcg/kg, intraop (start of surgery) AND Desmopressin, IV, 0.3 mcg/kg 6 hours after 1st dose
Outcomes	*Primary outcome* Blood loss Bleeding time Hb and platelet count Drainage loss Mean total blood loss
Notes	**Sponsorship source:** Non-pharmaceutical, desmopressin supplied by Ferring AB free of charge. **Country:** Sweden **Setting:** Not reported **Comments:** None **Authors name:** P.A. Flordal **Institution:** Danderyd Hospital **Email:** Not reported **Address:** Departments of Surgery, Danderyd Hospital, S-182 88 Danderyd, Sweden **Native language of paper:** English **Reference type:** Full text (2) **Trial registration number:** Not applicable, but when checked trial registration number not found **Was it translated for this review:** No

B.1.4.24 Garcia Enguita 1998

Methods	**Study design:** RCT **Intention to treat analysis:** Not reported **Length of duration of study:** Not reported **Power calculation reached:** Not reported **Transfusion strategy:** Not reported **Was the trial stopped early:** No
Participants	**Baseline Characteristics** Placebo *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males)*: Not reported *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 15 *Number of participants receiving treatment*: Not reported *Number of participants analysed*: Not reported *Dropout rate*: Not reported Aprotinin *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males)*: Not reported *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported

	Co-morbidities: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 15 *Number of participants receiving treatment*: Not reported *Number of participants analysed*: Not reported *Dropout rate*: Not reported Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males)*: Not reported *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: Not reported *Number of participants receiving treatment*: Not reported *Number of participants analysed*: Not reported *Dropout rate*: Not reported **Included criteria:** Patients undergoing elective cementless revision THR or bilateral THR **Excluded criteria:** Impaired coagulation and renal function **Pre-treatment:** Not reported **If TKR, is tourniquet used:** Not applicable **Indication for surgery:** Not reported **Type of anaesthetic:** Combined epidural and light general anaesthesia **Type of surgery:** Mixed, revision THR and bilateral primary

	THR
Interventions	**Intervention Characteristics** Placebo Before induction of anaesthesia a test dose of 5ml of the study drug was administered over 2 minutes followed by a continuous infusion (loading dose 2 million KIU of Aprotinin or 200ml of saline over 30 minutes followed by 0.5 million KIU/h of Aprotinin or 50ml/ h of saline for the duration of surgery. Placebo, IV, 200mls, intraop loading infusion over 30 mins + Placebo Placebo, IV, 50mls, intraop, infusion until end of surgery Aprotinin Before induction of anaesthesia a test dose of 5ml of the study drug was administered over 2 minutes followed by a continuous infusion (loading dose 2 million KIU of Aprotinin or 200ml of saline over 30 minutes followed by 0.5 million KIU/h of Aprotinin or 50ml/ h of saline for the duration of surgery. Aprotinin, IV, 2 ^6 KIU, intraop, loading dose over 30 mins + Aprotinin, IV, 0.5 ^6 KIU, intraop, infusion until end of surgery
Outcomes	*Primary outcome* Blood loss Need for homologous transfusion *Secondary outcome* Not reported
Notes	**Sponsorship source:** Not reported **Country:** Spain **Setting:** single-centre **Comments:** None **Authors name:** M.A. Garcia-Enguita **Institution:** Hospital Miguel Servet **Email:** Not reported **Address:** Department of Anesthesiology, Hospital Miguel Servet, Zaragoza, Spain **Native language of paper:** English **Reference type:** Abstract (1)

	Trial registration number: Not applicable, but when checked trial registration number not found **Was it translated for this review:** No

B.1.4.25 Garneti 2004

Methods	**Study design:** RCT **Intention to treat analysis:** Yes **Length of duration of study:** Not reported **Power calculation reached:** Not reported **Transfusion strategy:** We established no defined criteria for administering blood transfusion in this trial, and this could be a source of bias. For patients who required transfusion, the median units of blood transfused were the same in the 2 groups **Was the trial stopped early:** No
Participants	**Baseline Characteristics** Placebo *Age (years) (mean SD)*: 67.6 (11.4) *Ethnicity*: Not reported *Gender (males)*: Not reported *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 25 *Number of participants receiving treatment*: 25 *Number of participants analysed*: 25 *Dropout rate*: 0/25 (0%) TXA *Age (years) (mean SD)*: 69.6 (11.99)

	Ethnicity: Not reported *Gender (males)*: Not reported *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 25 *Number of participants receiving treatment*: 25 *Number of participants analysed*: 25 *Dropout rate*: 0/25 (0%) Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males)*: Not reported *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 50 *Number of participants receiving treatment*: 50 *Number of participants analysed*: 50 *Dropout rate*: 0/ 50 (0%) **Included criteria:** 1) diagnosis of primary osteoarthritis of the hip necessitating THR **Excluded criteria:** Not reported

	Pre-treatment: Unclear **If TKR, is tourniquet used:** Not applicable **Indication for surgery:** Osteoarthritis **Type of anaesthetic:** Spinal anaesthetic **Type of surgery:** Primary THR
Interventions	**Intervention Characteristics** Placebo 10mg/kg of intravenous tranexamic acid or a similar volume of normal saline (placebo) as a bolus at anaesthesia. A dose of 10 mg/kg was suggested by the Drug Information Department at Cheltenham General Hospital, after contacting Pharmacia. Placebo, IV, intraop (at anaesthesia) TXA Patients were randomized using a random number technique to receive either 10mg/kg of intravenous tranexamic acid or a similar volume of normal saline (placebo) as a bolus anaesthesia. TXA, IV, 10mg/kg, intraop (at anaesthesia)
Outcomes	*Primary outcome* Bleeding from the femoral canal *Secondary outcome* Not reported
Notes	**Sponsorship source:** None **Country:** UK **Setting:** single-centre **Comments:** Mean and SD calculated from text. **Authors name:** N. Garneti **Institution:** Cheltenham General Hospital **Email:** Not reported **Address:** 7 Woodlea Gate, Meanwood, Leeds LS6 4SR, United Kingdom **Native language of paper:** English **Reference type:** Full Text (1) **Trial registration number:** Not applicable, but when checked trial registration number not found

	Was it translated for this review: No

B.1.4.26 Georgiadis 2013

Methods	**Study design:** RCT **Intention to treat analysis:** Yes **Length of duration of study:** 16.5 months **Power calculation reached:** Not reported **Transfusion strategy:** Patients were transfused for symptomatic anemia (defined as light-headedness, presyncope, fatigue precluding participation in therapy, palpitations, or shortness of breath not due to other causes) with hemoglobin (HgB) of 8.0 g/dl or any HgB below 7.0g/dl **Was the trial stopped early:** No
Participants	**Baseline Characteristics** Placebo *Age (years) (mean SD)*: 64.5 (8.2) *Ethnicity*: Not reported *Gender (males, females)*: 12, 39 *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: 0/51 (0%) *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 51 *Number of participants receiving treatment*: 51 *Number of participants analysed*: 51 *Dropout rate*: 0/51 (0%) TXA *Age (years) (mean SD)*: 67.0 (9.0) *Ethnicity*: Not reported *Gender (males, females)*: 19, 31

	Length of surgery (minutes) (mean SD): Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: 0/50 (0%) *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 50 *Number of participants receiving treatment*: 50 *Number of participants analysed*: 50 *Dropout rate*: 0/51 (0%) Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males, females)*: Not reported *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery? (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: Not reported *Number of participants receiving treatment*: Not reported *Number of participants analysed*: Not reported *Dropout rate*: Not reported **Included criteria:** 1) All patients undergoing unilateral primary TKA **Excluded criteria:** 1) Religious objection to autologous blood transfusion, 2) Preoperative use of anticoagulant medication seven days prior to surgery, 3) History of fibrinolytic disorder or blood dyscrasia, cerebrovascular accident (CVA), myocardial infarction (MI), New York Heart

	Association Class III or IV heart failure (NYHA III-IV), atrial fibrillation, 4) History of deep vein thrombosis (DVT) or pulmonary embolus (PE), 5) Preoperative International Normalized Ratio (INR) N 1.4, activated partial thromboplastin time (aPTT) N 1.4 ×normal, platelets b 140,000/mm3, 6) Renal failure defined as creatinine N 1.1 mg/dL or glomerular filtration rate b 60 mL/min/1.73 m2 **Pre-treatment:** No **If TKR, is tourniquet used:** Yes **Indication for surgery:** Not reported **Type of anaesthetic:** Mixed spinal (77/101) and general (24/101) anaesthesia balanced across groups **Type of surgery:** Primary TKR
Interventions	**Intervention Characteristics** Placebo Placebo solution (75 mL normal saline). [100mL 0.9% NS, applied topically - taken from NCT page] Placebo, IA, intraop (after component placing, prior to tourniquet deflation) TXA Tranexamic acid (2.0 g in 75 mL normal saline) or placebo solution(75 mL normal saline) was sterilely prepared by a non-affiliated compounding pharmacy with no involvement in patient care and was delivered to our institution's research pharmacy. g, 75 mL of TNA or placebo solution was sterilely opened on the back table and applied to the wound TXA, IA, 2g, intraop (after component placing, prior to tourniquet deflation)
Outcomes	*Primary outcome* Perioperative blood loss *Secondary outcome* Not reported
Notes	**Sponsorship source:** Not reported **Country:** USA **Setting:** Single-centre **Comments:** Mean RBC units and SD worked out from text **Authors name:** A.G. Georgiadis

	Institution: Rush University Medical Centre **Email:** Not reported **Address:** Department of Orthopaedic Surgery, Henry Ford Hospital, CFP-642, 2799 W. Grand Blvd., Detroit, MI 48202 **Native language of paper:** English **Reference type:** Full text (1), Conference abstract (1), Trial registration (1) **Trial registration number:** NCT01370460 **Was it translated for this review:** No

B.1.4.27 Ghijselings 2015

Methods	**Study design:** RCT **Intention to treat analysis:** Unclear **Length of duration of study:** 16 months **Power calculation reached:** Not reported **Transfusion strategy:** Not reported **Was the trial stopped early:** No
Participants	**Baseline Characteristics** TXA, IV *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males)*: Not reported *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 60 *Number of participants receiving treatment*: 60 *Number of participants analysed*: 60

	Dropout rate: 0/60 (0%) TXA, IA *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males)*: Not reported *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 60 *Number of participants receiving treatment*: 60 *Number of participants analysed*: 60 *Dropout rate*: 0/60 (0%) Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males)*: Not reported *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: Not reported *Number of participants receiving treatment*: Not reported *Number of participants analysed*: Not reported *Dropout rate*: Not reported

	Included criteria: 1) All adults (patients over the age of eighteen years), 2) Scheduled for a primary unilateral total hip arthroplasty due to osteoarthritis at Ziekenhuis Oost-Limburg, Genk, Belgium **Excluded criteria:** 1) History of coagulopathy, 2) Allergy to tranexamic acid, 3) Preoperative anemia, 4) Fibrinolytic disorders, 5) History of arterial or venous thromboembolic disease, 6) Disturbances of colour vision, 7) Pregnancy, 8) Breastfeeding, 9) Major comorbidities, 10) Participation in another clinical trial **Pre-treatment:** NR **If TKR, is tourniquet used:** Not applicable **Indication for surgery:** Osteoarthritis **Type of anaesthetic:** Spinal anaesthesia **Type of surgery:** Primary THR
Interventions	**Intervention Characteristics** TXA, IV The sixty patients in the control group received a solution of 1.5 g TXA in 100 ml 0.9% saline solution, administered intravenously (IV) before closure. TXA, IV, 1.5g, intraop (before closure) AND Placebo, IA, intraop (after wound closure) TXA, IA A dose of 3 g TXA in 100 ml 0.9% saline solution was applied intra-articular (IA) in 60 patients just after wound closure through a drain. Placebo, IV, intraop (before closure) AND TXA, IA, 3g, intraop (after wound closure)
Outcomes	Primary outcome Postoperative blood loss Secondary outcome Not reported
Notes	**Sponsorship source:** Non-pharmaceutical **Country:** Belgium **Setting:** Not reported **Comments:** None **Authors name:** S. Ghijselings **Institution:** Leuven University Hospital

	Email: Not reported **Address:** Department of Orthopaedics, Leuven University Hospital Pallenberg, Leuven Belgium **Native language of paper:** English **Reference type:** Full text (1), Abstract (1), Trial registration (1) **Trial registration number:** NCT01940692 **Was it translated for this review:** No

B.1.4.28 Gill 2009

Methods	**Study design:** RCT **Intention to treat analysis:** Unclear **Length of duration of study:** 26 months **Power calculation reached:** Yes **Transfusion strategy:** The decision to transfuse blood was based on a predetermined laboratory value demonstrating a hemoglobin level of less than 10gm/dL and haematocrit level of less than 30%. These are conservative values outlined by Walsh and McClelland in postsurgical subjects. **Was the trial stopped early:** Yes
Participants	**Baseline Characteristics** Placebo *Age (years) (mean range)*: 61.4 (36–73) *Ethnicity*: Not reported *Gender (males, females)*: 2,3 *Length of surgery (minutes)*: 243.4 *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 5

	Number of participants receiving treatment: 5 *Number of participants analysed*: 5 *Dropout rate*: 0, 0% TXA *Age (years) (mean range)*: 66.6 (53–83) *Ethnicity*: Not reported *Gender (males, females)*: 1,4 *Length of surgery (minutes)*: 201.4 *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 5 *Number of participants receiving treatment*: 5 *Number of participants analysed*: 5 *Dropout rate*: 0,0% Overall *Age (years) (mean range)*: Not reported *Ethnicity*: Not reported *Gender (males, females)*: Not reported *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: Not reported *Number of participants receiving treatment*: Not reported

	Number of participants analysed: Not reported *Dropout rate*: Not reported **Included criteria:** 1) Findings consistent with the need for revision total hip arthroplasty **Excluded criteria:** 1) Any patients in need of primary total hip arthroplasty or those with a known prosthetic infection, 2) A bleeding or coagulation disorder, 3) Renal insufficiency (serum creatinine > two standard deviations for age), 4) History of deep venous thrombosis or pulmonary embolism were excluded from this study (theoretical concern of increased risk), 5) Prisoners and pregnant patients also were excluded **Pre-treatment:** No **If TKR, is tourniquet used:** Not applicable **Indication for surgery:** Not reported **Type of anaesthetic:** Not reported **Type of surgery:** Revision THR
Interventions	**Intervention Characteristics** Placebo A corresponding volume of normal saline was administered to patients in the placebo group in the same fashion as the tranexamic acid. Placebo, IV, intraop, bolus (at induction) AND Placebo, IV, intraop infusion until wound closed TXA Tranexamic acid was administered in the operating room as a 10mg/kg bolus before the induction of anaesthesia to ensure that there were no drug reactions. This was followed by 1mg/kg/hr infusion at the start of the surgery until the surgical wound was closed. TXA, IV, 10mg/kg, intraop, bolus (at induction) AND TXA, IV, 1mg/kg/hr intraop infusion until wound closed
Outcomes	Primary outcome Total number of blood transfusions Secondary outcome Incidence of deep venous thrombosis
Notes	**Sponsorship source:** Non-pharmaceutical **Country:** USA

	Setting: Single-centre **Comments:** None **Authors name:** J. Brian Gill **Institution:** Nebraska Foundation for Spinal Research **Email:** jbgill@nebraskaspinecenter.com **Address:** Nebraska Foundation for Spinal Research, 13616 California St, Suite 100, Omaha, NE 68154, USA **Native language of paper:** English **Reference type:** Full Text (1) **Trial registration number:** Not applicable, but when checked trial registration number not found **Was it translated for this review:** No

B.1.4.29 Gomez Barrena 2014

Methods	**Study design:** RCT **Intention to treat analysis:** Yes **Length of duration of study:** 10 months **Power calculation reached:** Yes **Transfusion strategy:** Blood transfusion was planned for patients with a hemoglobin level of<8.0 g/dL who were asymptomatic and appeared healthy. Transfusion was planned for patients with a level of <10.0 g/dL if they had (1) symptoms that were not well tolerated (including any organ dysfunction), were related to anemia, and were not attributable to another cause (myocardial ischemia or hypoxemia), or (2) ongoing blood loss. **Was the trial stopped early:** No
Participants	**Baseline Characteristics** TXA, IV *Age (years) (mean SD)*: 71.8 (10.3) *Ethnicity*: Not reported *Gender (males, females)*: 14, 25 *Length of surgery (minutes) (mean SD)*: 75.1 (14.1) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: 0 (0%) *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported

	ASA 1 (n/ N,%): 1/39 (3%) *ASA 2 (n/ N,%)*: 28/39 (72%) *ASA 3 (n/ N,%)*: 10/39 (26%) *ASA 4 (n/ N,%)*: 0/39 (0%) *Number of participants randomised*: 39 *Number of participants receiving treatment*: 39 *Number of participants analysed*: 39 *Dropout rate*: 0/ 39 (0%) TXA, IA *Age (years) (mean SD)*: 70.1 (9.1) *Ethnicity*: Not reported *Gender (males, females)*: 13, 26 *Length of surgery (minutes) (mean SD)*: 76.4 (15.5) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: 0 (0%) *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: 3/39 (8%) *ASA 2 (n/ N,%)*: 32/39 (82%) *ASA 3 (n/ N,%)*: 4/39 (10%) *ASA 4 (n/ N,%)*: 0/39 (0%) *Number of participants randomised*: 39 *Number of participants receiving treatment*: 39 *Number of participants analysed*: 39 *Dropout rate*: 0/ 39 (0%) Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males, females)*: Not reported *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported

	ASA 2 (n/ N,%): Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 78 *Number of participants receiving treatment*: 78 *Number of participants analysed*: 78 *Dropout rate*: 0 **Included criteria:** 1) All adult patients scheduled to undergo primary unilateral total knee replacement with cemented implant. **Excluded criteria:** 1) Absence of written informed consent, 2) Allergy to TXA, 3) Major comorbidities (severe ischemic cardiopathy, sleep apnoea syndrome, severe pulmonary disease, severe renal insufficiency, or hepatic failure), 4) Coagulopathy (preoperative platelet count <150,000/mm3, INR [international normalized ratio] >1.4, or prolonged partial thromboplastin time of >1.4 times normal), 5) A history of arterial or venous thromboembolic disease(cerebrovascular accident, DVT, or pulmonary thromboembolism), 6) A hematologic disorder (a hematopoietic, haemorrhagic, or thrombogenic disease), 7) Retinopathy (severe vision field limitation and/or colour distortion), 8) Refusal of blood products, 9) Pregnancy, 10) Breastfeeding, 11) Participation in another clinical trial during the last year. **Pre-treatment:** No **If TKR, is tourniquet used:** Yes **Indication for surgery:** Not reported **Type of anaesthetic:** Spinal anaesthesia **Type of surgery:** Primary TKR
Interventions	**Intervention Characteristics** TXA, IV Patients in the control group received a slow IV infusion of 100 mL of physiological saline solution containing a 15 mg/kg dose of TXA fifteen to twenty minutes before tourniquet release and a second identical dose three hours after surgery, on the basis of previous efficacy studies 22,23. In addition, patients in this group received a topical intra-articular placebo (100 mL of physiological saline solution). TXA, IV, 15mg/kg, intraop (15-20mins prior to tourniquet deflations) + Placebo, IA, intraop (half on tissue before closure, half on injected after skin closure) + TXA, IV,

	15mg/kg, 3 hours postop TXA, IA The experimental group received a topical intra-articular dose of 3 g of TXA (Amchafibrin; Rottapharm) in 100 mL of physiological saline solution (0.9% sodium chloride solution; Grifols) on the basis of previous studies that confirmed the high efficacy of this dosage13. Half of the volume was administered by irrigation to achieve tissue impregnation before joint closure, and the other half was administered intra-particularly after skin closure(through a 12-mm drain tube with the knee in a fully extended position after stapling and before tourniquet release). In addition, patients in this group received 100 mL of an IV placebo solution (physiological saline solution)fifteen to twenty minutes before tourniquet release and 100 mL three hours later. Placebo, IV, intraop (15-20mins prior to tourniquet deflations) + TXA, IA, 3g, intraop (half on tissue before closure, half on injected after skin closure) + Placebo, IV, 3 hours postop
Outcomes	Primary outcome: Postoperative blood transfusion Secondary outcome: Visible blood loss (as measured in the drain) Invisible blood loss (as estimated from the Nadler formula) Complications Severe adverse events Length of stay in the hospital Postoperative changes in active range of motion of the knee (which was measured with a standard clinical goniometer before and thirty days after the operation with the patient in a supine position)
Notes	**Sponsorship source:** Mixed non-pharmaceutical and pharmaceutical **Country:** Spain **Setting:** single-centre **Comments:** None **Authors name:** E. Gomez-Barrena **Institution:** La Paz University Hospital **Email:** egomezb@salud.madrid.org, egomezbarrena@gmail.com

	Address: Department of Orthopaedic Surgery and Traumatology, Hospital Universitario “La Paz”-IdiPAZ-UAM,Traumatolog´ıa 1ª planta,Paseo de la Castellana 261,28046 Madrid, Spain. **Native language of paper:** English **Reference type:** Full Text (1) Trial Registration (1) **Trial registration number:** 2011-003218-17 **Was it translated for this review:** No

B.1.4.30 Good 2003

Methods	**Study design:** RCT **Intention to treat analysis:** Yes **Length of duration of study:** Not reported **Power calculation reached:** Yes **Transfusion strategy:** If Hb was less than 90 g/litre, allogeneic leuco-depleted red blood cell concentrate was given in 250-ml units containing about 150 ml cells and 10±20 ml plasma. **Was the trial stopped early:** No
Participants	**Baseline Characteristics** Placebo *Age (years) (mean range)*: 72 (50-84) *Ethnicity*: Not reported *Gender (males, females)*: 6, 18 *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n, %)*: 0,0% *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n,%)*: 7, 29% *ASA 2 (n,%)*: 17, 71% *ASA 3 (n,%)*: 0,0% *ASA 4 (n,%)*: 0,0% *Number of participants randomised*: 27 *Number of participants receiving treatment*: Not reported

	Number of participants analysed: 24 *Dropout rate*: 3/27 (11.1%) TXA *Age (years) (mean range)*: 72 (46-83) *Ethnicity*: Not reported *Gender (males, females)*: 9, 18 *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n, %)*: 0,0% *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n,%)*: 8, 30% *ASA 2 (n,%)*: 19, 70% *ASA 3 (n,%)*: 0,0% *ASA 4 (n,%)*: 0,0% *Number of participants randomised*: 28 *Number of participants receiving treatment*: Not reported *Number of participants analysed*: 27 *Dropout rate*: 1/28 (3.7%) Overall *Age (years) (mean range)*: Not reported *Ethnicity*: Not reported *Gender (males, females)*: Not reported *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n,%)*: Not reported *ASA 2 (n,%)*: Not reported *ASA 3 (n,%)*: N*ot reported 4 (n,%)*: Not reported *Number of participants randomised*: Not reported *Number of participants receiving treatment*: Not reported *Number of participants analysed*: Not reported *Dropout rate*: Not reported

	Included criteria: 1) Elective total primary unilateral tricompartmental knee arthroplasty because of osteoarthrosis, 2) ASA I or II **Excluded criteria:** 1) History of coagulopathy, an abnormally great prothrombin or activated partial thrombin time, 2) Previous history of a thromboembolic event, 3) Treatment with aspirin or non-steroidal anti-inflammatory agents (NSAID) in the previous week, 4) Plasma creatinine greater than 115 mmol/litre in men and 100mmol/litre in women, 5) Acute infection (e.g. with leucocytosis or fever), 6) Malignant disease, 7) Patients with myocardial infarction in the preceding 12 months or those with unstable angina or coronary disease that would not allow haemodilution, 8) Patients given plasma or other treatment affecting coagulation during the peri operative period **Pre-treatment:** No **If TKR, is tourniquet used:** Yes **Indication for surgery:** Osteoarthrosis **Type of anaesthetic:** Spinal **Type of surgery:** Primary TKR
Interventions	**Intervention Characteristics** Placebo At the end of the surgical procedure, just before release of the tourniquet, tranexamic acid 10 mg kg±1 or placebo was infused i.v. (maximum dose 1000 mg). The dose was repeated after 3 h. Placebo, IV, intraop (just before tourniquet release) AND Placebo, IV, postop (3 hours postop) TXA At the end of the surgical procedure, just before release of the tourniquet, tranexamic acid 10 mg kg±1 or placebo was infused i.v. (maximum dose 1000 mg). The dose was repeated after 3 h. TXA, IV, 10mg/kg (MAX 1g), intraop (just before tourniquet release) AND TXA, IV, 10mg/kg (MAX 1g), postop (3 hours postop)
Outcomes	*Primary outcome:* Total blood loss *Secondary outcome:* Not reported
Notes	**Sponsorship source:** Non-pharmaceutical

	Country: Sweden **Setting:** Not reported **Comments:** None **Authors name:** L. Good **Institution:** University of Linkoping, S-581 85, Linkoping, Sweden **Email:** bjorn.lisander@lio.se **Address:** Department of Anaesthesiology and Intensive Care, Faculty of Health Sciences, University of Linkoping, S-581 85, Linkoping, Sweden **Native language of paper:** English **Reference type:** Full text (1) **Trial registration number:** Not applicable, but when checked trial registration number not found **Was it translated for this review:** No

B.1.4.31 Goyal 2017

Methods	**Study design:** RCT **Intention to treat analysis:** Yes **Length of duration of study:** 5 months + Follow up **Power calculation reached:** Yes **Transfusion strategy:** The triggers for transfusion were based on National Blood Authority Guidelines. These guidelines recommend red blood cell (RBC) transfusion with Hb levels of<7 g/dL. A single unit of RBCs for Hb levels between 7 and 10 g/dL is recommended if there is associated acute myocardial or cerebrovascular ischemia. Blood transfusion is not advised if the Hb level is >10 g/dL and is considered inappropriate for postoperative Hb levels more than 8 g/dL in the absence of acute myocardial or cerebrovascular ischemia. **Was the trial stopped early:** No
Participants	**Baseline Characteristics** TXA, IV *Age (years) (mean SD)*: 68.8 (7.4) *Ethnicity*: Not reported *Gender (males, females)*: 40, 47

	Length of surgery (minutes) (mean SD): 96.7 (25.2) *Proportion of participants on anticoagulants prior to surgery (n, %)*: Not reported *Incidence of preoperative anaemia*: 0/0 (0%) *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: 8/ 85, (9%) *ASA 2 (n/ N,%)*: 50/ 85, (59%) *ASA 3 (n/ N,%)*: 27/ 85, (32%) *ASA 4 (n/ N,%)*: 0/0 (0%) *Number of participants randomised*: 91 *Number of participants receiving treatment*: 91 *Number of participants analysed*: 85 *Dropout rate*: 6/ 91, (6.59%) TXA, IA *Age (years) (mean SD)*: 66.7 (8.9) *Ethnicity*: Not reported *Gender (males, females)*: 38, 43 *Length of surgery (minutes) (mean SD)*: 95.7 (20.5) *Proportion of participants on anticoagulants prior to surgery (n, %)*: Not reported *Incidence of preoperative anaemia*: 0/0 (0%) *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: 10/ 83, (12%) *ASA 2 (n/ N,%)*: 46/ 83, (55%) *ASA 3 (n/ N,%)*: 27/ 83, (32%) *ASA 4 (n/ N,%)* : 0/0 (0%) *Number of participants randomised*: 92 *Number of participants receiving treatment*: 92 *Number of participants analysed*: 83 *Dropout rate*: 9/ 92, (9.78%) Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males, females)*: Not reported *Length of surgery (minutes) (mean SD)*: Not reported

	Proportion of participants on anticoagulants prior to surgery (n, %): Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: Not reported *Number of participants receiving treatment*: Not reported *Number of participants analysed*: Not reported *Dropout rate*: Not reported **Included criteria:** 1) Patients undergoing primary unilateral TKA **Excluded criteria:** 1) Patients undergoing bilateral TKA, 2) History of thromboembolic events (deep vein thrombosis (DVT), pulmonary embolism, or cerebrovascular accident), 3) Renal dysfunction (plasma creatinine level >130 mmol/L), 4) Coagulopathy (international normalized ratio > 1.4), 5) Patients with preoperative anaemia (men with Hb < 13 g/dL; women with Hb < 12 g/dL) **Pre-treatment:** No **If TKR, is tourniquet used:** One surgeon did not use a tourniquet, 2 surgeons used it for the operative exposure only, while 1 surgeon used for the whole procedure. **Indication for surgery:** Not reported **Type of anaesthetic:** Spinal combined with sedation or general anaesthesia **Type of surgery:** Primary TKR
Interventions	**Intervention Characteristics** TXA, IV Group 2 (IV group) received 1000 mg (10 mL) of IV TXA 10 minutes before deflation of the tourniquet (if a tourniquet was used) or 10 minutes before incision (if a tourniquet was not used), 30 mL of IA saline to the knee joint after wound closure, and 2 more 1000 mg (10 mL) doses of IV TXA were given at 8 hourly intervals postoperatively. The rationale behind the use of 2 postoperative doses of IV TXA is to provide equal amount of TXA in the 2 groups. It is also the approved dosing regimen recommended by the pharmaceutical company for therapeutic use

	TXA, IV, 1g, intraop (10 mins before tourniquet deflation if used or 10mins before incision if tourniquet not used) AND Placebo, IA, intraop, after wound closure AND TXA, IV, 1g, postop 8 + 16 hours TXA, IA Group 1 (IA group) received 10 mL of saline IV 10 minutes before deflation of the tourniquet (if a tourniquet was used) or 10 minutes before incision (if a tourniquet was not used), 3000 mg (30mL) of IA TXA to the knee joint after wound closure, and 2 more 10 mL doses of IV saline were given at 8 hourly intervals postoperatively. The syringes used to inject TXA into the knee joint after wound closure were covered with an opaque dressing to keep the operating team blinded Placebo, IV, intraop (10 mins before tourniquet deflation if used or 10mins before incision if tourniquet not used) AND TXA, IA, 3g, intraop, after wound closure AND Placebo, IV, 1g, postop 8 + 16 hours
Outcomes	Primary outcome: Reduction in the Hb drop as measured by the difference in the preoperative and postoperative day 1 Hb level Secondary outcome: Difference between Hb levels preoperatively and at day 2 postoperatively, Transfusion requirements were measured as the proportion of patients requiring transfusion and the number of units transfused. Length of stay Complications
Notes	**Sponsorship source:** None **Country:** Australia **Setting:** Single-centre **Comments:** None **Authors name:** N. Goyal **Institution:** St George Private Hospital **Email:** Not reported **Address:** Sydney Knee Specialists, St George Private Hospital, Suite 8, 19 Kensington St, Kogarah, NewSouth Wales 2217, Australia **Native language of paper:** English **Reference type:** Full Text (1), Abstract (3), Trial

	registration (1) **Trial registration number:** ACTRN12614000582651 **Was it translated for this review:** No

B.1.4.32 Harley 2002

Methods	**Study design:** RCT **Intention to treat analysis:** No **Length of duration of study:** 19 months **Power calculation reached:** Yes **Transfusion strategy:** Packed red blood cells were transfused according to standardized guidelines that exist for orthopaedic patients at the study institution hemoglobin level less than 80 g/L or a haematocrit less than 0.24; patients having symptoms from their anemia (including tachycardia, dyspnoea, chest pain or recurrent syncope); or medical conditions that render the patient unable to compensate for diminished oxygen carrying capacity. **Was the trial stopped early:** No
Participants	**Baseline Characteristics** Placebo *Age (years) (mean SD)*: 69 (10) *Ethnicity*: Not reported *Gender (males, females)*: 11, 18 *Length of surgery (minutes) (mean SD)*: 80 (20) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: 15/ 29 (52%) *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 29 *Number of participants receiving treatment*: 29 *Number of participants analysed*: 24 *Dropout rate*: 5/ 29 (17.24%)

	EACA *Age (years) (mean SD)*: 69 (11) *Ethnicity*: Not reported *Gender (males, females)*: 10, 16 *Length of surgery (minutes) (mean SD)*: 77 (17) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: 21/ 26 (81%) *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 26 *Number of participants receiving treatment*: 26 *Number of participants analysed*: 22 *Dropout rate*: 4/ 26 (15.38%) Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males, females)*: Not reported *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: Not reported *Number of participants receiving treatment*: Not reported *Number of participants analysed*: Not reported *Dropout rate*: Not reported **Included criteria:** 1) All patients scheduled to undergo a

	primary THA by 1 of 4 experienced surgeons **Excluded criteria:** 1) Known allergy to EACA, 2) A history of renal or hepatic failure, 3) Coagulopathy, 4) Uncontrolled hypertension, 5) Symptomatic cardiac or pulmonary failure, 6) Known upper urinary tract bleeding **Pre-treatment:** No **If TKR, is tourniquet used:** NA **Indication for surgery:** primary and secondary osteoarthritis, Rheumatoid arthritis **Type of anaesthetic:** Mixed (at discretion of anaesthetist) **Type of surgery:** Primary THR
Interventions	**Intervention Characteristics** Placebo An EACA loading dose of 150mg/kg, or the equivalent dose of placebo, was administered as a bolus load over 20 minutes on the patient's arrival in the operating room. An hourly EACA infusion of 12.5mg/kg, or equivalent placebo, was subsequently administered for an additional 5 hours Placebo, IV, intraop (arrival of patient into theatre), 20min loading infusion + Placebo, IV, intraop, 5-hour infusion EACA An EACA loading dose of 150mg/kg, or the equivalent dose of placebo, was administered as a bolus load over 20 minutes on the patient's arrival in the operating room. An hourly EACA infusion of 12.5mg/kg, or equivalent placebo, was subsequently administered for an additional 5 hours EACA, IV, 150mg/kg, intraop (arrival of patient into theatre), 20min loading infusion + EACA, IV, 12.5mg/kg, intraop, 5-hour infusion
Outcomes	Primary outcome: Reduction in blood loss Secondary outcome: Hemoglobin levels Coagulation profiles Number of transfusions required
Notes	**Sponsorship source:** Not reported **Country:** Canada **Setting:** Single-centre

	Comments: None **Authors name:** B.J. Harley **Institution:** University of Alberta Hospital and Royal Alexandra Hospital **Email:** Not reported **Address:** Office of Orthopaedic Research, University of Alberta Hospital, 1F1.52 Walter Mackenzie Centre, 8440–112th Street, Edmonton AB **Native language of paper:** English **Reference type:** Full Text (1) Abstract (1) **Trial registration number:** Not applicable, but when checked trial registration number not found **Was it translated for this review:** No

B.1.4.33 Hayes 1996

Methods	**Study design:** RCT **Intention to treat analysis:** Yes **Length of duration of study:** Not reported **Power calculation reached:** Not reported **Transfusion strategy:** If the intraoperative blood loss was greater than the calculated maximum allowable blood loss, then transfusion with blood took place. **Was the trial stopped early:** No
Participants	**Baseline Characteristics** Placebo *Age (years) (mean SD)*: 72.9 (10.3) *Ethnicity*: Not reported *Gender (males, females) ASSUMED*: 7, 15 *Length of surgery (minutes) (mean SD)*: 99.6 (21.6) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported

	ASA 3 (n/ N,%): Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 20 *Number of participants receiving treatment*: 20 *Number of participants analysed*: 20 *Dropout rate*: 0/20 (0%) Aprotinin *Age (years) (mean SD)*: 70 (7.9) *Ethnicity*: Not reported *Gender (males/ females) ASSUMED*: 8, 12 *Length of surgery (minutes) (mean SD)*: 93.46 (24.6) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 20 *Number of participants receiving treatment*: 20 *Number of participants analysed*: 20 *Dropout rate*: 0/20 (0%) Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males, females) ASSUMED*: Not reported *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported

	ASA 4 (n/ N,%): Not reported *Number of participants randomised*: Not reported *Number of participants receiving treatment*: Not reported *Number of participants analysed*: Not reported *Dropout rate*: Not reported **Included criteria:** 1) Patients scheduled for elective total hip replacement surgery **Excluded criteria:** 1) Known hypersensitivity to aprotinin, 2) Preoperative renal, cardiac, hepatic, and pulmonary failure, 3) Uncontrolled hypertension, 4) Pre-existing coagulation abnormalities, 5) A recent history of thromboembolic events, 6) Patients with previous exposure to aprotinin **Pre-treatment:** No **If TKR, is tourniquet used:** Not applicable **Indication for surgery:** Not reported **Type of anaesthetic:** Spinal anaesthesia **Type of surgery:** Primary THR
Interventions	**Intervention Characteristics** Placebo Patients were randomly allocated to one of two groups: those who received aprotinin 2 million KIU intravenously (Iv) (Group A) and those who received placebo (Group C). Patients in Group C served as controls and were given an equal volume infusion consisting of 0.9% normal saline. Placebo, IV, preop, bolus + preop infusion (20mins prior to incision) Aprotinin Group A received aprotinin 50,000KIU (5 ml) IV over a ten-minute period. If there were no adverse sequelae, the remaining dose of 2 million KIU of aprotinin was given over 20 minutes prior to surgical incision. Aprotinin, IV, 0.5x10^6 KIU, preop, bolus + 2x10^6 preop infusion (20mins prior to incision)
Outcomes	Primary outcome: Blood loss Transfusion requirements Secondary outcome:

	Not reported
Notes	**Sponsorship source:** Part non-pharmaceutical **Country:** Ireland **Setting:** Not reported **Comments:** None **Authors name:** A. Hayes **Institution:** University Hospital Wilton **Email:** Not reported **Address:** Department of Clinical Pharmacology and Therapeutics, Cork University Hospital, Wilton, Cork, Ireland. **Native language of paper:** English **Reference type:** Full Text (1) **Trial registration number:** Not applicable, but when checked trial registration number not found **Was it translated for this review:** No

B.1.4.34 Hiippala 1995

Methods	**Study design:** RCT **Intention to treat analysis:** Unclear **Length of duration of study:** 6 months **Power calculation reached:** Not reported **Transfusion strategy:** If the haemoglobin concentration was less than 100 g/litre, concentrated red cells were given **Was the trial stopped early:** No
Participants	**Baseline Characteristics** Placebo *Age (years) (mean range)*: 70 (63-78) *Ethnicity*: Not reported *Gender (males, females)*: 3, 10 *Length of surgery (minutes) (mean SD)*: 106 (17) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported

	ASA 1 (n/ N,%): Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 14 *Number of participants receiving treatment*: Not reported *Number of participants analysed*: 13 *Dropout rate*: 1/14 (7.1%) TXA *Age (years) (mean range)*: 70 (56-82) *Ethnicity*: Not reported *Gender (males, females)*: 2, 13 *Length of surgery (minutes) (mean SD)*: 115 (18) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 15 *Number of participants receiving treatment*: Not reported *Number of participants analysed*: 15 *Dropout rate*: 0/15 (0%) Overall *Age (years) (mean range)*: Not reported *Ethnicity*: Not reported *Gender (males, females)*: Not reported *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported

	ASA 2 (n/ N,%): Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 29 *Number of participants receiving treatment*: Not reported *Number of participants analysed*: 28 *Dropout rate*: Not reported **Included criteria:** 1) Patients undergoing total knee arthroplasty **Excluded criteria:** Not reported **Pre-treatment:** No **If TKR, is tourniquet used:** Yes **Indication for surgery:** Osteoarthrosis, Rheumatoid arthritis **Type of anaesthetic:** Spinal **Type of surgery:** Primary TKR
Interventions	**Intervention Characteristics** Placebo Two to five minutes before deflating the tourniquet, the patients were given either a bolus of tranexamic acid (Cyklokapron, Pharmacia, Sweden)ISmgkg"1 or an equal volume of placebo (0.9% sodium chloride solution) i.v. within 1 min. Placebo, IV, intraop (2-5mins prior to tourniquet deflation) TXA Two to five minutes before deflating the tourniquet, the patients were given either a bolus of tranexamic acid (Cyklokapron, Pharmacia, Sweden)ISmgkg"1 or an equal volume of placebo (0.9% sodium chloride solution) i.v. within 1 min. TXA, IV, 15mg/kg, intraop (2-5mins prior to tourniquet deflation)
Outcomes	Primary outcome: Blood loss Secondary outcome: Not reported
Notes	**Sponsorship source:** Not reported

	Country: Finland **Setting:** Not reported **Comments:** None **Authors name:** S. Hiippala **Institution:** South Carelian Central Hospital **Email:** Not reported **Address:** Department of Orthopaedic Surgery; South Carelian Central Hospital, Kakelankatu 1, FIN- 53130 Lappeenranta, Finland. **Native language of paper:** English **Reference type:** Full text (1) **Trial registration number:** Not applicable, but when checked trial registration number not found **Was it translated for this review:** No

B.1.4.35 Hiippala 1997

Methods	**Study design:** RCT **Intention to treat analysis:** No **Length of duration of study:** 19 months **Power calculation reached:** Unclear **Transfusion strategy:** A transfusion of one or two units of red cells was ordered if the hemoglobin concentration decreased to less than 10 g/dL. **Was the trial stopped early:** No
Participants	**Baseline Characteristics** Placebo *Age (years) (mean SD)*: 69 (5) *Ethnicity*: Not reported *Gender (males, females)*: 8, 30 *Length of surgery (minutes) (mean SD)*: 96 (18) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported

	ASA 1 (n/ N,%): Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: Unclear *Number of participants receiving treatment*: Unclear *Number of participants analysed*: 38 *Dropout rate*: Unclear TXA *Age (years) (mean SD)*: 70 (7) *Ethnicity*: Not reported *Gender (males, females)*: 4, 35 *Length of surgery (minutes) (mean SD)*: 101 (21) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: Unclear *Number of participants receiving treatment*: Unclear *Number of participants analysed*: 39 *Dropout rate*: Unclear Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males, females)*: Not reported *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported

	ASA 2 (n/ N,%): Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 77 *Number of participants receiving treatment*: Not reported *Number of participants analysed*: Not reported *Dropout rate*: Not reported **Included criteria:** 1) Unilateral TKR patients **Excluded criteria:** Not reported **Pre-treatment:** No **If TKR, is tourniquet used:** Yes **Indication for surgery:** Osteoarthrosis, Rheumatoid arthritis **Type of anaesthetic:** Spinal anaesthesia **Type of surgery:** Primary TKR
Interventions	**Intervention Characteristics** Placebo Equal volume of NS was given to the patients in the placebo group. Placebo, IV, intraop (at tourniquet deflation) AND Placebo, IV, 3-4 hours post initial dose + 6-7 hours post. TXA Patients in the treatment group (TA) were given 15 mg/kg of tranexamic acid (Cyklokapron@; Pharmacia, Uppsala, Sweden) intravenously just before the tourniquet was deflated. Two additional doses of 10 mg/ kg were given during the operation day, the first in the recovery room 3-4 h after the initial dose and the second 6-7 h later on the surgical ward. TXA, IV, 15mg/kg, intraop (at tourniquet deflation) AND TXA, IV, 10mg/kg, 3-4 hours post initial dose + 6-7 hours post.
Outcomes	Primary outcome: Blood loss Transfusion requirements Secondary outcome: Not reported

Notes	**Sponsorship source:** Not reported **Country:** Finland **Setting:** Single-centre **Comments:** Counted number of patients rather than number of operations **Authors name:** S. Hiippala **Institution:** South Carelian Central Hospital **Email:** Not reported **Address:** Department of Anesthesia, Helsinki University Central Hospital, Haartmaninkatu 4, FIN-00290 Helsinki, Finland. **Native language of paper:** English **Reference type:** Full text (1) **Trial registration number:** Not applicable, but when checked trial registration number not found **Was it translated for this review:** No

B.1.4.36 Husted 2003

Methods	**Study design:** RCT **Intention to treat analysis:** Yes **Length of duration of study:** Not reported **Power calculation reached:** Yes **Transfusion strategy:** If a patient had a reduction in hemoglobin exceeding 25% of the starting level and had clinical symptoms, a blood transfusion(s) was given. **Was the trial stopped early:** No
Participants	**Baseline Characteristics** Placebo *Age (years) (mean)*: 67 *Ethnicity*: Not reported *Gender (males, females)*: 6, 14 *Length of surgery (mean, minutes)*: 76 *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported

	Co-morbidities: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 20 *Number of participants receiving treatment*: 20 *Number of participants analysed*: 20 *Dropout rate*: 0/20 (0%) TXA *Age (years) (mean)*: 65 *Ethnicity*: Not reported *Gender (males, females)*: Not reported *Length of surgery (mean, minutes)*: 76 *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 20 *Number of participants receiving treatment*: 20 *Number of participants analysed*: 20 *Dropout rate*: 0/20 (0%) Overall *Age (years) (mean)*: Not reported *Ethnicity*: Not reported *Gender (males, females)*: Not reported *Length of surgery (mean, minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported

	ASA 1 (n/ N,%): Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: Not reported *Number of participants receiving treatment*: Not reported *Number of participants analysed*: Not reported *Dropout rate*: Not reported **Included criteria:** 1) Patients scheduled for primary total hip arthroplasty due to arthrosis or osteonecrosis of the femoral head **Excluded criteria:** 1) Rheumatoid arthritis, 2) Malignancy, 3) Previous thromboembolic episodes, 4) Ischemic heart disease, 5) Previous subarachnoid bleeding, 6) Haematuria, 7) Body weight > 100 kg **Pre-treatment:** No **If TKR, is tourniquet used:** Not applicable **Indication for surgery:** Arthrosis or osteonecrosis of the femoral head **Type of anaesthetic:** Spinal anaesthetic **Type of surgery:** Primary THR
Interventions	**Intervention Characteristics** Placebo Patients randomized to receiving placebo (saline) were given a bolus intravenous injection of 20 mL about 15 minutes before the operation followed by a continuous infusion of 1 L of saline during 10hours. Placebo, IV, preop (15 mins before incision), bolus + intraop infusion for 10 hours TXA Patients randomized to receiving tranexamic acid were given a bolus intravenous injection of 10 mg/kg (maximum 1 g) during 10 minutes about 15 minutes before the incision, followed by a continuous infusion of 1 mg/kg/hour dissolved in 1 L of saline for 10 hours (maximum 1 g/10 hours). TXA, IV, 10mg/kg, preop (15 mins before incision) bolus + 1mg/kg/hr, intraop, infusion for 10 hours (max 1g)
Outcomes	Primary outcome:

	Pre and postoperative bleeding Number of blood transfusions Secondary outcome: None reported
Notes	**Sponsorship source:** Not reported **Country:** Denmark **Setting:** Not reported **Comments:** Mean worked out from text, unable to work out SD from text. **Authors name:** H. Husted **Institution:** Hvidovre University Hospita **Email:** henrikhusted@dadlnet.dk **Address:** Departments of Orthopaedics, Hvidovre University Hospital and Amager University Hospital, Copenhagen Hospital Corporation, Denmark **Native language of paper:** English **Reference type:** Full Text (1) **Trial registration number:** Not applicable, but when checked trial registration number not found **Was it translated for this review:** No

B.1.4.37 Jansen 1999

Methods	**Study design:** RCT **Intention to treat analysis:** Yes **Length of duration of study:** Not reported **Power calculation reached:** Not reported **Transfusion strategy:** The indication for postoperative transfusion was set at a packed cell volume (PCV) of less than 26% in any of the postoperative measures. **Was the trial stopped early:** No
Participants	**Baseline Characteristics** Placebo *Age (years) (mean, range)*: 71.0 (64-84) *Ethnicity*: Not reported *Gender (males, females)*: 3, 18

	Length of surgery (minutes) (mean SD): 94.4 (27.2) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: 0/21, (0%) *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: 0/0 (0%) *Number of participants randomised*: 21 *Number of participants receiving treatment*: 21 *Number of participants analysed*: 21 *Dropout rate*: 0/ 21, (0%) TXA *Age (years) (mean, range)*: 70.7 (62-80) *Ethnicity*: Not reported *Gender (males, females)*: 5, 16 *Length of surgery (minutes) (mean SD)*: 84.7 (15.9) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: 0/ 21, (0%) *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: 0/0 (0%) *Number of participants randomised*: 21 *Number of participants receiving treatment*: 21 *Number of participants analysed*: 21 *Dropout rate*: 0/ 21, (0%) Overall *Age (years) (mean, range)*: Not reported *Ethnicity*: Not reported *Gender (males, females)*: Not reported *Length of surgery (minutes) (mean SD)*: Not reported

	Proportion of participants on anticoagulants prior to surgery (n/ N, %): Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: Not reported *Number of participants receiving treatment*: Not reported *Number of participants analysed*: Not reported *Dropout rate*: Not reported **Included criteria:** 1) ASA I–III patients, 2) Diagnosed with osteoarthrosis, 3) Undergoing unilateral bicondylar cemented total knee arthroplasty **Excluded criteria:** 1) Known allergy to tranexamic acid, 2) Preoperative hepatic or renal dysfunction, 3) Serious cardiac or respiratory disease, 4) Congenital or acquired coagulopathy, 5) A history of, or evolving, thromboembolic disease **Pre-treatment:** No **If TKR, is tourniquet used:** Yes **Indication for surgery:** Osteoarthrosis **Type of anaesthetic:** General anaesthetic **Type of surgery:** Primary TKR
Interventions	**Intervention Characteristics** Placebo Tranexamic acid 15 mg kg–1 (Exacyl, Bournonville Pharma, Belgium) or an equal volume of saline, in a double-blind manner,30 min before inflation of the tourniquet and surgery, and repeated subsequently every 8 h for 3 days. Placebo, IV, intraop (30 mins prior to tourniquet inflation AND Placebo, IV, post 1st dose every 8 hours for 3 days TXA Patients were allocated randomly to receive tranexamic acid 15 mg kg–1 (Exacyl, Bournonville Pharma, Belgium) or an equal volume of saline, in a double-blind manner,30 min before inflation of the tourniquet and surgery, and repeated subsequently every 8 h for 3 days.

	TXA, IV, 15mg/kg, intraop (30 mins prior to tourniquet inflation AND TXA, IV, 15mg/kg, post 1st dose every 8 hours for 3 days
Outcomes	Primary outcome: Blood loss Blood transfusion requirements Blood coagulation Thromboembolic complications Secondary outcome: Not reported
Notes	**Sponsorship source:** Partly funded by pharmaceutical company **Country:** Belgium **Setting:** Not reported **Comments:** None **Authors name:** A.J. Jansen **Institution:** Vrije Universiteit Brussel **Email:** Not reported **Address:** Department of Anaesthesiology, Academisch Ziekenhuis, Vrije Universiteit Brussel, Laarbeeklaan 101, B-1090 Brussels, Belgium **Native language of paper:** English **Reference type:** Abstract (1) Full Text (1) **Trial registration number:** Not applicable, but when checked trial registration number not found **Was it translated for this review:** No

B.1.4.38 Janssens 1994

Methods	**Study design:** RCT **Intention to treat analysis:** Not reported **Length of duration of study:** Not reported **Power calculation reached:** Not reported **Transfusion strategy:** Packed red blood cells were transfused to maintain a haematocrit of 30%. **Was the trial stopped early:** No

Participants	**Baseline Characteristics** Placebo *Age (years) (mean SD)*: 65.3 (15.3) *Ethnicity*: Not reported *Gender (males, females)*: 6, 14 *Length of surgery (minutes) (mean SD)*: 176 (32) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 20 *Number of participants receiving treatment*: 20 *Number of participants analysed*: 20 *Dropout rate*: 0 Aprotinin *Age (years) (mean SD)*: 64.9 (13.2) *Ethnicity*: Not reported *Gender (males, females)*: 10, 10 *Length of surgery (minutes) (mean SD)*: 169 (27) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 20 *Number of participants receiving treatment*: 20 *Number of participants analysed*: 20 *Dropout rate*: 0

	Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males, females)*: Not reported *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 40 *Number of participants receiving treatment*: Not reported *Number of participants analysed*: Not reported *Dropout rate*: Not reported **Included criteria:** Patients scheduled for primary elective total hip replacement **Excluded criteria:** 1) Known allergy to aprotinin, 2) Preoperative renal or hepatic failure, 3) Uncontrolled hypertension (i.e. diastolic blood pressure equal or greater than 100mmHg), 4) Clinical cardiac or pulmonary failure, 5) Preoperative coagulopathy suspected by clinical history or preoperative blood coagulation tests (platelet count, prothrombin time, and activated partial thromboplastin time [aPTT]) **Pre-treatment:** No **If TKR, is tourniquet used:** Not applicable **Indication for surgery:** NR **Type of anaesthetic:** General **Type of surgery:** Primary THR
Interventions	**Intervention Characteristics** Placebo Saline (10,000 kallikrein inactivator units [kIU]/ml) given as a bolus injection of 2 x 10(6) kIU over 30 minutes followed by an infusion of 5 x 10(5) kIU/ h until the end of surgery, with a maximum dose of 3.5 x 10(6) kIU

	Placebo, IV, ml, intraop, bolus + infusion until the end of surgery. Aprotinin Preservative free aprotinin (10,000 kallikrein inactivator units (KIU)/ml) given as a bolus injection of 2 x 10^6 KIU over 30 min followed by an infusion of 5 x 10^5 KIU/h until the end of surgery with a maximum dose of 3.5 x 10 ^6 KIU Aprotinin, IV, 2 x 10^6 KIU, intraop bolus + 5 x 10^5 KIU/h infusion. (MAX 3.5 x 10 ^6 KIU total) until the end of surgery.
Outcomes	Primary outcome: Blood loss Transfusion requirements Secondary outcome: Not reported
Notes	**Sponsorship source:** Not reported **Country:** Belgium **Setting:** Single-centre **Comments:** None **Authors name:** M. Janssens **Institution:** University Hospital of Liege **Email:** Not reported **Address:** Department of Anesthesiology, University Hospital of Liege, Domaine du Sart Tilman, B 4000 Liege, Belgium **Native language of paper:** English **Reference type:** Full text (1) **Trial registration number:** Not applicable, but when checked trial registration number not found **Was it translated for this review:** No

B.1.4.39 Jeserschek 2003

Methods	**Study design:** RCT **Intention to treat analysis:** Yes **Length of duration of study:** Not reported

	Power calculation reached: Yes **Transfusion strategy:** The intraoperative transfusion of red blood cells (RBC) depended on the estimation of the blood loss by the anaesthetist. **Was the trial stopped early:** No
Participants	**Baseline Characteristics** Placebo *Age (years) (mean SD)*: 74 (6.7) *Ethnicity*: Not reported *Gender (males, females)*: 5, 3 *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 8 *Number of participants receiving treatment*: 8 *Number of participants analysed*: 8 *Dropout rate*: 0/8, (0%) Aprotinin *Age (years) (mean SD)*: 67 (12.0) *Ethnicity*: Not reported *Gender (males, females)*: 2, 6 *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported

	ASA 4 (n/ N,%): Not reported *Number of participants randomised*: 8 *Number of participants receiving treatment*: 8 *Number of participants analysed*: 8 *Dropout rate*: 0/8 (0%) Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males, females)*: Not reported *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 16 *Number of participants receiving treatment*: 16 *Number of participants analysed*: 16 *Dropout rate*: 0 **Included criteria:** Aseptic or septic failure of a hip or knee prosthesis or undergoing resection of a soft-tissue sarcoma, was enrolled in the study **Excluded criteria:** 1) Known or suspected allergy to aprotinin or previous treatment with the drug **Pre-treatment:** Not reported **If TKR, is tourniquet used:** Not applicable **Indication for surgery:** Aseptic or septic failure of a hip or knee prosthesis or undergoing resection of a soft-tissue sarcoma **Type of anaesthetic:** Not reported **Type of surgery:** Revision TKR, Revision THR
Interventions	**Intervention Characteristics** Placebo

	At the beginning of the operation the patients received either 1 x 106KIU of aprotinin as a loading dose followed by continuous infusion of 500 000 KIU/hour, or the same volume of normal saline. Placebo, IV, intraop, bolus AND Placebo, IV, intraop, infusion Aprotinin At the beginning of the operation the patients received either 1 x 106KIU of aprotinin as a loading dose followed by continuous infusion of 500 000 KIU/hour, or the same volume of normal saline. Aprotinin, IV, 1 x 10^6 KIU intraop, bolus AND Aprotinin, IV, 0.5 x 10^6, intraop, infusion
Outcomes	Primary outcome: Blood loss Transfusion requirements Secondary outcome: Not reported
Notes	**Sponsorship source:** None **Country:** Austria **Setting:** Not reported **Comments:** Calculated mean age and SD revision THR patients only. Length surgery and hospital stay includes resection for cancer surgery and therefore not included in our analysis. **Authors name:** R. Jeserschek **Institution:** Karl-Franzens University School of Medicine **Email:** Not reported **Address:** University School of Medicine, Auenbruggerplatz 29, AT-8036 Graz, Austria **Native language of paper:** English **Reference type:** Full text (1) **Trial registration number:** Not applicable, but when checked trial registration number not found **Was it translated for this review:** No

B.1.4.40 Johansson 2005

Methods	**Study design:** RCT **Intention to treat analysis:** Per-protocol analysis **Length of duration of study:** 17 **Power calculation reached:** Yes **Transfusion strategy:** The guideline threshold for blood transfusion was an Hb level of 90 g/L, with consideration of clinical well-being **Was the trial stopped early:** No
Participants	**Baseline Characteristics** Placebo *Age (years) (mean SD)*: 68 (8) *Ethnicity*: Not reported *Gender (males, females)*: 28, 25 *Length of surgery (minutes) (mean SD)*: 89 (20) *Proportion of participants on anticoagulants prior to surgery (n, %)*: 0 *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: Not reported *Number of participants receiving treatment*: Not reported *Number of participants analysed*: 53 *Dropout rate*: Not reported TXA *Age (years) (mean SD)*: 69 (7) *Ethnicity*: Not reported *Gender (males, females)*: 25, 22 *Length of surgery (minutes) (mean SD)*: 84 (22) *Proportion of participants on anticoagulants prior to surgery (n, %)*: 0

	Incidence of preoperative anaemia: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: Not reported *Number of participants receiving treatment*: Not reported *Number of participants analysed*: 47 *Dropout rate*: Not reported Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males, females)*: 47, 53 *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n, %)*: 0 *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 119 *Number of participants receiving treatment*: 119 *Number of participants analysed*: 100 *Dropout rate*: 19/119,16.0% **Included criteria:** 1) Planned THA due to osteoarthrosis, 2) No history or laboratory signs of bleeding disorders (activated partial thrombin, prothrombin time, and thrombocyte count within standard limits), 3) Absence of malignancy and rheumatic joint disease, 4) No consumption of aspirin or NSAIDs within a week before surgery, 5) No history of coagulopathy or thromboembolic events, 6) Plasma creatinine levels below 115 µmol/L in men and 100 µmol/L in women. **Excluded criteria:** Not reported

	Pre-treatment: No **If TKR, is tourniquet used:** Not applicable **Indication for surgery:** Osteoarthrosis **Type of anaesthetic:** Spinal **Type of surgery:** Primary THR
Interventions	**Intervention Characteristics** Placebo Immediately before the start of the operation, the patients received a bolus infusion of TXA (15 mg/kg) mixed in 100 mL normal saline, or the same volume of placebo Placebo, IV, 100ml, preop, single dose TXA Immediately before the start of the operation, the patients received a bolus infusion of TXA (15 mg/kg) mixed in 100 mL normal saline, or the same volume of placebo TXA, IV, 15mg/kg, preop, single dose
Outcomes	Primary outcome: Blood loss Need for blood transfusion Postoperative complications (wound complications and thromboembolic events) Secondary outcome: Not reported
Notes	**Sponsorship source:** Non-pharmaceutical **Country:** Sweden **Setting:** Multi-centre **Comments:** Health Research Council in the South-East of Sweden **Authors name:** Torsten Johansson **Institution:** University of Linköping **Email:** Torsten.Johansson@lio.se **Address:** Division of Orthopaedics and Sports Medicine, Department of Neuroscience and Locomotion, Faculty of Health Sciences, University of Linköping, Sweden **Native language of paper:** English

	Reference type: Full text (1) **Trial registration number:** Not applicable, but when checked trial registration number not found **Was it translated for this review:** No

B.1.4.41 Jules-Elysee 2019

Methods	**Study design:** RCT **Intention to treat analysis:** Yes **Length of duration of study:** 12 months **Power calculation reached:** Yes **Transfusion strategy:** Not reported **Was the trial stopped early:** No
Participants	**Baseline Characteristics** TXA, IV *Age (years) (mean SD)*: 65.6 (8.4) *Ethnicity*: Hispanic or Latino: 0/ 31, 0%; Not Hispanic or Latino 31/ 31, 100%; Unknown or not reported 0/ 31, 0% *Gender (males, females)*: Males: 11/ 31, 35.5%; Females 20/ 31, 64.5% *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: 28/ 31, 90.3% *ASA 3 (n/ N,%)*: 3/ 31, 9.7% *ASA 4 (n/ N,%)*: 0/ 31, 0% *Number of participants randomised*: 33 *Number of participants receiving treatment*: 32 *Number of participants analysed*: 31 *Dropout rate*: 2/ 33, 6.1% TXA, Topical *Age (years) (mean SD)*: 65.0 (6.9) *Ethnicity*: Hispanic or Latino: 4/ 32, 12.5%; Not Hispanic or

	Latino 28/ 32, 87.5%; Unknown or not reported 0/ 32, 0% *Gender (males, females)*: Males: 20/ 32, 62.5%; Females 12/ 32, 37.5% *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: 0/ 32, 0% *ASA 2 (n/ N,%)*: 32/ 32, 100% *ASA 3 (n/ N,%)*: 0/ 32, 0% *ASA 4 (n/ N,%)*: 0/ 32, 0% *Number of participants randomised*: 33 *Number of participants receiving treatment*: 32 *Number of participants analysed*: 32 *Dropout rate*: 1/ 33, 3.03% Overall *Age (years) (mean SD)*: 65.3 (7.6) *Ethnicity*: Hispanic or Latino: 4/ 63, 6.3%; Not Hispanic or Latino 59/ 63, 93.7%; Unknown or not reported 0/ 63, 0% *Gender (males, females)*: Males: 31/ 63, 49.2%; Females 32/ 63, 50.8% *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: 0/ 63, 0% *ASA 2 (n/ N,%)*: 60/ 63, 95.2% *ASA 3 (n/ N,%)*: 3/ 63, 4.8% *ASA 4 (n/ N,%)*: 0/ 63, 0% *Number of participants randomised*: 66 *Number of participants receiving treatment*: 64 *Number of participants analysed*: 63 *Dropout rate*: 3/ 66, 4.5% **Included criteria:** 1. Patients undergoing primary

	unilateral total knee replacement with a participating surgeon, 2. Patients aged 18-80 **Excluded criteria:** 1. All patients on steroid therapy regardless of dose, duration, or treatment or those requiring stress-dose steroids preoperatively 2. Patients who will require postoperative use of Coumadin, Xarelto, or Plavix 3. Use of non-steroidal anti-inflammatory drugs (NSAIDs) within 1 week of surgery 4. Hypersensitivity to tranexamic acid 5. Renal dysfunction (Creatinine clearance < 40 ml/min) 6. Hepatic dysfunction (AST or ALT 2x upper limit of normal) 7. Cardiac exclusions: coronary stent, history of myocardial infarction, positive stress test, atrial fibrillation, advanced coronary artery disease 8. Advanced chronic obstructive pulmonary disease or advanced interstitial lung disease 9. History of venous thromboembolism 10. Hypercoagulability (e.g. antiphospholipid syndrome, genetic hypercoagulability with or without prior venous thromboembolism) 11. History of stroke or transient ischemic attack **If TKR, is tourniquet used:** Yes **Indication for surgery:** Osteoarthritis **Type of anaesthetic:** Spinal-epidural anaesthesia **Type of surgery:** Primary TKA
Interventions	**Intervention Characteristics** TXA, IV Prior to tourniquet inflation, the patients in the IV group received 1.0 g of IV TXA and the topical group received 100 mL of an IV placebo (saline solution). Three hours after the first administration of the IV TXA or placebo, an identical preparation was administered in the post-anaesthesia care unit (PACU). Five minutes prior to final tourniquet release, the topical group received 3.0 g of TXA in 75 mL of saline solution and the IV group received 75 mL of saline solution directly on the wound TXA, IV, 1g, intraop + 1g, post-op, Placebo, topical, 75cc, postop TXA, Topical Patients will receive 3g tranexamic acid in 75mL solution topically in the operating room, approximately 5 minutes before the tourniquet is released. It will sit for 5 minutes before the solution is suctioned off by the surgeon. They will also receive 2 intravenous saline solutions: one in the operating room before inflation of the tourniquet, and one in the post-anaesthesia care unit 3 hours after the first solution was given.

	TXA, Topical, 3g, intraop, + Placebo, IV, intraop, postop
Outcomes	Primary outcome: Level of PAP complex in plasma of peripheral blood 4 hours after tourniquet release Secondary outcome: PF1.2 IL-6 TXA levels in collected peripheral and wound blood Total amount of drainage Total amount of estimated blood loss over the course of the hospital stay Total hidden amount of blood loss over the course of the hospital stay The time to discharge from physical therapy (PT) Length of the hospital stay Hemoglobin and haematocrit levels Units of blood transfused were measured until hospital discharge. Prevalence of thrombosis was also assessed.
Notes	**Sponsorship source:** Non-pharmaceutical (Hospital for Special Surgery, New York) **Country:** USA **Setting:** Single-centre **Comments:** 1. Data given for DVT/ PE... Not split individually for DVT and PE. So, data not extracted. **Authors name:** K. Jules-Elysee **Institution:** Hospital for Special Surgery **Email:** JulesElyseeK@HSS.EDU **Address:** Department of Anaesthesiology, Critical Care & Pain Management, Hospital for Special Surgery, New York, NY **Native language of paper:** English **Reference type:** Full text (1), trial registration (1) **Trial registration number:** NCT02540226 **Was it translated for this review:** No

B.1.4.42 Kakar 2009 Bilateral TKR

Methods	**Study design:** RCT **Intention to treat analysis:** Not reported **Length of duration of study:** Not reported **Power calculation reached:** Not reported **Transfusion strategy:** Before the surgery, Hb transfusion trigger point was determined for each patient according to the following criteria: for patients over 60 years and associated cardiopulmonary disease the transfusion trigger was 10 g dL−1 whereas for other patients, the transfusion trigger was 8 g dL–1. **Was the trial stopped early:** No
Participants	**Baseline Characteristics** Saline Uni. (CU) *Age (years) (mean SD)*: 66.2 (4.8) *Ethnicity*: Not reported *Gender (males, females)*: 4,8 *Length of surgery (minutes) (mean SD)*: 92.1 (10.8) *Proportion of participants on anticoagulants prior to surgery (n, %)*: 0 *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 12 *Number of participants receiving treatment*: 12 *Number of participants analysed*: 12 *Dropout rate*: 0 Saline Bi. (CB) *Age (years) (mean SD)*: 67.15 (6.9) *Ethnicity*: Not reported *Gender (males, females)*: 3,10 *Length of surgery (minutes) (mean SD)*: 152 (17.3)

	Proportion of participants on anticoagulants prior to surgery (n, %): Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 13 *Number of participants receiving treatment*: 13 *Number of participants analysed*: 13 *Dropout rate*: 0 TXA Uni. (TU) *Age (years) (mean SD)*: 62.4 (9.4) *Ethnicity*: Not reported *Gender (males, females)*: 3, 9 *Length of surgery (minutes) (mean SD)*: 96.8 (17.7) *Proportion of participants on anticoagulants prior to surgery (n, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 12 *Number of participants receiving treatment*: 12 *Number of participants analysed*: 12 *Dropout rate*: 0 TXA Bi. (TB) *Age (years) (mean SD)*: 63.13 (16.8) *Ethnicity*: Not reported *Gender (males, females)*: 4,9 *Length of surgery (minutes) (mean SD)*: 154 (11.5) *Proportion of participants on anticoagulants prior to*

	surgery (n, %): Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 13 *Number of participants receiving treatment*: 13 *Number of participants analysed*: 13 *Dropout rate*: 0 Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males, females)*: Not reported *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: Not reported *Number of participants receiving treatment*: Not reported *Number of participants analysed*: Not reported *Dropout rate*: Not reported **Included criteria:** Primary cemented total knee arthroplasties (both unilateral (U/L) and bilateral (B/L) **Excluded criteria:** Patients were excluded if they had one of the following criteria: 1) Known or suspected allergy to medications used (TAX, local anaesthetics, midazolam, pethidine, propofol), 2) Inherited or acquired haemostatic diseases, 3) Abnormal coagulation screening tests (platelet count, prothrombin time, activated partial thromboplastin time), 4) Ingestion of aspirin or other nonsteroidal anti-

	inflammatory drugs within seven days of surgery, 5) Renal or hepatic insufficiency, 6) Pregnancy, 7) History of deep venous thrombosis (DVT) or pulmonary embolism or history of ocular pathology or ophthalmological procedure other than corrective lenses. **Pre-treatment:** No **If TKR, is tourniquet used:** Yes **Indication for surgery:** Not reported **Type of anaesthetic:** Spinal and epidural **Type of surgery:** Primary unilateral TKR and bilateral TKR
Interventions	**Intervention Characteristics** Saline Uni. (CU) Patients in Group CU and CB received an equivalent volume of physiologic saline. Placebo, IV, intraop, infusion (unilateral) Saline Bi. (CB) Patients in Group CU and CB received an equivalent volume of physiologic saline. Placebo, IV, intraop, infusion (bilateral) TXA Uni. (TU) In Group TU and TB, Tranexamic acid was given immediately before inflation of the tourniquet. After a test dose of 1mL, patients received a dose of 10 mg.kg–1 IV followed by an infusion of 1 mg.kg–1, 1hr–1 until skin closure. TXA, IV, 10mg/kg intraop, 1mg/kg intraop infusion (unilateral) TXA Bi. (TB) In Group TU and TB, Tranexamic acid was given immediately before inflation of the tourniquet. After a test dose of 1mL, patients received a dose of 10 mg.kg–1 IV followed by an infusion of 1 mg.kg–1, 1hr–1 until skin closure. TXA, IV, 10mg/kg intraop, 1mg/kg intraop infusion (bilateral)
Outcomes	Primary outcome: Blood loss Postoperative blood transfusions Incidence of deep vein thrombosis

	Coagulation abnormality Secondary outcome: Not reported
Notes	**Sponsorship source:** Not reported **Country:** India **Setting:** Not reported **Comments:** None **Authors name:** P. N. Kakar **Institution:** Fortis Hospital **Email:** pn_kakar@hotmail.com **Address:** Head of the Department of Anesthesia, Fortis Hospital, Shalimar Bagh, New Delhi. **Native language of paper:** English **Reference type:** Full text (1) **Trial registration number:** Not applicable, but when checked trial registration number not found **Was it translated for this review:** No

B.1.4.43 Kakar 2009 Unilateral TKR

Methods	**Study design:** RCT **Intention to treat analysis:** Not reported **Length of duration of study:** Not reported **Power calculation reached:** Not reported **Transfusion strategy:** Before the surgery, Hb transfusion trigger point was determined for each patient according to the following criteria: for patients over 60 years and associated cardiopulmonary disease the transfusion trigger was 10 g dL−1 whereas for other patients, the transfusion trigger was 8 g dL–1. **Was the trial stopped early:** No
Participants	**Baseline Characteristics** Saline Uni. (CU) *Age (years) (mean SD)*: 66.2 (4.8) *Ethnicity*: Not reported *Gender (males, females)*: 4,8

	Length of surgery (minutes) (mean SD): 92.1 (10.8) *Proportion of participants on anticoagulants prior to surgery (n, %)*: 0 *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 12 *Number of participants receiving treatment*: 12 *Number of participants analysed*: 12 D*ropout rate*: 0 Saline Bi. (CB) *Age (years) (mean SD)*: 67.15 (6.9) *Ethnicity*: Not reported *Gender (males, females)*: 3,10 *Length of surgery (minutes) (mean SD)*: 152 (17.3) *Proportion of participants on anticoagulants prior to surgery (n, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 13 *Number of participants receiving treatment*: 13 *Number of participants analysed*: 13 *Dropout rate*: 0 TXA Uni. (TU) *Age (years) (mean SD)*: 62.4 (9.4) *Ethnicity*: Not reported *Gender (males, females)*: 3, 9 *Length of surgery (minutes) (mean SD)*: 96.8 (17.7)

	Proportion of participants on anticoagulants prior to surgery (n, %): Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 12 *Number of participants receiving treatment*: 12 *Number of participants analysed*: 12 *Dropout rate*: 0 TXA Bi. (TB) *Age (years) (mean SD)*: 63.13 (16.8) *Ethnicity*: Not reported *Gender (males, females)*: 4,9 *Length of surgery (minutes) (mean SD)*: 154 (11.5) *Proportion of participants on anticoagulants prior to surgery (n, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 13 *Number of participants receiving treatment*: 13 *Number of participants analysed*: 13 *Dropout rate*: 0 Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males, females)*: Not reported *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to*

	surgery (n, %): Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: Not reported *Number of participants receiving treatment*: Not reported *Number of participants analysed*: Not reported *Dropout rate*: Not reported **Included criteria:** Primary cemented total knee arthroplasties (both unilateral (U/L) and bilateral (B/L) **Excluded criteria:** Patients were excluded if they had one of the following criteria: 1) Known or suspected allergy to medications used (TAX, local anaesthetics, midazolam, pethidine, propofol), 2) Inherited or acquired haemostatic diseases, 3) Abnormal coagulation screening tests (platelet count, prothrombin time, activated partial thromboplastin time), 4) Ingestion of aspirin or other nonsteroidal anti-inflammatory drugs within seven days of surgery, 5) Renal or hepatic insufficiency, 6) Pregnancy, 7) History of deep venous thrombosis (DVT) or pulmonary embolism or history of ocular pathology or ophthalmological procedure other than corrective lenses. **Pre-treatment:** No **If TKR, is tourniquet used:** Yes **Indication for surgery:** Not reported **Type of anaesthetic:** Spinal and epidural **Type of surgery:** Primary unilateral TKR and bilateral TKR
Interventions	**Intervention Characteristics** Saline Uni. (CU) Patients in Group CU and CB received an equivalent volume of physiologic saline. Placebo, IV, intraop, infusion (unilateral) Saline Bi. (CB) Patients in Group CU and CB received an equivalent volume of physiologic saline.

	Placebo, IV, intraop, infusion (bilateral) TXA Uni. (TU) In Group TU and TB, Tranexamic acid was given immediately before inflation of the tourniquet. After a test dose of 1mL, patients received a dose of 10 mg.kg–1 IV followed by an infusion of 1 mg.kg–1, 1hr–1 until skin closure. TXA, IV, 10mg/kg intraop, 1mg/kg intraop infusion (unilateral) TXA Bi. (TB) In Group TU and TB, Tranexamic acid was given immediately before inflation of the tourniquet. After a test dose of 1mL, patients received a dose of 10 mg.kg–1 IV followed by an infusion of 1 mg.kg–1, 1hr–1 until skin closure. TXA, IV, 10mg/kg intraop, 1mg/kg intraop infusion (bilateral)
Outcomes	Primary outcome: Blood loss Postoperative blood transfusions Incidence of deep vein thrombosis Coagulation abnormality Secondary outcome: Not reported
Notes	**Sponsorship source:** Not reported **Country:** India **Setting:** Not reported **Comments:** None **Authors name:** P. N. Kakar **Institution:** Fortis Hospital **Email:** pn_kakar@hotmail.com **Address:** Head of the Department of Anaesthesia, Fortis Hospital, Shalimar Bagh, New Delhi. **Native language of paper:** English **Reference type:** Full text (1) **Trial registration number:** Not applicable, but when checked trial registration number not found

	Was it translated for this review: No

B.1.4.44 Kang 2021

Methods	**Study design:** RCT **Intention to treat analysis:** Yes **Length of duration of study:** 8 months (September 2019 and May 2020) + FU (2 weeks) = 8.5 months **Power calculation reached:** No **Transfusion strategy:** Blood transfusions was administered to patients with postoperative Hb level of less than 70 g/L or any organ dysfunction related to anemia regardless of Hb level **Was the trial stopped early:** No
Participants	**Baseline Characteristics** TXA, IV 1g pre-incision, IA 1.5g intraop, IV 1g 3 hours postop *Age (years) (mean SD)*: 66.4 (5.9) *Ethnicity*: Not reported *Gender (males, females)*: 4/48 M 8.3%, 44/ 48 F 91.6% *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n, %)*: 0/ 48, 0% *Incidence of preoperative anaemia*: 0/ 48, 0% *Co-morbidities*: Rheumatoid arthritis *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 52 *Number of participants receiving treatment*: 52 *Number of participants analysed*: 48 *Dropout rate*: 4/ 52, 7.7% TXA, IV 1g pre-incision, IA 1.5g intraop, IV 1g 3, 6 and 12 hours post op *Age (years) (mean SD)*: 66.5 (5.5) *Ethnicity*: Not reported

	Gender (males, females): 6/ 49 M 12.24%, 43/ 49 F 87.8% *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Rheumatoid arthritis *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 52 *Number of participants receiving treatment*: 52 *Number of participants analysed*: 49 *Dropout rate*: 3/ 52, 5.8% Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males, females)*: Not reported *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n, %)*: Not reported *Incidence of preoperative anaemia*: Patients with preoperative Hb level < 12 g/dL were administered erythropoietin 10,000 U orally once a day; the Hb level was checked regularly, and the administration was stopped when Hb level reached > 15 g/dL *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 104 *Number of participants receiving treatment*: 104 *Number of participants analysed*: 97 *Dropout rate*: 7/ 104, 6.7% **Included criteria:** 1) Patients aged 50–75 years who

	underwent primary unilateral TKA for RA **Excluded criteria:** 1) a diagnosis of other types of arthritis (i.e., not RA) 2) renal dysfunction 3) severe cardiovascular or cerebrovascular diseases 4) patients who reported prolonged use of oral anticoagulant drugs 5) acquired colour vision disorder 6) active intravascular coagulation patients 7) history of seizures **If TKR, is tourniquet used:** Yes **Indication for surgery:** Rheumatoid Arthritis **Type of anaesthetic:** General **Type of surgery:** Primary TKR
Interventions	**Intervention Characteristics** TXA, IV 1g pre-incision, IA 1.5g intraop, IV 1g 3 hours postop IV-TXA (1 g) was administered 10 min before skin incision by an anaesthesiologist, and tranexamic acid(1.5 g dissolved in 10 mL of normal saline) was administered via articular injection by a surgeon after cavity suture during the surgery. Patients in group A received one dose of IV-TXA (1 g) 3 h postoperatively, while those in group B received three doses of IV-TXA (1 g) 3,6, and 12 h postoperatively TXA, IV 1g pre-incision, IA 1.5g intraop, IV 1g 3 hours postop TXA, IV 1g pre-incision, IA 1.5g intraop, IV 1g 3, 6 and 12 hours post op IV-TXA (1 g) was administered 10 min before skin incision by an anaesthesiologist, and tranexamic acid (1.5 g dissolved in 10 mL of normal saline) was administered via articular injection by a surgeon after cavity suture during the surgery. Group B received three doses of IV-TXA (1 g) 3, 6, and 12 h postoperatively TXA, IV 1g pre-incision, IA 1.5g intraop, IV 1g 3, 6 and 12 hours post op
Outcomes	Primary outcome: Perioperative haematocrit (Hct) and Hb levels Coagulation index Renal function Blood loss Secondary outcome: Adverse events (e.g., DVT, PE, wound complications, infection, and acute renal failure)

	Transfusion rate Adverse events
Notes	**Sponsorship source:** Non-pharmaceutical (This study was supported by the Foundation of Health and Family planning Commission of Shanghai, China (Grant No. ZY (2018–2020)-FWTX-6023)) **Country:** China **Setting:** Single-centre **Comments:** None **Authors name:** B-X Kang **Institution:** Shanghai Guanghua Hospital of Integrated Traditional Chinese and Western Medicine **Email:** Lian-bo Xiao: xiao_lianbo@163.com; Xiao-jun Gao: 13501735927@139.com **Address:** Shanghai University of Traditional Chinese Medicine, Shanghai Guanghua Hospital of Integrated Traditional Chinese and Western Medicine, Shanghai 200052, CN, China **Native language of paper:** English **Reference type:** Full text (1), study protocol (1), trial registration (1) **Trial registration number:** ChiCTR1099925913 **Was it translated for this review:** No

B.1.4.45 Kang 2021a

Methods	**Study design:** RCT **Intention to treat analysis:** Yes **Length of duration of study:** 12 months (May 2019 to May 2020) + 2 weeks (follow-up) = 12.5 months **Power calculation reached:** Not reported **Transfusion strategy:** The criterion for transfusion was a postoperative Hb value of less than 70 g/L in asymptomatic patients or between 70 g/L and 10 g/L in symptomatic patients **Was the trial stopped early:** No
Participants	**Baseline Characteristics** TXA, IV 1 dose postop

	Age (years) (mean SD): 71.4 (4.0) *Ethnicity*: Not reported *Gender (males, females)*: 19 M (19%), 81 F (81%) *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n, %)*: Not reported *Incidence of preoperative anaemia*: These patients were excluded *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 100 *Number of participants receiving treatment*: 100 *Number of participants analysed*: 100 *Dropout rate*: 0/ 100, 0% TXA, IV 2 doses postop *Age (years) (mean SD)*: 71.8 (4.1) *Ethnicity*: Not reported *Gender (males, females)*: 20 M (20%), 80 F (80%) *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n, %)*: Not reported *Incidence of preoperative anaemia*: These patients were excluded *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 100 *Number of participants receiving treatment*: 100 *Number of participants analysed*: 100 *Dropout rate*: 0/ 100, 0%

	TXA, IV 3 doses postop *Age (years) (mean SD)*: 71.3 (4.7) *Ethnicity*: Not reported *Gender (males, females)*: 17 M (17%), 83 F (83%) *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n, %)*: Not reported *Incidence of preoperative anaemia*: These patients were excluded *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 100 *Number of participants receiving treatment*: 100 *Number of participants analysed*: 100 *Dropout rate*: 0/ 100, 0% Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males, females)*: Not reported *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n, %)*: Not reported *Incidence of preoperative anaemia*: These patients were excluded *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 300 *Number of participants receiving treatment*: 300 *Number of participants analysed*: 300

	Dropout rate: 0/ 300, 0% **Included criteria:** (i) patients must have been diagnosed with stage III or IV KOA according to the Kellgren–Lawrence classification18; (ii) patients had undergone unilateral primary TKA by the same surgery team; (iii) patients were aged 60–80 years; **Excluded criteria:** (i) patients with other types of arthritis; (ii) flexion deformity ≥30, patients with varus/valgus deformity ≥30; (iii) patients who underwent bilateral TKA; (iv) patients with preoperative anemia (hemoglobin [Hb] < 120 g/L for women, <130 g/L for men)19, renal dysfunction, or severe cardiovascular or cerebrovascular diseases, and patients with prolonged use of oral anticoagulant drugs. **If TKR, is tourniquet used:** Yes - tourniquet time: Group A 75.1 +/- 7.4 Group B 75.5 +/- 7.3 Group C 75.1 +/- 7.3 (minutes) **Indication for surgery:** Osteoarthritis **Type of anaesthetic:** General **Type of surgery:** Unilateral primary TKA
Interventions	**Intervention Characteristics** TXA, IV 1 dose postop One dose (1 g) of IV-TXA before skin incision combined with one dose (1.5 g) of intra-articular tranexamic acid (IA-TXA) followed by a single dose of IV-TXA (1 g) for 3 h TXA, IV, 1g, pre-op + TXA, IA, 1.5g, pre-op + TXA, IV, 1g, post-op TXA, IV 2 doses postop One dose (1 g) of IV-TXA before skin incision combined with one dose (1.5 g) of intra-articular tranexamic acid (IA-TXA) followed by two doses of IV-TXA (1 g) for 3 and 6 h TXA, IV, 1g, pre-op + TXA, IA, 1.5g, pre-op + TXA, IV, 1g, repeated dose, 3hrs and 6hrs TXA, IV 3 doses postop One dose (1 g) of IV-TXA before skin incision combined with one dose (1.5 g) of intra-articular tranexamic acid (IA-TXA) followed by three doses of IV-TXA (1 g) for 3, 6, and 12 h TXA, IV, 1g, pre-op + TXA, IA, 1.5g, pre-op + TXA, IV, 1g, repeated dose, 3hrs, 6hrs and 12hrs
Outcomes	Primary outcome: Total Blood loss

	Hidden blood loss Maximum haemoglobin drop Need for blood transfusion Secondary outcome: Mean level of postoperative CRP D-dimer Complications Adverse events
Notes	**Sponsorship source:** Non-Pharmaceutical (This study was supported by the Foundation of Health and Family planning Commission of Shanghai (grant no. ZY (2018-2020)-FWTX-6023). **Country:** China **Setting:** single-centre **Comments:** None **Authors name:** B-X Kang **Institution:** Shanghai Guanghua Hospital of Integrated Traditional Chinese and Western Medicine **Email:** Lian-bo Xiao: xiao_lianbo@163.com; Xiao-xue Hu: ghyyxiaoxue@163.com **Address:** Department of Orthopaedics, Guanghua Hospital Shanghai University of Traditional Chinese Medicine, No. 540 Xinhua Road, Changning District, Shanghai, **Native language of paper:** English **Reference type:** Full text (1), study protocol (1), trial registration (1) **Trial registration number:** ChiCTR1900022737 **Was it translated for this review:** No

B.1.4.46 Karnezis 1994

Methods	**Study design:** RCT **Intention to treat analysis:** Unclear **Length of duration of study:** 18+ months **Power calculation reached:** Not reported **Transfusion strategy:** Homologous blood was used when reinfusion of autologous blood was completed and when haematocrit levels were less than 22 to 24 per cent.

	Was the trial stopped early: No
Participants	**Baseline Characteristics** Placebo *Age (years) (mean SD)*: 66 (9.3) *Ethnicity*: Not reported *Gender (males, females)*: 9, 10 *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Mean ASA (SD): 2.1 (0.2) *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 19 *Number of participants receiving treatment*: 19 *Number of participants analysed*: 19 *Dropout rate*: 0/19 (0%) Desmopressin *Age (years) (mean SD)*: 65 (5.3) *Ethnicity*: Not reported *Gender (males, females)*: 7, 10 *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities* : Mean ASA (SD): 2.1 (0.5) *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 17 *Number of participants receiving treatment*: 17

	Number of participants analysed: 17 *Dropout rate*: 0/17 (0%) Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males, females)*: Not reported *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: Not reported *Number of participants receiving treatment*: Not reported *Number of participants analysed*: Not reported *Dropout rate*: Not reported **Included criteria:** 1) Scheduled for a primary total hip or total knee arthroplasty **Excluded criteria:** 1) History of operative intervention involving the hip or knee, 2) Coagulation disorder, 3) Coronary artery disease, 4) Patients who had received Coumadin (warfarin) or heparin within seven days before the operation, 5) Patients scheduled to have a bilateral total hip or knee arthroplasty or a revision operation **Pre-treatment:** No **If TKR, is tourniquet used:** Yes **Indication for surgery:** End stage degenerative osteoarthrosis or rheumatoid arthritis **Type of anaesthetic:** General anaesthesia **Type of surgery:** Primary THR and primary TKR
Interventions	**Intervention Characteristics** Placebo Approximately thirty minutes before complete closure of the wound, a single dose of 0.3 microgram per kilogram of

	body mass of desmopressin (Roren Pharmaceutical, Fort Washington, Pennsylvania) in fifty millilitres of physiological saline solution was administered intravenously over a twenty-minute period to the patients in the desmopressin group. The control group received a saline-solution placebo in the identical manner. Placebo, IV, intraop (30 mins before wound closure) Desmopressin Approximately thirty minutes before complete closure of the wound, a single dose of 0.3 microgram per kilogram of body mass of desmopressin (Roren Pharmaceutical, Fort Washington, Pennsylvania) in fifty millilitres of physiological saline solution was administered intravenously over a twenty-minute period to the patients in the desmopressin group. The control group received a saline-solution placebo in the identical manner. Desmopressin, IV, 0.3mcg/kg, intraop (30 mins before wound closure)
Outcomes	Primary outcome: Postoperative bleeding Postoperative transfusion requirements Secondary outcome: Not reported
Notes	**Sponsorship source:** None **Country:** USA **Setting:** Single-centre **Comments:** None **Authors name:** T.A. Karnezis **Institution:** University of Chicago **Email:** Not reported **Address:** Department of Orthopaedic Surgery, North-western University 303 East Chicago Avenue, Room 9-037, Chicago, Illinois 60611-3008. **Native language of paper:** English **Reference type:** Full Text (1) **Trial registration number:** Not applicable, but when checked trial registration number not found **Was it translated for this review:** No

B.1.4.47 Karnezis 1994a

Methods	**Study design:** RCT **Intention to treat analysis:** Unclear **Length of duration of study:** 18 months **Power calculation reached:** Not reported **Transfusion strategy:** Homologous blood was used when reinfusion of autologous blood was completed and when haematocrit levels were less than 22 to 24 per cent. **Was the trial stopped early:** No
Participants	**Baseline Characteristics** Placebo *Age (years) (mean SD)*: 67 (6.7) *Ethnicity*: Not reported *Gender (males, females)*: 14, 16 *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Mean ASA (SD): 1.9 (0.5) *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 30 *Number of participants receiving treatment*: 30 *Number of participants analysed*: 30 *Dropout rate*: 0/30 (0%) Desmopressin *Age (years) (mean SD)*: 65 (7.8) *Ethnicity*: Not reported *Gender (males, females)*: 12, 14 *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n, %)*: Not reported

	Incidence of preoperative anaemia: Not reported *Co-morbidities*: Mean ASA (SD): 1.9 (0.3) *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 26 *Number of participants receiving treatment*: 26 *Number of participants analysed*: 26 *Dropout rate*: 0/26 (0%) Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males, females)*: Not reported *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: Not reported *Number of participants receiving treatment*: Not reported *Number of participants analysed*: Not reported *Dropout rate*: Not reported **Included criteria:** 1) Scheduled for a primary total hip or total knee arthroplasty **Excluded criteria:** 1) History of operative intervention involving the hip or knee, 2) Coagulation disorder, 3) Coronary artery disease, 4) Patients who had received Coumadin (warfarin) or heparin within seven days before the operation, 5) Patients scheduled to have a bilateral total hip or knee arthroplasty or a revision operation **Pre-treatment:** No

	If TKR, is tourniquet used: Not applicable **Indication for surgery:** End stage degenerative osteoarthrosis or rheumatoid arthritis **Type of anaesthetic:** General anaesthetic **Type of surgery:** Primary THR and primary TKR
Interventions	**Intervention Characteristics** Placebo Approximately thirty minutes before complete closure of the wound, a single dose of 0.3 microgram per kilogram of body mass of desmopressin (Roren Pharmaceutical, Fort Washington, Pennsylvania) in fifty millilitres of physiological saline solution was administered intravenously over a twenty-minute period to the patients in the desmopressin group. The control group received a saline-solution placebo in the identical manner. Placebo, IV, intraop (30 mins before wound closure) Desmopressin Approximately thirty minutes before complete closure of the wound, a single dose of 0.3 microgram per kilogram of body mass of desmopressin (Roren Pharmaceutical, Fort Washington, Pennsylvania) in fifty millilitres of physiological saline solution was administered intravenously over a twenty-minute period to the patients in the desmopressin group. The control group received a saline-solution placebo in the identical manner. Desmopressin, IV, 0.3mcg/kg, intraop (30 mins before wound closure)
Outcomes	Primary outcome: Postoperative bleeding Postoperative transfusion requirements Secondary outcome: Not reported
Notes	**Sponsorship source:** None **Country:** USA **Setting:** single-centre **Comments:** None **Authors name:** T.A. Karnezis **Institution:** University of Chicago

	Email: Not reported **Address:** Department of Orthopaedic Surgery, Northwestern University 303 East Chicago Avenue, Room 9-037, Chicago, Illinois 60611-3008. **Native language of paper:** English **Reference type:** Full Text (1) **Trial registration number:** Not applicable, but when checked trial registration number not found **Was it translated for this review:** No

B.1.4.48 Kayupov 2017

Methods	**Study design:** RCT **Intention to treat analysis:** Per protocol **Length of duration of study:** 6 months **Power calculation reached:** Yes **Transfusion strategy:** The transfusion protocol for the study participants was planned for a hemoglobin level of less than 7.0 g/dL. If a transfusion was to be given at a hemoglobin level higher than 7.0 g/dL, it would only be performed secondary to a specific patient history (i.e., cardiac disease) under the request of an internal medicine physician. **Was the trial stopped early:** No
Participants	**Baseline Characteristics** TXA, IV *Age (years) (mean SD)*: 63 (10) *Ethnicity*: Not reported *Gender (males, female)*: 11, 26 *Length of surgery (minutes) (mean SD)*: 90 (19) *Proportion of participants on anticoagulants prior to surgery (n, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: 1/ 37 (2.7%) *ASA 2 (n/ N,%)*: 27/ 37 (73.0%) *ASA 3 (n/ N,%)*: 9/ 37 (24.3%) *ASA 4 (n/ N,%)*: 0/ 37 (0%)

	Number of participants randomised: 38 *Number of participants receiving treatment*: 37 *Number of participants analysed*: 37 *Dropout rate*: 1/ 37 (2.7%) TXA, oral *Age (years) (mean SD)*: 62 (11) *Ethnicity*: Not reported *Gender (males, female)*: 13, 21 *Length of surgery (minutes) (mean SD)*: 82 (14) *Proportion of participants on anticoagulants prior to surgery? (n, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: 1/ 34 (2.9%) *ASA 2 (n/ N,%)*: 25/ 32 (78.1%) *ASA 3 (n/ N,%)*: 8/ 34 (23.5%) *ASA 4 (n/ N,%)*: 0/ 34 (0%) *Number of participants randomised*: 40 *Number of participants receiving treatment*: 34 *Number of participants analysed*: 34 *Dropout rate*: 6/ 40 (15%) Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males, female)*: Not reported *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: Not reported *Number of participants receiving treatment*: Not reported

	Number of participants analysed: Not reported *Dropout rate*: Not reported **Included criteria:** 1) Patients scheduled to undergo unilateral primary TKA **Excluded criteria:** 1) Known allergy to TXA, 2) History of renal failure or kidney transplant, 3) A history of arterial thromboembolic event (e.g. myocardial infarction, stroke) within the past year, 4) Placement of an arterial stent within the past year, 5) History of thromboembolic event, or refusal to receive blood products **Pre-treatment:** No **If TKR, is tourniquet used:** Yes **Indication for surgery:** Not reported **Type of anaesthetic:** Mixed spinal and general anaesthesia **Type of surgery:** Primary TKR
Interventions	**Intervention Characteristics** TXA, IV Patients in the intravenous tranexamic acid group received the standard dosing for our institution of 1 g of tranexamic acid in 10 mL of normal saline solution given as an intravenous bolus immediately prior to incision along with a total dose of 750 mg of ascorbic acid in the form of three 250-mg tablets as a placebo 2 hours prior to the incision TXA, IV, 1g, intraop (prior to skin incision) AND Placebo, oral, preop (2 hours prior to incision) TXA, oral Patients randomized to the oral tranexamic acid group were administered a total oral dose of 1,950 mg of tranexamic acid using 3 tablets of 650 mg approximately 2 hours prior to incision and a placebo dose of 10 mL of normal saline solution immediately prior to incision Placebo, IV, intraop (prior to skin incision) AND TXA, 1.95mg, oral, preop (2 hours prior to incision)
Outcomes	*Primary outcomes:* Reduction of hemoglobin concentration *Secondary outcomes:* Postoperative calculated blood loss postoperative calculated hemoglobin loss

	transfusion rate number of blood units transfused length of hospital stay incidence of thromboembolic events
Notes	**Sponsorship source:** Non-pharmaceutical **Country:** USA **Setting:** Single-centre **Comments:** None **Authors name:** YA Fillingham **Institution:** Rush University Medical Center **Email:** Not reported **Address:** Department of Orthopaedic Surgery, Rush University Medical Center, Chicago, Illinois **Native language of paper:** English **Reference type:** Full Text (1) Trial registration (1) **Trial registration number:** NCT02233101 **Was it translated for this review:** No

B.1.4.49 Kayupov 2017a

Methods	**Study design:** RCT **Intention to treat analysis:** Per-protocol **Length of duration of study:** 10 **Power calculation reached:** Yes **Transfusion strategy:** Transfusions were administered if the hemoglobin level was <7.0 g/dL or if it was deemed necessary by an internal medicine physician secondary to patient-specific medical comorbidities or symptoms. **Was the trial stopped early:** No
Participants	**Baseline Characteristics** TXA, IV *Age (years) (mean SD)*: 55 (12) *Ethnicity*: Not reported *Gender (males, females)*: 22, 21 *Length of surgery (minutes) (mean SD)*: 67 (12)

	Proportion of participants on anticoagulants prior to surgery (n, %): Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: 4/ 43 (9.3%) *ASA 2 (n/ N,%)*: 32/ 43 (74.2%) *ASA 3 (n/ N,%)*: 7/ 43 (16.3) *ASA 4 (n/ N,%)*: 0/ 43 (0%) *Number of participants randomised*: 43 *Number of participants receiving treatment*: 43 *Number of participants analysed*: 43 *Dropout rate*: 0/ 43 (0%) TXA, Oral *Age (years) (mean SD)*: 60 (10) *Ethnicity*: Not reported *Gender (males, females)*: 20, 20 *Length of surgery (minutes) (mean SD)*: 70 (16) *Proportion of participants on anticoagulants prior to surgery (n, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: 2/ 40 (5%) *ASA 2 (n/ N,%)*: 31/ 40 (77.5%) *ASA 3 (n/ N,%)*: 7/ 40 (17.5%) *ASA 4 (n/ N,%)*: 0/ 40 (0%) *Number of participants randomised*: 46 *Number of participants receiving treatment*: 40 *Number of participants analysed*: 40 *Dropout rate*: 6/46 (13%) Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males, females)*: Not reported *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to*

	surgery (n, %): Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: Not reported *Number of participants receiving treatment*: Not reported *Number of participants analysed*: Not reported *Dropout rate*: Not reported **Included criteria:** 1) Patients scheduled to undergo cement less primary unilateral total hip replacement **Excluded criteria:** 1) History of renal failure, 2) Kidney transplant, 3) History of an arterial thromboembolic event such as myocardial infarction or stroke within the past year, 4) Placement of an arterial stent within the past year, 5) Any history of deep venous thrombosis or pulmonary embolism, 6) declined to participate or to consent to receive blood products **Pre-treatment:** No **If TKR, is tourniquet used:** Not applicable **Indication for surgery:** Not reported **Type of anaesthetic:** Combined spinal-epidural anaesthesia **Type of surgery:** Primary THR
Interventions	**Intervention Characteristics** TXA, IV Patients in the intravenous tranexamic acid group received the standard dosing for our institution of 1 g of tranexamic acid in 10 mL of normal saline solution given as an intravenous bolus immediately prior to incision along with a total dose of 750 mg of ascorbic acid in the form of three 250-mg tablets as a placebo 2 hours prior to the incision TXA, IV, 1g, intraop (prior to skin incision) AND Placebo, oral, preop (2 hours prior to incision) TXA, oral Patients randomized to the oral tranexamic acid group were administered a total oral dose of 1,950 mg of tranexamic acid using 3 tablets of 650 mg approximately 2

	hours prior to incision and a placebo dose of 10 mL of normal saline solution immediately prior to incision Placebo, IV, intraop (prior to skin incision) AND TXA, 1.95mg, oral, preop (2 hours prior to incision)
Outcomes	*Primary outcomes:* Reduction of hemoglobin concentration *Secondary outcomes:* Postoperative calculated blood loss postoperative calculated hemoglobin loss transfusion rate number of blood units transfused length of hospital stay incidence of thromboembolic events
Notes	**Sponsorship source:** None **Country:** USA **Setting:** Not reported **Comments:** Mean units and SD calculated from paper. **Authors name:** E. Kayupov **Institution:** Rush University Medical Center **Email:** craigdv@rushortho.com **Address:** Rush University Medical Center, Chicago, Illinois **Native language of paper:** English **Reference type:** Full Text (1) Trial registration (1) **Trial registration number:** NCT02233101 **Was it translated for this review:** No

B.1.4.50 King 2019

Methods	**Study design:** RCT **Intention to treat analysis:** Per protocol **Length of duration of study:** 13 months (August 2017 to September 2018) + 6 weeks (follow-up) = 14.5 months **Power calculation reached:** Yes **Transfusion strategy:** Blood transfusion was performed on all patients with a haemoglobin below 80 g/L or at higher haemoglobin levels dependent on patient specific

	indications as outlined by the National Blood Authority of Australia **Was the trial stopped early:** No
Participants	**Baseline Characteristics** TXA, Oral *Age (years) (mean SD)*: 65.4 (8.8) *Ethnicity*: Not reported *Gender (males, females)*: 14 M (56.0%), 11 F (44%) *Length of surgery (minutes)*: 138.2 (20.8) *Proportion of participants on anticoagulants prior to surgery (n, %)*: use of anticoagulants or antithrombotic within 7 days of surgery *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: BMI 30.1 (4.8) *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 31 *Number of participants receiving treatment*: 28 *Number of participants analysed*: 25 *Dropout rate*: 6/ 31, 19.4% TXA, Combined topical/IV/oral *Age (years) (mean SD)*: 63.8 (9.7) *Ethnicity*: Not reported *Gender (males, females)*: 12 M (42.9%), 16 F (57.1%) *Length of surgery (minutes)*: 140.5 (21.4) *Proportion of participants on anticoagulants prior to surgery (n, %)*: use of anticoagulants or antithrombotic within 7 days of surgery *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: BMI 30.2 (4.6) *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported

	ASA 4 (n/ N,%): Not reported *Number of participants randomised*: 33 *Number of participants receiving treatment*: 28 *Number of participants analysed*: 28 *Dropout rate*: 5/ 33, 15.2% Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males, females)*: 26 M, 27F *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n, %)*: use of anticoagulants or antithrombotic within 7 days of surgery *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 64 *Number of participants receiving treatment*: 56 *Number of participants analysed*: 53 *Dropout rate*: 11/ 64, 17.2% **Included criteria:** Patients scheduled for TKA by the collaborating orthopaedic surgeon during the trial period. All participants were required to be over the age of 18 and able to provide informed consent prior to surgery. **Excluded criteria:** Bilateral TKA, allergy to TXA, history of bleeding disorders, use of anticoagulants or antithrombotic within 7 days of surgery, inability to take apixaban as post-surgical venous thromboembolism (VTE) prophylaxis, and the presence of contraindications to the use of TXA. **Pre-treatment:** No **If TKR, is tourniquet used:** No **Indication for surgery:** Not reported **Type of anaesthetic:** Not reported **Type of surgery:** Primary TKA

Interventions	**Intervention Characteristics** TXA, Oral The study group received an oral 1 g dose two hours prior to the commencement of surgery, a second 1 g oral dose two hours post-surgery and a final 1 g oral dose six hours post-surgery TXA, Oral, 1g, preop + 1g, 2hrs post-op + 1g, 6hrs post-op TXA, Combined topical/IV/oral The control group received a 3 g topical application of TXA perioperatively, a 1 g IV dose TXA dose at two hours post-surgery and a final 1 g oral dose six hours post-surgery. TXA, IA, 3g, intraop + TXA, IV, 1g, 2hrs, post-op + TXA, Oral, 1g, 6hrs post-op
Outcomes	Primary outcome: Hb levels Blood loss Incidence of DVT Secondary outcome: Adverse events Blood transfusion
Notes	**Sponsorship source:** Non-pharmaceutical (Funding for this study was provided by John Flynn Private Hospital and the Quality Use of Medicines Network, Griffith University.) **Country:** Australia **Setting:** Not reported **Comments:** None **Authors name:** L. King **Institution:** John Flynn Hospital **Email:** n.bernaitis@griffith.edu.au **Address:** School of Pharmacy & Pharmacology, Gold Coast Campus, Griffith University, QLD 4222, Australia **Native language of paper:** English **Reference type:** Full text (1) **Trial registration number:** ACTRN12617000617369 **Was it translated for this review:** No

B.1.4.51 Langdown 2000

Methods	**Study design:** RCT **Intention to treat analysis:** Not reported **Length of duration of study:** Not reported **Power calculation reached:** Not reported **Transfusion strategy:** Not reported **Was the trial stopped early:** No
Participants	**Baseline Characteristics** Placebo *Age (years) (mean SD)*: 72.8 (8.8) *Ethnicity*: Not reported *Gender (males)*: Not reported *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: Not reported *Number of participants receiving treatment*: Not reported *Number of participants analysed*: Not reported *Dropout rate*: Not reported Aprotinin *Age (years) (mean SD)*: 70.0 (9.7) *Ethnicity*: Not reported *Gender (males)*: Not reported *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported

	Co-morbidities: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: Not reported *Number of participants receiving treatment*: Not reported *Number of participants analysed*: Not reported *Dropout rate*: Not reported Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males)*: Not reported *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery? (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 60 *Number of participants receiving treatment*: Not reported *Number of participants analysed*: Not reported *Dropout rate*: Not reported **Included criteria:** Patients with a diagnosis of primary osteoarthritis of the hip necessitating THA **Excluded criteria:** Not reported **Pre-treatment:** Age only reported **If TKR, is tourniquet used:** Not applicable **Indication for surgery:** Primary osteoarthritis of the hip **Type of anaesthetic:** Spinal **Type of surgery:** Primary THR

Interventions	**Intervention Characteristics** Placebo 1.5 x 106 KIU (Kallikrein inactivation units) of intravenous aprotinin or a similar volume of normal saline as a placebo as a bolus at the time of anaesthesia. Placebo saline mls, IV, preop Aprotinin 1.5 x 106 KIU (Kallikrein inactivation units) of intravenous aprotinin or a similar volume of normal saline as a placebo as a bolus at the time of anaesthesia. Aprotinin, IV, 1.5 x 10^6 KIU, preop
Outcomes	Primary outcome: Total blood loss Postoperative hemoglobin Transfusion requirement Secondary outcome: Not reported
Notes	**Sponsorship source:** None **Country:** UK **Setting:** Not reported **Comments:** None **Authors name:** A.J. Langdown **Institution:** John Radcliffe Hospital **Email:** Not reported **Address:** 83 Naunton Crescent, Leckhampton, Cheltenham, GL53 7BE UK **Native language of paper:** English **Reference type:** Full text (1) **Trial registration number:** Not applicable, but when checked trial registration number not found **Was it translated for this review:** No

B.1.4.52 Lei 2017 knees

Methods	**Study design:** RCT **Intention to treat analysis:** Yes

	Length of duration of study: 4.5 months (4 months + 2 weeks FU) **Power calculation reached:** Yes **Transfusion strategy:** According to the guidelines by the National Ministry of Health, patients were transfused only when the post-operative hemoglobin (Hb) level was less than 70 g/L or 70 to 100 g/L with symptoms related to anemia develop, such as light-headedness, palpitation, tachypnoea, or decreased exercise tolerance. **Was the trial stopped early:** No
Participants	**Baseline Characteristics** TXA, IV pre-op + TXA, IV 3 and 6hrs post-op *Age (years) (mean SD)*: 63.6 (7.6) *Ethnicity*: Not reported *Gender (males, females)*: 10 M, 43 F *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: 0/53 (0%) *Co-morbidities (n/ N, %)*: Hypertension 32/53 (60.3%), Diabetes 6/53 (11.3%) *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 53 *Number of participants receiving treatment*: 53 *Number of participants analysed*: 53 *Dropout rate*: 0/53 (0%) TXA, IV pre-op + TXA, IV 3, 6 and 9hrs post-op *Age (years) (mean SD)*: 66.4 (8.4) *Ethnicity*: Not reported *Gender (males, females)*: 7 M, 42 F *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: 0/49 (0%)

	Co-morbidities (n/ N, %): Hypertension 29/49 (59.1%), Diabetes 6/49 (12.2%) *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 49 *Number of participants receiving treatment*: 49 *Number of participants analysed*: 49 *Dropout rate*: 0/49 (0%) TXA, IV pre-op + TXA, IV 9 and 12hrs post-op *Age (years) (mean SD)*: 65.6 (8.4) *Ethnicity*: Not reported *Gender (males, females)*: 10 M, 47 F *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: 0/57 (0%) *Co-morbidities (n/ N, %)*: Hypertension 36/57 (63.2%), Diabetes 12/49 (24.4%) *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 57 *Number of participants receiving treatment*: 57 *Number of participants analysed*: 57 *Dropout rate*: 0/57 (0%) Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males)*: Not reported *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported

	Incidence of preoperative anaemia: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 159 *Number of participants receiving treatment*: 159 *Number of participants analysed*: 159 *Dropout rate*: 0/ 159 (0%) **Included criteria:** 1) Scheduled to have primary unilateral TKA for osteoarthritis or rheumatoid arthritis 2) Aged 18 years or older **Excluded criteria:** 1) Revisions 2) Bilateral procedures 3) Flexion deformity ≥30°, Varus/valgus deformity ≥ 30° 4) Patients with anaemia (<120 g/L for female, <130 g/L for male) 5) Pre-operative hepatic or renal dysfunction 6) Serious cardiac or cerebrovascular problems 7) Previous history of deep venous thrombosis or pulmonary embolism 8) Congenital or acquired clotting disorders 9) Contraindications for the use of TXA **Pre-treatment:** No **If TKR, is tourniquet used:** No **Indication for surgery:** Osteoarthritis or rheumatoid arthritis **Type of anaesthetic:** General anaesthesia **Type of surgery:** Primary TKR
Interventions	**Intervention Characteristics** TXA, IV pre-op + TXA, IV 3 and 6hrs post-op Group A: the patients received one bolus of 20 mg/kg IV-TXA prior to skin incision, two boluses of 10 mg/kg IV-TXA three and six hours later, and 10 mg/kg of normal saline was intravenously injected nine and 12 hours later TXA, IV, 20mg/kg, intraop (prior to skin incision) AND TXA, IV, 10mg/kg, intra/postop 3+6 hours after 1st dose + Placebo, IV, postop 9+12 hours after 1st dose TXA, IV pre-op + TXA, IV 3, 6 and 9hrs post-op Group B: a single bolus of 20 mg/kg IV-TXA was administered before skin incision, 10 mg/kg of TXA was administered three, six and nine hours later, and another

	10 mg/kg of normal saline was administered 12 hours later TXA, IV, 20mg/kg, intraop (prior to skin incision) AND TXA, IV, 10mg/kg, intra/postop 3+6+9 hours after 1st dose + Placebo, IV, postop 12 hours after 1st dose TXA, IV pre-op + TXA, IV 9 and 12hrs post-op Group C: a dosage of 20 mg/kg IV-TXA was administered before skin incision, and 10 mg/kg of TXA was administered three, six, nine, and 12 hours later. TXA, IV, 20mg/kg, intraop (prior to skin incision) AND TXA, IV, 10mg/kg, intra/postop 3+6+9+12 hours after 1st dose
Outcomes	Primary outcome: Hidden blood loss Secondary outcome: Hb decline Fibrinolysis parameters [fibrinogen degradation products (FDP), D-dimer] Inflammatory factors [interleukin-6 (IL-6) Knee Range of motion Length of hospital stay Complications
Notes	**Sponsorship source:** Non-pharmaceutical **Country:** China **Setting:** Single-centre **Comments:** None **Authors name:** Y. Lei **Institution:** Sichuan University **Email:** peifux@126.com **Address:** Department of Orthopaedics, West China Hospital, Sichuan University, 37# Wainan Guoxue Road, Chengdu 610041, People's Republic of China **Native language of paper:** English **Reference type:** Full Text (1) Trial Registration (1) **Trial registration number:** ChiCTR-INR-16009288 **Was it translated for this review:** No

B.1.4.53 Lei 2018 hips

Methods	**Study design:** RCT **Intention to treat analysis:** Yes **Length of duration of study:** 8 months (5 + 3 months FU) **Power calculation reached:** Yes **Transfusion strategy:** Patients were transfused according to the guidelines by the National Ministry of Health, and either of the following leads to consideration of transfusion: patient has a hemoglobin (Hb) level of 70 g/L or less or patient has a Hb level between 70 g/L and 100 g/L with symptoms related to anemia develop, such as dizziness, cardiopalmus, tachypnoea, or decreased exercise tolerance. **Was the trial stopped early:** No
Participants	**Baseline Characteristics** TXA, IV, pre-op + 2 doses TXA, IV post-op *Age (years) (mean SD)*: 54.3 (12.6) *Ethnicity*: Not reported *Gender (males, females)*: 19 M, 31 F *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: 0/50 (0%) *Incidence of preoperative anaemia (n/ N, %)*: Not reported *Co-morbidities (n/ N, %)*: Hypertension 15/50 (30%) *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 50 *Number of participants receiving treatment*: 50 *Number of participants analysed*: 50 *Dropout rate*: 0/ 50, (0%) TXA, IV, pre-op + 3 doses TXA, IV post-op *Age (years) (mean SD)*: 50.0 (12.2) *Ethnicity*: Not reported *Gender (males, females)*: 22 M, 28 F

	Length of surgery (minutes): Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: 0/50 (0%) *Incidence of preoperative anaemia (n/ N, %)*: Not reported *Co-morbidities (n/ N, %)*: Hypertension 9/50 (18%) *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 50 *Number of participants receiving treatment*: 50 *Number of participants analysed*: 50 *Dropout rate*: 0/ 50 (0%) TXA, IV, pre-op + 4 doses TXA, IV post-op *Age (years) (mean SD)*: 53.2 (13.0) *Ethnicity*: Not reported *Gender (males, females)*: 20 M, 30 F *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: 0/50 (0%) *Incidence of preoperative anaemia (n/N, %)*: Not reported *Co-morbidities (n/ N, %)*: Hypertension 9/50 (24%) *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 50 *Number of participants receiving treatment*: 50 *Number of participants analysed*: 50 *Dropout rate*: 0/ 50 (0%) Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males, females)*: Not reported *Length of surgery (minutes)*: Not reported

	Proportion of participants on anticoagulants prior to surgery (n/ N, %): Not reported *Incidence of preoperative anaemia (n/ N, %)*: Not reported *Co-morbidities (n/ N, %)*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 150 *Number of participants receiving treatment*: Not reported *Number of participants analysed*: 150 *Dropout rate*: 0/150 (0%) **Included criteria:** 1) Patients undergoing primary unilateral THA **Excluded criteria:** 1) Known allergies to TXA 2) Administration of any anti-inflammatory or antiplatelet drugs 7 days before operation 3) Previous history of deep venous thrombosis or pulmonary embolism, clotting disorders, cardiac or cerebrovascular problem (history of myocardial infarction, angina, atrial fibrillation, or previous stroke) 4) Kidney or liver failure **Pre-treatment:** No **If TKR, is tourniquet used:** Not applicable **Indication for surgery:** Osteoarthritis secondary to developmental dysplasia of the hip, Osteonecrosis of the femoral head, Osteoarthritis **Type of anaesthetic:** General anaesthesia **Type of surgery:** Primary THR
Interventions	**Intervention Characteristics** TXA, IV, pre-op + 2 doses TXA, IV post-op To each patient of all groups, one dose of 20 mg/kg intravenous (IV)-TXA was given prior to skin incision, with 2 doses of 1-g (100-mL) IV-TXA given 3 and 6 hours later. Group A served as the control group and received another 2 doses of 100-mL normal saline 9 and 12 hours after the first dose; Group B received one 1-g dose of IV-TXA 9 hours later and one 100- mL dose of normal saline 12 hours later; and group C received another 2 doses of 1-g IV-TXA 9 and 12 hours after the first dose. The patients, attending surgeons, data controller, and analyst were blinded to interventions.

	TXA, IV, 20mg/kg preop AND TXA, IV, 1g, post-op 3 + 6 hours after 1st dose AND Placebo, IV, postop 9 + 12 hours TXA, IV, pre-op + 3 doses TXA, IV post-op Group B received one 1-g dose of IV-TXA 9 hours later and one 100-mL dose of normal saline 12 hours later; TXA, IV, 20mg/kg preop AND TXA, IV, 1g, post-op 3 + 6 + 9 hours after 1st dose AND Placebo, IV, postop 12 hours TXA, IV, pre-op + 4 doses TXA, IV post-op Group C received another 2 doses of 1-g IV-TXA 9 and 12 hours after the first dose. TXA, IV, 20mg/kg preop AND TXA, IV, 1g, post-op 3 + 6 + 9 + 12 hours after 1st dose
Outcomes	Primary outcome: Hidden blood loss Secondary outcome: Total blood loss Maximum hemoglobin (Hb) drop Transfusion rate Length of hospital stay Complications
Notes	**Sponsorship source:** Not reported **Country:** China **Setting:** single-centre **Comments:** None **Authors name:** Y. Lei **Institution:** Sichuan University **Email:** Not reported **Address:** Department of Orthopaedics, West China Hospital, Sichuan University, 37# Wainan Guoxue Road, Chengdu 610041, People's Republic of China. **Native language of paper:** English **Reference type:** Full Text (1) Trial Registration (1) **Trial registration number:** ChiCTR-INR-16009288 **Was it translated for this review:** No

B.1.4.54 Lei 2020

Methods	**Study design:** RCT **Intention to treat analysis:** Yes **Length of duration of study:** 8 months (May 2017 to January 2018) + 3 months (follow-up) = 11 months **Power calculation reached:** Yes **Transfusion strategy:** Decisions to transfuse were made based on the guidelines by the National Ministry of Health: (1) patient has a hemoglobin (Hb) level of 70 g/L or less; (2) patients whose Hb level was between 70 g/L and 100 g/L but who had symptoms related to anemia develop, such as dizziness, increased heart rates, tachypnoea, or decreased exercise tolerance. **Was the trial stopped early:** No
Participants	**Baseline Characteristics** TXA, IV 20mg + 3 x TXA, IV 1g *Age (years) (mean SD)*: 66.2 (8.3) *Ethnicity*: Not reported *Gender (males, females)*: 7/ 50 M (14%), 43/ 50 F (86%) *Length of surgery (minutes)*: 72.4 (11.1) *Proportion of participants on anticoagulants prior to surgery (n, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Hypertension: 30/ 50 *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 50 *Number of participants receiving treatment*: Not reported *Number of participants analysed*: 50 *Dropout rate*: 0/ 50, 0% TXA, IV 20mg + 4 x TXA, IV 1g *Age (years) (mean SD)*: 66.9 (7.9) *Ethnicity*: Not reported *Gender (males, females)*: 9/ 50 M (18%), 41/ 50 F (82%)

	Length of surgery (minutes): 71.8 (10.4) *Proportion of participants on anticoagulants prior to surgery (n, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Hypertension: 29/ 50 *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 50 *Number of participants receiving treatment*: Not reported *Number of participants analysed*: 50 *Dropout rate*: 0/ 50, 0% TXA, IV 20mg + 5 x TXA, IV 1g *Age (years) (mean SD)*: 66.2 (7.7) *Ethnicity*: Not reported *Gender (males, females)*: 10/ 50 M (20%), 40/ 50 F (80%) *Length of surgery (minutes)*: 72.2 (11.1) *Proportion of participants on anticoagulants prior to surgery (n, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Hypertension: 31/ 50 *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 50 *Number of participants receiving treatment*: Not reported *Number of participants analysed*: 50 *Dropout rate*: 0/ 50, 0% Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males, females)*: Not reported *Length of surgery (minutes)*: Not reported

	Proportion of participants on anticoagulants prior to surgery (n, %): Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 202 *Number of participants receiving treatment*: Not reported *Number of participants analysed*: 200 *Dropout rate*: 0/ 200, 0% **Included criteria:** Patients undergoing TKA **Excluded criteria:** The exclusion criteria were cardiovascular problems or cerebrovascular conditions (history of myocardial infarction, angina, atrial fibrillation, or previous stroke), kidney or liver failure, previous history of deep venous thrombosis or pulmonary embolism, allergies to drugs used. **Pre-treatment:** No **If TKR, is tourniquet used:** The exclusion criteria were cardiovascular problems or cerebrovascular conditions (history of myocardial infarction, angina, atrial fibrillation, or previous stroke), kidney or liver failure, previous history of deep venous thrombosis or pulmonary embolism, allergies to drugs used. **Indication for surgery:** Osteoarthrosis or rheumatoid arthritis **Type of anaesthetic:** General **Type of surgery:** Unilateral TKA
Interventions	**Intervention Characteristics** TXA, IV 20mg + 3 x TXA, IV 1g Group B: the patients received one dose of 20 mg/kg IV-TXA 5 to 15 min before the skin incision, and three doses of 1-g (100-mL) IV-TXA 3, 6 and 12 h later TXA, IV, 20mg/ kg, preop + TXA, IV, 1g, 3hrs, 6hrs, 12hrs postop TXA, IV 20mg + 4 x TXA, IV 1g Group C: the patients received one dose of 20 mg/kg IV-TXA 5 to 15 min before the skin incision, and four doses of

	1-g (100-mL) IV-TXA 3, 6, 12 and 18 h later TXA, IV, 20mg/ kg, preop + TXA, IV, 1g, 3hrs, 6hrs, 12hrs, 18hrs postop TXA, IV 20mg + 5 x TXA, IV 1g Group D: the patients received one dose of 20 mg/kg IV-TXA 5 to 15 min before the skin incision, and five doses of 1-g (100-mL) IV-TXA 3, 6, 12, 18 and 24 h later TXA, IV, 20mg/ kg, preop + TXA, IV, 1g, 3hrs, 6hrs, 12hrs, 18hrs, 24hrs postop
Outcomes	Primary outcome: Hidden blood loss Secondary outcome: Allogeneic transfusion Level of inflammatory markers [C-reactive protein (CRP) and interleukin-6 (IL-6)] and fibrinolysis parameter Length of hospital stay Transfusion rate Complications
Notes	**Sponsorship source:** Non-pharmaceutical (This study was funded by the National Health and Family Planning Commission of the People's Republic of China (CN) program (201302007).) **Country:** China **Setting:** Single-centre **Comments:** 1. It is unclear as to what Group A (control) were treated with, therefore this group was not used **Authors name:** Y. Lei **Institution:** The First Affiliated Hospital of Chongqing Medical University **Email:** Wei Huang: huangw511@163.com **Address:** Department of Orthopedics, The First Affiliated Hospital of Chongqing Medical University, Chongqing 400016, People's Republic of China **Native language of paper:** English **Reference type:** Full text (1), trial registration (1) **Trial registration number:** ChiCTR-INR-16009288 **Was it translated for this review:** No

B.1.4.55 Lemay 2004

Methods	**Study design:** RCT **Intention to treat analysis:** Yes **Length of duration of study:** Not reported **Power calculation reached:** No **Transfusion strategy:** Before the surgery, a Hb transfusion trigger point was determined for each patient according to the following criteria: for men over 60 year, women over 65 year, and patients with a history of atherosclerotic disease, left ventricular dysfunction (ejection fraction < 35%),severe pulmonary obstructive disease (forced expiratory volume in one second < 1.5 Lmin–1), or ingestion of calcium channel blockers, the transfusion trigger was 90 g·L–1. For all other patients, the transfusion trigger was 70 g·L–1, but they could be reclassified to the higher trigger by the attending physician (anaesthesiologist or physician in charge of the postoperative period) if they had signs of hemodynamic instability (heart rate > 120 beats·min–1 or a systolic blood pressure decrease by > 20% of preoperative value) despite adequate volume replacement. **Was the trial stopped early:** No
Participants	**Baseline Characteristics** Placebo *Age (years) (mean SD)*: 53.6 (12.8) *Ethnicity*: Not reported *Gender (males, females)*: 13, 6 *Length of surgery (minutes) (mean SD)*: 101.4 (22.4) *Proportion of participants on anticoagulants prior to surgery (n, %)*: Not reported *Incidence of preoperative anaemia (n/ N, %)*: 0/19 (0%) *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: 9/19 (47.4%) *ASA 2 (n/ N,%)*: 10/19 (52.6%) *ASA 3 (n/ N,%)*: 0/19 (0%) *ASA 4 (n/ N,%)*: 0/19 (0%) *Number of participants randomised*: 20 *Number of participants receiving treatment*: Not reported *Number of participants analysed*: 19

	Dropout rate: 1/20 (5%) TXA *Age (years) (mean SD)*: 59.7 (10.3) *Ethnicity*: Not reported *Gender (males, females)*: 12, 8 *Length of surgery (minutes) (mean SD)*: 106.6 (26.4) *Proportion of participants on anticoagulants prior to surgery (n, %)*: Not reported *Incidence of preoperative anaemia (n/ N, %)*: 0/20 (0%) *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: 6/20 (30%) *ASA 2 (n/ N,%)*: 12/20 (60%) *ASA 3 (n/ N,%)*: 2/20 (10%) *ASA 4 (n/ N,%)*: 0/20 (0%) *Number of participants randomised*: 20 *Number of participants receiving treatment*: 20 *Number of participants analysed*: 20 *Dropout rate*: 0/20 (0%) Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males, females)*: Not reported *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n, %)*: Not reported *Incidence of preoperative anaemia (n/ N, %)*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: Not reported *Number of participants receiving treatment*: Not reported *Number of participants analysed*: Not reported *Dropout rate*: Not reported

	Included criteria: 1) Patients were eligible for this study if they were ASA class I to III, 2) Undergoing primary THR **Excluded criteria:** 1) History of previous ipsilateral hip surgery, 2) Known or suspected allergy to medications used (TA, local anaesthetics, midazolam, fentanyl, propofol, or dalteparin), 3) Anemia [hemoglobin (Hb) <115 g·L–1 for women, Hb < 130 g·L–1 for men], 4) Inherited or acquired haemostatic diseases, 5) Abnormal coagulation screening tests (platelet count, prothrombin time, activated partial thromboplastin time), 6) Ingestion of aspirin or other nonsteroidal anti-inflammatory drugs within seven days of surgery, 7) Renal (serum creatinine > two standard deviation for age) or hepatic insufficiency, 8) Pregnancy, 9) History of deep venous thrombosis (DVT) or pulmonary embolism, 10) History of ocular pathology or ophthalmological procedure other than corrective lenses **Pre-treatment:** No **If TKR, is tourniquet used:** Not applicable **Indication for surgery:** Not reported **Type of anaesthetic:** Spinal anaesthetic **Type of surgery:** Primary THR
Interventions	**Intervention Characteristics** Placebo Patients in Group P received an equivalent volume of physiologic saline. Placebo, IV, preop (immediately before surgery) AND Placebo, IV, intraop infusion until skin closure TXA In Group TXA, TXA was given immediately before the surgery. After a test dose of 1 mL, patients received a dose of 10 mg·kg–1 iv followed by an infusion of 1 mg·kg–1·hr–1 until skin closure. Patients in Group P received an equivalent volume of physiologic saline. TXA, IV, 10mg/kg, preop (immediately before surgery) AND TXA, IV, 10mg/kg, intraop infusion until skin closure
Outcomes	Primary outcome: Intraoperative and total blood losses Transfusion requirements Secondary outcome: Not reported

Notes	**Sponsorship source:** Non-pharmaceutical **Country:** Canada **Setting:** Not reported **Comments:** Number of units transfused reported includes autologous pre-donated blood transfusion units. As such, no results extracted. **Authors name:** J.Guay **Institution:** Hôpital Maisonneuve-Rosemont **Email:** joanne.guay@umontreal.ca **Address:** Département d'anesthésie-réanimation, Hôpital Maisonneuve-Rosemont, 5415, boul. l'Assomption, Montréal, Québec H1T 2M4, Canada **Native language of paper:** English **Reference type:** Full text (1) **Trial registration number:** Not applicable, but when checked trial registration number not found **Was it translated for this review:** No

B.1.4.56 Levine 2014

Methods	**Study design:** RCT **Intention to treat analysis:** Yes **Length of duration of study:** Not reported (Routine clinical follow-up occurred at 2, 6 and 12 weeks after surgery with radiographic analysis being performed at 6 weeks). **Power calculation reached:** No **Transfusion strategy:** Not reported **Was the trial stopped early:** No
Participants	**Baseline Characteristics** TXA, IV, Uniform dose *Age (years) (mean SD)*: 62.26 (7.31) *Ethnicity*: Not reported *Gender (males, females)*: 7, 13 *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported

	Incidence of preoperative anaemia: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 20 *Number of participants receiving treatment*: 20 *Number of participants analysed*: 20 *Dropout rate*: 0, 0% TXA, IV, Weighted dose *Age (years) (mean SD)*: 66.50 (9.65) *Ethnicity*: Not reported *Gender (males, females)*: 8, 12 *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery? (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 20 *Number of participants receiving treatment*: 20 *Number of participants analysed*: 20 *Dropout rate*: 0, 0% Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males, females)*: Not reported *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery? (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported

	Co-morbidities: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Mean ASA only reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: Not reported *Number of participants receiving treatment*: Not reported *Number of participants analysed*: Not reported *Dropout rate*: Not reported **Included criteria:** 1) Consecutive patients that were candidates for TKA **Excluded criteria:** 1) Age less than 18, age greater than 85, 2) Prior history of an open surgical procedure on the operative knee, 3) Significant cardiac disease, 4) History of a previous venothromboembolic (VTE) event **Pre-treatment:** No **If TKR, is tourniquet used:** Yes **Indication for surgery:** Osteoarthritis **Type of anaesthetic:** Not reported **Type of surgery:** Primary TKR
Interventions	**Intervention Characteristics** TXA, IV, Uniform dose We therefore elected to compare two of the more common regimens in the literature, a uniform 1 g dose versus a weighted, 20 mg/kg dose. For both groups the TA was administered as an infusion just prior to tourniquet release TXA, IV, 1g, intraop (10mins prior to tourniquet deflation) TXA, IV, Weighted dose We therefore elected to compare two of the more common regimens in the literature, a uniform 1 g dose versus a weighted, 20 mg/kg dose. For both groups the TA was administered as an infusion just prior to tourniquet release TXA, IV, 20mg.kg, intraop (10mins prior to tourniquet deflation)
Outcomes	Primary outcome: Intra-operative blood loss Post-operative drain output

	Tourniquet time Surgery time Complications Transfusion requirements Preoperative and post-operative hemoglobin and haematocrit values
Notes	**Sponsorship source:** Non-pharmaceutical **Country:** USA **Setting:** Single-centre **Comments:** Decision made to not extract from control arm as historical cohort with no placebo. **Authors name:** B.R. Levine **Institution:** Rush University Medical Centre, Chicago, Illinois **Email:** Not reported **Address:** Rush University Medical Centre, 1611 W. Harrison St, Ste 300Chicago, Illinois 60612. **Native language of paper:** English **Reference type:** Full Text (1) Trial Registration (1) **Trial registration number:** NCT01651806 **Was it translated for this review:** No

B.1.4.57 Llau 1998

Methods	**Study design:** RCT **Intention to treat analysis:** Not reported **Length of duration of study:** Not reported **Power calculation reached:** Not reported **Transfusion strategy:** The patients were transfused 1 packed red cells (PRC) when Hb < 9g %. Hb was determined two hours after each PRC transfusion. **Was the trial stopped early:** No
Participants	**Baseline Characteristics** Placebo *Age (years) (mean SD)*: 67 (7) *Ethnicity*: Not reported

	Gender (males): Not reported *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 10 *Number of participants receiving treatment*: Not reported *Number of participants analysed*: Not reported *Dropout rate*: Not reported Aprotinin *Age (years) (mean SD)*: 68 (8) *Ethnicity*: Not reported *Gender (males)*: Not reported *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 10 *Number of participants receiving treatment*: Not reported *Number of participants analysed*: Not reported *Dropout rate*: Not reported Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males)*: Not reported

	Length of surgery (minutes): Not reported *Proportion of participants on anticoagulants prior to surgery (n, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: Not reported *Number of participants receiving treatment*: Not reported *Number of participants analysed*: Not reported *Dropout rate*: Not reported **Included criteria:** Primary THR, ASA 1/2 **Excluded criteria:** Not reported **Pre-treatment:** Not reported **If TKR, is tourniquet used:** Not applicable **Indication for surgery:** Not reported **Type of anaesthetic:** General anaesthetic **Type of surgery:** Primary THR
Interventions	**Intervention Characteristics** Placebo 2 x 10(6) KIU Aprotinin during 30 minutes or normal saline in the same volume and time immediately after anaesthesia induction. Placebo, IV, intraop (immediately after induction) Aprotinin 2 x 10(6) KIU Aprotinin during 30 minutes or normal saline in the same volume and time immediately after anaesthesia induction. Aprotinin, IV, 2 x 10^6 KIU, intraop (immediately after induction)
Outcomes	Primary outcome: Reduction of bleeding Transfusion requirements

	Incidence of deep vein thrombosis Secondary outcome: Not reported
Notes	**Sponsorship source:** Not reported **Country:** Spain **Setting:** Single-centre **Comments:** None **Authors name:** J.V. Llau **Institution:** Hospital Clinico Universitario **Email:** Not reported **Address:** Anaesthesia and Critical care Dept, Hospital Clinico Universitario Valencia, Spain **Native language of paper:** English **Reference type:** Abstract (1) **Trial registration number:** Not applicable, but when checked trial registration number not found **Was it translated for this review:** No

B.1.4.58 Lopez Picado 2017

Methods	**Study design:** RCT **Intention to treat analysis:** Not reported **Length of duration of study:** 24 months **Power calculation reached:** Yes **Transfusion strategy:** Before starting the surgery, transfusion trigger levels were set at 8.5 g/dL of Hb under normovolemic conditions and at 9 g/dL in cases of moderate cardiac or respiratory diseases or symptoms of acute anemia (angina, hypotension, dyspnoea). **Was the trial stopped early:** No
Participants	**Baseline Characteristics** Placebo *Age (years) (mean SD)*: 67.5 (12.1) *Ethnicity*: Not reported *Gender (males, females)*: 21, 16 *Length of surgery (minutes) (mean SD)*: 65 (18)

	Proportion of participants on anticoagulants prior to surgery (n/ N, %): Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: 12/37 (32.4) *ASA 2 (n/ N,%)*: 22/37 (59.5) *ASA 3 (n/ N,%)*: 3/37 (8.1) *ASA 4 (n/ N,%)*: 0/0 (0) *Number of participants randomised*: 40 *Number of participants receiving treatment*: 39 *Number of participants analysed*: 37 *Dropout rate*: 3/40 (7.5%) TXA, One dose *Age (years) (mean SD)*: 69.2 (10.2) *Ethnicity*: Not reported *Gender (males, females)*: 16, 19 *Length of surgery (minutes) (mean SD)*: 67 (19) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: 13/35 (37.2) *ASA 2 (n/ N,%)*: 20/35 (57.1) *ASA 3 (n/ N,%)*: 2/35 (5.7) *ASA 4 (n/ N,%)*: 0/0 (0) *Number of participants randomised*: 38 *Number of participants receiving treatment*: 35 *Number of participants analysed*: 35 *Dropout rate*: 3/38 (7.89%) TXA, Two dose *Age (years) (mean SD)*: 62.5 (13.0) *Ethnicity*: Not reported *Gender (males, females)*: 20, 16 *Length of surgery (minutes) (mean SD)*: 68 (16) *Proportion of participants on anticoagulants prior to*

	surgery (n/ N, %): Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: 12/36 (33.3) *ASA 2 (n/ N,%)*: 24/36 (66.7) *ASA 3 (n/ N,%)*: 0/36 (0) *ASA 4 (n/ N,%)*: 0/0 (0) *Number of participants randomised*: 38 *Number of participants receiving treatment*: 37 *Number of participants analysed*: 36 *Dropout rate*: 2/38 (5.26%) Overall *Age (years) (mean SD)*: 66.4 (12.1) *Ethnicity*: Not reported *Gender (males, females)*: 57, 51 *Length of surgery (minutes) (mean SD)*: 66 (17) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: 37/108 (34.3) *ASA 2 (n/ N,%)*: 66/108 (61.6) *ASA 3 (n/ N,%)*: 5/108 (4.6) *ASA 4 (n/ N,%)*: 0/0 (0) *Number of participants randomised*: 113 *Number of participants receiving treatment*: 111 *Number of participants analysed*: 108 *Dropout rate*: 7/113 (6.2%) **Included criteria:** All ASA physical status I to III patients older than 18 years with no known allergy to TXA were invited to participate. **Excluded criteria:** 1) Pregnancy or breastfeeding, 2) Severe vascular ischemia, 3) History of venous thrombosis, pulmonary embolism or diseases causing embolism, 4) Known coagulopathies, 5) Long-term treatment with acetylsalicylic acid or nonsteroidal anti-inflammatory drugs not discontinued before surgery, 6) A hemoglobin (Hb)

	concentration <10 mg/dL, 7) Moderate renal impairment, 8) Liver cirrhosis, 9) Any contraindications to prophylaxis with enoxaparin. **Pre-treatment:** No **If TKR, is tourniquet used:** Not applicable **Indication for surgery:** Arthrosis **Type of anaesthetic:** Spinal **Type of surgery:** Primary THR
Interventions	**Intervention Characteristics** Placebo Patients assigned to control group (CG) received an IV infusion of 100 mL of 0.9% saline over a 10-minute period after instituting regional anaesthesia and before starting surgery. Three hours later, they received a further of 100 mL of 0.9% saline over 10 minutes. Placebo, 100mls, IV, preop AND Placebo, 100mls, IV, 3 hours postop TXA, One dose Patients assigned to single-dose TXA group (SDG) received an IV infusion of 15 mg/kg TXA (Amchafibrin®,Rottapharm, Barcelona, Spain) in 100 mL of 0.9% saline over a 10-minute period after the institution of regional anaesthesia and before the start of surgery. Three hours after the first infusion, they received a second infusion over 10 minutes but this time with 100 mL of 0.9% saline alone. TXA, 15mg/kg, IV, preop AND Placebo, 100mls, IV, 3 hours, postop TXA, Two dose Patients assigned to this 2-dose TXA group (TDG) received 10 mg/kg TXA (Amchafibrin®, Rottapharm, Barcelona, Spain). As in the SDG, this was diluted in 100 mL of 0.9% saline and infused IV (intravenous) over 10 minutes, after instituting regional anaesthesia and before starting surgery, and 3 hours later after the start of surgery, they received a second infusion at the same dose and rate as the first. TXA 15mg/kg, IV, preop AND TXA, 15mg/kg, IV, 3 hours postop
Outcomes	Primary outcome: Total blood loss at 48 hours Blood transfusions given

	Secondary outcome: Blood loss up to 1 hour and 6 hours after surgery Intra (in the operating theatre) and postoperative blood loss Rates of thrombosis Complications
Notes	**Sponsorship source:** None **Country:** Spain **Setting:** Multi-centre **Comments:** None **Authors name:** B. Barrachina **Institution:** Araba University Hospital **Email:** borjabarra@gmail.com **Address:** Servicio de Anestesiología y Reanimación, Hospital Universitario de Araba- Sede Txagorritxu, c/ Jose Atxotegui s/n, 01009 Vitoria-Gasteiz, Alava, Spain **Native language of paper:** English **Reference type:** Full text (2), Trial registration (1) **Trial registration number:** NCT01199627 **Was it translated for this review:** No

B.1.4.59 Molloy 2007

Methods	**Study design:** RCT **Intention to treat analysis:** Yes **Length of duration of study:** 10 months + FU **Power calculation reached:** Yes **Transfusion strategy:** The post-operative haematocrit measured at eight hours determined if a transfusion was indicated from a protocol with a threshold of 0.25. **Was the trial stopped early:** No
Participants	**Baseline Characteristics** TXA *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported

	Gender (males): Not reported *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: 50/ 50, 100% *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 50 *Number of participants receiving treatment*: 50 *Number of participants analysed*: 50 *Dropout rate*: 0/ 50, (0%) Fibrin spray *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males)*: Not reported *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: 50/ 50, 100% *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 50 *Number of participants receiving treatment*: 50 *Number of participants analysed*: 50 *Dropout rate*: 0/ 50, (0%) Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males)*: Not reported

	Length of surgery (minutes): Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: Not reported *Number of participants receiving treatment*: Not reported *Number of participants analysed*: Not reported *Dropout rate*: Not reported **Included criteria:** 1) Patients scheduled to undergo a primary TKR, 2) Pre-operative haemoglobin (Hb) level of 13.0 g/dl **Excluded criteria:** 1) Previous surgery to the knee, with the exception of meniscectomy, 2) Bleeding disorders, platelet or bone-marrow disorders, 3) A level of creatinine > 250 µmol/l since this is a contraindication to the administration of tranexamic acid, 4) A history of thromboembolism. **Pre-treatment:** Unclear **If TKR, is tourniquet used:** Yes **Indication for surgery:** NR **Type of anaesthetic:** Spinal **Type of surgery:** Primary TKR
Interventions	**Intervention Characteristics** TXA Those randomised to the tranexamic group received 500 mg of tranexamic acid intravenously five minutes before deflation of the tourniquet and a repeat dose three hours later TXA, IV, 0.5mg, intraop (5 mins prior to tourniquet deflation) AND TXA, IV, 0.5mg, post op 3 hours after 1st dose Fibrin spray Those patients randomised to the topical fibrin group received 10 ml of the reconstituted product

	intraoperatively, with 6 ml sprayed on to the posterior capsule and surrounding soft tissues before the prosthesis was inserted, and the remaining 4 ml sprayed on to the bone which was exposed after placement of the prosthesis and on the soft tissues after closure of the capsule. Fibrin, IA, 10ml, intraop - 6ml before prosthesis inserted, 4ml to exposed bone after prosthesis placement and soft tissue
Outcomes	Primary outcome: Calculated total blood loss Secondary outcome: Transfusion requirements Post-operative leg swelling Pain scores Length of stay in hospital Rate of complications Rate of proximal deep-venous thrombosis (DVT)
Notes	**Sponsorship source:** Pharmaceutical **Country:** UK **Setting:** Not reported **Comments:** None **Authors name:** D. Molloy **Institution:** Musgrave Park Hospital **Email:** dennis.molloy@greenpark.n-i.nhs.uk **Address:** Orthopaedic Outcomes Department, Musgrave Park Hospital, Stockmans Lane, Belfast,BT9 7JB, Northern Ireland. **Native language of paper:** English **Reference type:** Abstract (1) Full Text (1) **Trial registration number:** Not applicable, but when checked trial registration number not found **Was it translated for this review:** No

B.1.4.60 Morales-Avalos 2021

Methods	**Study design:** RCT **Intention to treat analysis:** Yes

	Length of duration of study: 4 months (February 2020 to June 2020) + 90 days (follow-up) = 7 months **Power calculation reached:** Yes **Transfusion strategy:** Blood transfusion was performed in case a patient had either an Hb level less than 7 g/dl or evolved with any anemia-related organ dysfunction (palpitation, shortness of breath or bad mental status not due to other causes) with the Hb level between 7 and 10 g/dl **Was the trial stopped early:** No
Participants	**Baseline Characteristics** TXA, oral, 1.3g, 2 hrs pre-incision, 6 and 12 h postop *Age (years) (mean SD)*: 66.2 (11.23) *Ethnicity*: Not reported *Gender (males, females)*: 24/51 M (47.05%); 27/ 51 F (52.95%) *Length of surgery (minutes) (mean, SD)*: 68.44 (10.23) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: 0/ 51, 0% *Incidence of preoperative anaemia*: 0/ 51, 0% *Co-morbidities*: Diabetes mellitus 16/ 51 (31.37%); Hypertension 19/ 51 (37.25%); Rheumatoid arthritis 5/ 51 (9.80%); History of contralateral total hip replacement 7/ 51 (13.73%); Dyslipidaemia 2/ 51 (3.92%); Another systemic disorder (asthma, COPD, cancer, chronic renal failure, chronic liver disease, ischemic stroke or haemorrhagic stroke, osteoporosis, etc 13/ 51 (25.49%) *ASA 1 (n/ N,%)*: 3/ 51 (5.88%) *ASA 2 (n/ N,%)*: 47/ 51 (92.16%) *ASA 3 (n/ N,%)*: 1/ 51 (1.96%) *ASA 4 (n/ N,%)*: 0/ 51, (0%) *Number of participants randomised*: 51 *Number of participants receiving treatment*: 51 *Number of participants analysed*: 51 *Dropout rate*: 0/ 51, 0% EACA, oral, 2g, 2hrs pre-incision, 6 and 12 h postop *Age (years) (mean SD)*: 64.5 (9.18) *Ethnicity*: Not reported *Gender (males, females)*: 26/ 51 M (50.98%); 25/ 51 F

	(49.02%) *Length of surgery (minutes)*: 65.34 (11.34) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Diabetes mellitus (n/%) 15/ 51 (29.41%); Hypertension 17/ 51 (33.33%); Rheumatoid arthritis 7/ 51 (13.73%); History of contralateral total hip replacement 9/ 51 (17.64%); Dyslipidaemia 4/ 51 (7.84%); Another systemic disorder (asthma, COPD, cancer, chronic renal failure, chronic liver disease, ischemic stroke or haemorrhagic stroke, osteoporosis, etc 11/ 51 (21.57%) *ASA 1 (n/ N,%)*: 5/ 51 9.80% *ASA 2 (n/ N,%)*: 44/ 51 86.28% *ASA 3 (n/ N,%)*: 2/ 51 3.92% *ASA 4 (n/ N,%)*: 0/ 51, 0% *Number of participants randomised*: 51 *Number of participants receiving treatment*: 51 *Number of participants analysed*: 51 *Dropout rate*: 0/ 51, 0% Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males, females)*: 50 M, 52 F *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 102 *Number of participants receiving treatment*: 102 *Number of participants analysed*: 102 *Dropout rate*: 0/ 102, 0%

	Included criteria: All patients over 18 years; undergoing cement less primary unilateral THA for osteoarthritis, osteonecrosis of the femoral head (Ficat III or IV), or developmental dysplasia of hip (Crowe I/II); ASA I–III **Excluded criteria:** Patients with anemia (<120 g/l for female, <130 g/l for male); patients with bilateral arthroplasty; planned revision surgery; developmental dysplasia of the hip (Crowe III/IV); prosthetic surgery for a fracture of the femoral head or neck or acetabulum; infected patients; pregnancy; lactating patients; use of oral contraceptives; a BMI more than 35 kg/m2; history of an arterial thrombotic event such as stroke or myocardial infarction in the last year; placement of an arterial stent within the last year; history of deep vein thrombosis (DVT) or pulmonary embolism; history of congenital or acquired clotting disorder; family history of thrombotic conditions; medication history of anticoagulant or antiplatelet prophylaxis in the perioperative period; complicated primary THAs with osteotomy; an existing implant removal or bone grafting; kidney failure; kidney transplant; anaphylaxis to either EACA or TXA; declined to consent receiving blood products; unable to ingest or receive the medication orally **If TKR, is tourniquet used:** Not applicable **Indication for surgery:** Osteoarthritis, osteonecrosis of the femoral head, developmental dysplasia of hip **Type of anaesthetic:** Mixed general and spinal (For TXA spinal (n/%) 47 (92.16) For EACA 48 (94.12) For TXA general (n/%) 4 (7.84) for EACA general 2 (3.92) 0.555 **Type of surgery:** Primary THA
Interventions	**Intervention Characteristics** TXA, oral, 1.3g, 2 hrs pre-incision, 6 and 12 h postop The oral TXA group received 1.3 g of TXA (two tablets of 650 mg) (Lysteda, Pierre Fabre,Mexico City, Mexico) approximately 2 h before the incision, and the same dose was repeated 6 and 12 h postoperatively TXA, oral, 1.3g, 2hrs pre-incision, 6 and 12hrs postop EACA, oral, 2g, 2hrs pre-incision, 6 and 12 h postop The oral EACA group received 2 g of EACA (two tablets of 1000 mg) (Amikar, Wyeth, Quebec,Canada) at the same times previously described. (approximately 2 h before the incision, and the same dose was repeated 6 and 12 h postoperatively.) The oral EACA group received 2 g of EACA (two tablets of 1000 mg) (Amikar, Wyeth, Quebec,Canada) at the same

	times previously described
Outcomes	Primary outcome: Total Blood Loss Hidden Blood Loss External Blood Loss Transfusion rate Secondary outcome: Transfusion rate IBL Hb, and Hct drop Drain output Readmission Mortality Pain indicated by the patients using the visual analog scale (VAS) Functionality using the Harris hip score (HHS) Range of motion (these last three as indirect indicators of functional deficit and pain secondary to the presence of intra-articular bleeding) Adverse effects Complications
Notes	**Sponsorship source:** Not reported (There is no funding source) **Country:** Mexico **Setting:** Single-centre **Comments:** None **Authors name:** R. Morales-Avalos **Institution:** Universidad Autonoma de Nuevo Leo´ n (U.A.N.L.), Monterrey **Email:** rodolfot59@hotmail.com **Address:** Hip Unit, Department of Orthopaedic Surgery and Traumatology, 4th Floor of the Central Building, School of Medicine and University Hospital 'Dr Jose´ Eleuterio Gonza´lez', Universidad Autonoma de Nuevo Leo´ n (U.A.N.L.), Av. Francisco I. Madero and Dr Edua **Native language of paper:** English

	Reference type: Full text (1), trial registration (1) **Trial registration number:** NCT04187014 **Was it translated for this review:** No

B.1.4.61 Murkin 1995

Methods	**Study design:** RCT **Intention to treat analysis:** Yes **Length of duration of study:** 17 months **Power calculation reached:** No **Transfusion strategy:** Transfusion criteria for packed red blood cells (PRBC) were defined prospectively. PRBC transfusion was permitted for intraoperative blood loss exceeding 15% of blood volume, where blood volume was estimated as kilograms of body weight (BW) X 70 mL for patients younger than 60 year, and BW X 65 mL for males and BW X 60 mL for females 60 year or older, or for postoperative hemoglobin concentration less than 8.0 g/dL. **Was the trial stopped early:** No
Participants	**Baseline Characteristics** Placebo *Age (years) (mean SEM)*: 65.5 (3.4) *Ethnicity*: Not reported *Gender (males, females)*: 11, 13 *Length of surgery (minutes) (mean SEM)*: 194 (11.0) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: 4/ 24 (16.7%) *Incidence of preoperative anaemia*: Not reported *Co-morbidities (n/ N, %)*: Diabetes mellitus 0/24 (0%), preoperative Hypertension 1/24 (4.2%) *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 24 *Number of participants receiving treatment*: 24 *Number of participants analysed*: 24

	Dropout rate: 0/24 (0%) Aprotinin *Age (years) (mean SEM)*: 66.9 (2.8) *Ethnicity*: Not reported *Gender (males, females)*: 9, 20 *Length of surgery (minutes) (mean SEM)*: 180 (7.5) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: 7/ 29 (24.1%) *Incidence of preoperative anaemia*: Not reported *Co-morbidities (n/ N, %)*: Diabetes mellitus 6/29 (20.7%), preoperative Hypertension 2/29 (6.9%) *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 29 *Number of participants receiving treatment*: 29 *Number of participants analysed*: 29 *Dropout rate*: 0/29 (0%) Overall *Age (years) (mean SEM)*: Not reported *Ethnicity*: Not reported *Gender (males, females)*: Not reported *Length of surgery (minutes) (mean SEM)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 53 *Number of participants receiving treatment*: Not reported *Number of participants analysed*: Not reported

	Dropout rate: Not reported **Included criteria:** 1) Patients undergoing revision THA or primary bilateral THA **Excluded criteria:** 1) Previously known allergy or exposure to aprotinin, 2) History of pancreatitis, 3) Impaired renal function defined as increased serum creatinine > 150 pmol/L for females or > 170 pmol/L for males, 4) Biochemical evidence of hepatic dysfunction, 5) Age < 18 year **Pre-treatment:** No **If TKR, is tourniquet used:** Not applicable **Indication for surgery:** Not reported **Type of anaesthetic:** General anaesthesia **Type of surgery:** Revision THR and bilateral THR
Interventions	**Intervention Characteristics** Placebo Placebo-treated patients received an equivalent volume of 0.9% saline. Test dose in both arms: Placebo, IV, intraop, bolus AND Placebo, IV, infusion until 1-hour post-surgery Aprotinin Prior to induction of anaesthesia, a test dose of 5 mL of study drug was administered over 5 min followed by a continuous infusion for the duration of surgery and for 1 h postoperatively. Patients weighing between 60 and 80 kg, and randomized to receive aprotinin, were administered a loading dose of 2 million kallikrein inactivation units (KIU) (200 mL) over 15 min followed by an infusion of 0.5 million KIU (50 mL) per hour; those weighing less than 60 kg or more than 80 kg received a loading dose of 2.8 mL/kg (10,000 KIU/mL) and an infusion of 0.7 mL * kg-’ * h-l. Test dose in both arms: For 60-80kg people: Aprotinin, IV, 2 x10 ^6 KIU, intraop, bolus AND Aprotinin, IV, 0.5 x 10^6 KIU infusion until 1-hour post-surgery OR for people 60-80kg: Aprotinin, IV, 2.8ml/kg (10,000 KIU/ml), intraop AND Aprotinin, IV, 0.7ml/kg, infusion until 1 hour postop
Outcomes	Primary outcome: Intraoperative blood loss Amount of blood products transfused Incidence of deep venous thrombosis Total blood loss Biochemical markers of hepatic and renal function

	Secondary outcome: Not reported
Notes	**Sponsorship source:** Unclear (searched for 'miles Canada inc' - but no relevant hits) **Country:** Canada **Setting:** Not reported **Comments:** None **Authors name:** J.M. Murkin **Institution:** University of Western Ontario **Email:** Not reported **Address:** Department of Anesthesia, University Hospital, University of Western Ontario, 339 Windermere Road, London, Ontario, Canada N6A 5A5 **Native language of paper:** English **Reference type:** Full text (1) **Trial registration number:** Not applicable, but when checked trial registration number not found **Was it translated for this review:** No

B.1.4.62 Murkin 2000

Methods	**Study design:** RCT **Intention to treat analysis:** No **Length of duration of study:** Not reported **Power calculation reached:** No **Transfusion strategy:** Patients had transfusion of whole blood or packed red blood cells if the postoperative haematocrit was 18 percent or less or if clinically warranted. **Was the trial stopped early:** No
Participants	**Baseline Characteristics** Placebo *Mean age (years) (mean)*: 63.2 *Ethnicity*: White: 64 (94%); Black: 2 (3%); Hispanic: 2 (3%) *Gender (males, females)*: 32, 36 *Mean operating time (minutes) (mean)*: 69 *Proportion of participants on anticoagulants prior to*

	surgery (n/ N, %): Not reported *Incidence of preoperative anaemia (n/ N, %)*: 0/73 (0%) *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 73 *Number of participants receiving treatment*: 68 *Number of participants analysed*: 68 *Dropout rate*: 5/73 (6.9%) Aprotinin 500,000 KIU (Low dose) *Mean age (years) (mean)*: 63.7 *Ethnicity* : White: 66(96%); Black: 2 (3%); Hispanic: 1 (1%) *Gender (males, females)*: 34, 35 *Mean operating time (minutes) (mean)*: 67 *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia (n/ N, %)*: 0/76 (0%) *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 76 *Number of participants receiving treatment*: 69 *Number of participants analysed*: 69 *Dropout rate*: 7/76 (9.2%) Aprotinin 250,000 KIU per hour (Med. dose) *Mean age (years) (mean)*: 65.5 *Ethnicity* : White: 68 (100%); Black: 0 (0%); Hispanic: 0 (0%) *Gender (males, females)*: 27, 41 *Mean operating time (minutes)*: 67 *Proportion of participants on anticoagulants prior to*

	surgery (n/ N, %): Not reported *Incidence of preoperative anaemia (n/ N, %)*: 0/ 75 (0%) *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 75 *Number of participants receiving treatment*: 68 *Number of participants analysed*: 68 *Dropout rate*: 7/75 (9.3%) Aprotinin 500,000 KIU per hour (High dose) *Mean age (years) (mean)*: 63.4 *Ethnicity*: White: 72 (96%); Black: 2 (3%); Hispanic: 1 (1%) *Gender (males, females)*: 46, 29 *Mean operating time (minutes)*: 68 *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia (n/ N, %)*: 0/ 77 (0%) *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: NR *ASA 2 (n/ N,%)*: NR *ASA 3 (n/ N,%)*: NR *ASA 4 (n/ N,%)*: NR *Number of participants randomised*: 77 *Number of participants receiving treatment*: 75 *Number of participants analysed*: 75 *Dropout rate*: 2/77 (2.6%) Overall *Mean age (years) (mean)*: Not reported *Ethnicity*: Not reported *Gender (males, females)*: Not reported *Mean operating time (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported

	Incidence of preoperative anaemia (n/ N, %): Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: Not reported *Number of participants receiving treatment*: Not reported *Number of participants analysed*: Not reported *Dropout rate*: Not reported **Included criteria:** 1) Patients at least 18 years old, 2) Scheduled for an elective unilateral primary total hip replacement **Excluded criteria:** 1) Patients who had received aprotinin previously or who had a known or suspected allergy to aprotinin or warfarin were excluded, 2) Pregnant women and those of child-bearing age, 3) Patients who had participated in an investigational drug study within the previous thirty days, 4) Those who refused donor-blood products, 5) Patients with a history of deep-vein thrombosis, pulmonary embolism, diabetes mellitus, 6) Serum creatinine level above the upper limit of normal (1.5 milligrams per decilitre [133 micromoles per litre]), 7) Impaired renal function (a serum creatinine level of greater than 2.5 milligrams per decilitre [221 micromoles per litre]), 8) Failure of a major organ system, or an important medical illness (for example, decompensated congestive heart failure or notably elevated levels of hepatic enzymes) **Pre-treatment:** No **If TKR, is tourniquet used:** Not applicable **Indication for surgery:** Not reported **Type of anaesthetic:** Regional or general anaesthetic **Type of surgery:** Primary THR
Interventions	**Intervention Characteristics** Placebo After transfer to the operating room and initiation of monitoring, all patients received a one millilitre test dose intravenously (taken from the loading dose) before or after the induction of anaesthesia. If there was no evidence of hypersensitivity to the drug after at least ten minutes, the full loading dose was administered after the induction of anaesthesia, either regional or general. The contents of

	four fifty-millilitre vials of study medication were drawn up, injected into a sterile infusion bag, and continuously infused at a rate of fifty millilitres per hour until the procedure was completed and the skin was closed. Seventy-three patients received the placebo. Placebo, IV, intraop, ?loading/infusion or both Aprotinin 500,000 KIU (Low dose) Seventy-six patients received a loading dose of 500,000 KIU of aprotinin but no subsequent continuous infusion (low dose) Aprotinin, IV, 0.5 x 10^6 KIU intraop, loading dose only Aprotinin 250,000 KIU per hour (Med. dose) Seventy-five patients received a 1,000,000-KIU loading dose followed by continuous infusion of 250,000 KIU per hour (medium dose) Aprotinin, IV, 1 x 10^6, intraop, loading dose AND Aprotinin, IV, 0.25 x 10 ^6 KIU/hr infusion (from induction to skin closure) Aprotinin 500,000 KIU per hour (High dose) Seventy-seven patients received a loading dose of 2,000,000 KIU followed by continuous infusion of 500,000 KIU per hour (high dose) Aprotinin, IV, 2 x 10^6, intraop, loading dose AND Aprotinin, IV, 0.5 x 10 ^6 KIU/hr infusion (from induction to skin closure)
Outcomes	Primary outcome: Percentage of patients who required allogeneic or autologous blood or packed red blood cells through the seventh postoperative day. Secondary outcome: Number of units transfused. Prevalence of deep venous thrombosis
Notes	**Sponsorship source:** Pharmaceutical **Country:** Canada and USA **Setting:** multi-centre **Comments:** Red cell transfusions - unsure whether these include allogeneic or autologous units. **Authors name:** J.M. Murkin **Institution:** University of Western Ontario

	Email: Not reported **Address:** Department of Anaesthesia, London Health Sciences Center UC, University of Western Ontario, 339 Windermere Road, London, Ontario N6A 5A5, Canada. **Native language of paper:** English **Reference type:** Full Text (1) **Trial registration number:** Not applicable, but when checked trial registration number not found **Was it translated for this review:** No

B.1.4.63 NCT02922582

Methods	**Study design:** RCT **Intention to treat analysis:** Yes **Length of duration of study:** 12 months (Participants were recruited between October 28, 2016 and October 12, 2017 at 4 US sites. The study was terminated on 27-Nov-2017 due to low enrolment). Follow-up length not reported **Power calculation reached:** No **Transfusion strategy:** Transfusion requirements consistent with each institution's transfusion policy. **Was the trial stopped early:** Yes - slow to recruit
Participants	**Baseline Characteristics** DepoTXA 400mg *Age (years) (mean SD)*: 65 (7.12) *Ethnicity*: Hispanic or Latino 0/ 4, 0%; NOT Latino/ Hispanic 4/ 4, 100%; Unknown or not reported 0/ 4, 0% *Gender (males, females)*: Males: 1/4, 25%, Females: 3/ 4, 75% *Length of surgery (minutes) (mean, SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported

	Number of participants randomised: 4 *Number of participants receiving treatment*: 4 *Number of participants analysed*: 4 *Dropout rate*: 0/ 4, 0% DepoTXA 800mg *Age (years) (mean SD)*: 66 (1.73) *Ethnicity*: Hispanic or Latino 0/ 3, 0%; NOT Latino/ Hispanic 3/ 3, 100%; Unknown or not reported 0/ 3, 0% *Gender (males, females)*: Males: 1/3, 33.3%, Females: 2/ 3, 66.7% *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 4 *Number of participants receiving treatment*: 3 *Number of participants analysed*: 3 *Dropout rate*: 0/ 4, 0% DepoTXA 1200mg *Age (years) (mean SD)*: 59.3 (5.38) *Ethnicity*: Hispanic or Latino 0/ 4, 0%; NOT Latino/ Hispanic 4/4, 100%; Unknown or not reported 0/ 4, 0% *Gender (males, females)*: Males: 2/4, 50%, Females: 2/ 4, 50% *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported

	ASA 3 (n/ N,%): Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 4 *Number of participants receiving treatment*: 4 *Number of participants analysed*: 4 *Dropout rate*: 0/ 4, 0% TXA, IV *Age (years) (mean SD)*: 58.0 (6.16) *Ethnicity*: Hispanic or Latino 0/ 4, 0%; NOT Latino/ Hispanic 4/ 4, 100%; Unknown or not reported 0/ 4, 0% *Gender (males, females)*: Males: 2/4, 50%, Females: 2/ 4, 50% *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 4 *Number of participants receiving treatment*: 4 *Number of participants analysed*: 4 *Dropout rate*: 0/ 4, 0% Overall *Age (years) (mean SD)*: 61.8 (6.19) *Ethnicity*: Hispanic or Latino 0/ 15, 0%; NOT Latino/ Hispanic 15/ 15, 100%; Unknown or not reported 0/ 4, 0% *Gender (males, females)*: Males: 6/15, 40%, Females: 9/ 15, 60% *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported

	ASA 1 (n/ N,%): Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 16 *Number of participants receiving treatment*: 15 *Number of participants analysed*: 15 *Dropout rate*: 0/ 16, 0% **Included criteria:** Male or female, ≥18 years of age at screening. Scheduled to undergo elective unilateral open TKA under general, spinal, or regional anaesthesia. American Society of Anaesthesiology (ASA) physical status 1, 2, or 3. Female subject must be surgically sterile; or at least 2 years postmenopausal; or have a monogamous partner who is surgically sterile; or practicing double-barrier contraception; or practicing abstinence (must agree to use double-barrier contraception in the event of sexual activity); or using an insertable, injectable, or transdermal, contraceptive approved by the FDA for greater than 2 months prior to screening and commit to the use of an acceptable form of birth control for the duration of the study and for 30 days after completion of the study. Able to provide informed consent, adhere to the study visit schedule, and complete all study assessments. **Excluded criteria:** Currently pregnant, nursing, or planning to become pregnant during the study or within 1 month after study drug administration. Planned concurrent surgical procedure (e.g., bilateral TKA). Prior open knee surgery on ipsilateral knee. Prior arthroscopy is permitted. Subjects taking a medication with a known procoagulant effect (e.g., combination hormonal contraceptives, Factor IX complex concentrates or anti-inhibitor coagulant concentrates, or all-trans retinoic acid). Contraindication or hypersensitivity to TXA. History of thrombosis or prior Venous thromboembolism (VTE). Known coagulopathy or active intravascular clotting. Prior myocardial infarction. Prior cardiovascular accident (stroke) or subarachnoid haemorrhage. History of epilepsy. Presence of an intravascular stent. History of impaired kidney function, chronic respiratory disease, rheumatoid arthritis, coagulopathy, or loss of sensation in extremities. Renal insufficiency (serum creatinine level >2 mg/dL). Anemia (Hb level <10 g/dL). Uncontrolled anxiety, psychiatric, or neurological disorder that might interfere with study assessments. Acquired defective colour vision. Malignancy in the last 2 years, with the exception of non-metastatic basal cell or squamous cell carcinoma of the skin or localized carcinoma in situ of the cervix. Suspected or

	known history of drug or alcohol abuse within the previous year. Body weight <50 kg (110 pounds) or a body mass index >44 kg/m2. Administration of an investigational drug within 30 days or 5 elimination half-lives of such investigational drug, whichever is longer, prior to study drug administration, or planned administration of another investigational product or procedure during the subject's participation in this study. **If TKR, is tourniquet used:** Yes **Indication for surgery:** Unclear **Type of anaesthetic:** General, spinal, or regional anaesthesia **Type of surgery:** Unilateral open TKA
Interventions	**Intervention Characteristics** DepoTXA 400mg Single injection of DepoTXA 400 mg into the joint space via catheter prior to capsular closure TXA, Intracapsular, 400mg, intraop DepoTXA 800mg Single injection of DepoTXA 800 mg into the joint space via catheter prior to capsular closure TXA, Intracapsular, 800mg, intraop DepoTXA 1200mg Single injection of DepoTXA 1200 mg into the joint space via catheter prior to capsular closure TXA, Intracapsular, 1200mg, intraop TXA, IV 1g of IV TXA at the end of surgery TXA, IV, 1g, intraop
Outcomes	Primary outcome: Area Under the Plasma Concentration-versus-time Curve from Time 0 Extrapolated to Infinity After Drug Administration Area Under the Plasma Concentration-versus-time Curve from Time 0 to the Last Collection Time After Drug Administration Maximum Plasma Concentration Time to Maximum Plasma Concentration

	Apparent Terminal Elimination Rate Constant Apparent Terminal Elimination Half-life Secondary outcome: Summary of Neurological Assessments Incidence of Reoperation Due to Hematoma or Wound Dehiscence Incidence of Transfusion Number of Participants With 90˚ Passive and Active Knee Flexion Time to Complete Timed Up-and-Go (TUG) Test Change in Knee and Thigh Measurements Area Under the Curve (AUC) of NRS
Notes	**Sponsorship source:** Pharmaceutical (Pacira Pharmaceuticals) **Country:** USA **Setting:** Multi-centre **Comments:** 1. All information extracted here has come solely from the trial's NCT page. 2. Reoperation data given but not for bleeding (which is what we want) but for hematoma and wound Dehiscence **Authors name:** Dr Hassan Danesi (Study Director) **Institution:** Pacira Pharmaceuticals, Inc. 5 Sylvan Way Parsippany, NJ 07054 (973) 254-3560 **Email:** jim.jones@pacira.com **Address:** Pacira Pharmaceuticals, Inc. 5 Sylvan Way Parsippany, NJ 07054 (973) 254-3560 **Native language of paper:** Trial registration only - English **Reference type:** Trial registration (1) **Trial registration number:** NCT02922582 **Was it translated for this review:** No

B.1.4.64 Niskanen 2005

Methods	**Study design:** RCT **Intention to treat analysis:** Per protocol (mentions 'on-treatment' analysis being done) **Length of duration of study:** Unclear

	Power calculation reached: Yes **Transfusion strategy:** Even though we had an indicative 0.28–0.30 level of haematocrit for blood transfusions, it was the clinical situation that determined the need for blood transfusions **Was the trial stopped early:** No
Participants	**Baseline Characteristics** Placebo *Age (years) (mean SD)*: 65 (8.2) *Ethnicity*: Not reported *Gender (males, females)*: 7, 13 *Length of surgery (minutes) (mean SD)*: 96 (12) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: 0/ 20 (0%) *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 20 *Number of participants receiving treatment*: 20 *Number of participants analysed*: 20 *Dropout rate*: 0/20 (0%) TXA *Age (years) (mean SD)*: 66 (9.1) *Ethnicity*: Not reported *Gender (males, females)*: 6, 13 *Length of surgery (minutes) (mean SD)*: 93 (12) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: 0/ 19 (0%) *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported

	ASA 3 (n/ N,%): Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 20 *Number of participants receiving treatment*: 20 *Number of participants analysed*: 19 *Dropout rate*: 1/19 (5.3%) Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males, females)*: Not reported *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: Not reported *Number of participants receiving treatment*: Not reported *Number of participants analysed*: Not reported *Dropout rate*: Not reported **Included criteria:** 1) Patients scheduled for a cemented hip arthroplasty for osteoarthritis **Excluded criteria:** 1) Patients with rheumatoid arthritis and osteonecrosis, 2) Patients with known coagulation disturbances including thromboembolic events, 3) Patients using warfarin related preparations, 4) Patients with allergy to tranexamic acid, 5) Patients with signs of renal insufficiency **Pre-treatment:** No **If TKR, is tourniquet used:** Not applicable **Indication for surgery:** Osteoarthritis **Type of anaesthetic:** Spinal (or general) (1 patient had general) **Type of surgery:** Primary THR

Interventions	**Intervention Characteristics** Placebo Half of the patients received a corresponding dose of saline. The first injection was given intravenously over 5–10 min, immediately before the operation. The next two doses of tranexamic acid or placebo were given 8 h and 16 h after the first injection Placebo, IV, preop (5-10mins prior) AND Placebo, IV, postop 8 + 16 hours postop TXA Half of the patients received 3 doses of tranexamic acid (100 mg/mL, Cyklokapron, Pharmacia, later Pfizer) 10 mg/kg of body weight mixed in 100 mL saline. Half of the patients received a corresponding dose of saline. The first injection was given intravenously over 5–10 min, immediately before the operation. The next two doses of tranexamic acid or placebo were given 8 h and 16h after the first injection. TXA, IV, 10mg/kg, preop (5-10mins prior) AND TXA, IV, 10mg/kg postop 8 + 16 hours postop
Outcomes	*Primary outcome*: Blood loss during the operation Amount of drainage after the operation *Secondary outcome*: Number of transfused units of red cells Wound leakage postoperatively Swelling Ecchymoses of the thigh Haematocrit Possible complications
Notes	**Sponsorship source:** Pharmaceutical **Country:** Finland **Setting:** Single-centre **Comments:** None **Authors name:** Raimo O Niskanen **Institution:** Päijät-Häme Central Hospital Lahti **Email:** raimo.niskanen@fimnet.fi **Address:** Departments of Orthopedics, Päijät-Häme Central

	Hospital Lahti, Rheumatism Foundation Hospital, Heinola, Finland **Native language of paper:** English **Reference type:** Full text (1) **Trial registration number:** Not applicable, but when checked trial registration number not found **Was it translated for this review:** No

B.1.4.65 North 2016

Methods	**Study design:** RCT **Intention to treat analysis:** Yes **Length of duration of study (months):** 17 **Power calculation reached:** No **Transfusion strategy:** Patients were transfused at Hgb<7 g/dL in all cases and in cases of symptomatic anemia when Hgb<8 g/dL **Was the trial stopped early:** No
Participants	**Baseline Characteristics** TXA, IV *Age (years) (mean, SD)*: 64.1±12.0 *Ethnicity*: Not reported *Gender (male) (n, %)* : 38 (54) *Length of surgery*: Not reported *Proportion of participants on anticoagulants prior to surgery*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n, %)*: 0/ 70, (0%) *ASA 2 (n, %)*: 16/ 70, (23%) *ASA 3 (n, %)*: 52/ 70, (75%) *ASA 4 (n, %)*: 0/ 70, (0%) *Number of participants randomised*: 70 *Number of participants receiving treatment*: 70 *Number of participants analysed*: 70 *Dropout rate*: 0

	TXA, IA *Age (years) (mean, SD)*: 65.7±10.6 *Ethnicity*: Not reported *Gender (male) (n, %)* : 39 (57) *Length of surgery*: Not reported *Proportion of participants on anticoagulants prior to surgery*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n, %)*: 1/ 69, 1% *ASA 2 (n,%)*: 20/ 69, 29% *ASA 3 (n,%)*: 47/ 69, 68% *ASA 4 (n, %)*: 1/ 69, 1% *Number of participants randomised*: 69 *Number of participants receiving treatment*: 69 *Number of participants analysed*: 69 *Dropout rate*: 0 Overall *Age (years) (mean, SD)*: 64.9±11.3 *Ethnicity*: Not reported *Gender (male) (n, %)*: 77, 55 *Length of surgery*: Not reported *Proportion of participants on anticoagulants prior to surgery*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n, %)*: 1/ 139, (1%) *ASA 2 (n,%)*: 36/ 139, (26%) *ASA 3 (n,%)*: 99/ 139, (72%) *ASA 4 (n, %)*: 1/ 139, (1%) *Number of participants randomised*: 139 *Number of participants receiving treatment*: 139 *Number of participants analysed*: 139 *Dropout rate*: 0 **Included criteria:** All patients scheduled for primary,

	unilateral THA were flagged for study inclusion. **Excluded criteria:** 1) Cemented femoral or acetabular component, 2) Current medical management of DVT or PE, 3) Previous embolic stroke or SAH, 4) Active liver disease with abnormal coagulation profile, 5) Alteration to colour vision, 6) Epilepsy, 7) Previous surgery on the planned operative hip, 8) Current treatment with OCP or HRT **Pre-treatment:** No **Type of surgery:** Primary THR **Indication for surgery:** Any **If TKR, is tourniquet used:** Not applicable **Type of anaesthetic:** Both (evenly distributed)
Interventions	**Intervention Characteristics** TXA, IV The patient was randomized to receive 2.0 g of either topical or IV TXA in 100 ml of 0.9% normal saline solution. Two solutions labelled “IV” and “Topical” accompanied the patient to the operating room (one solution contained the 2.0 g of TXA and the other contained saline placebo) The IV solution was administered by anaesthesia in two 50-ml doses, each over 20 minutes using a pump to ensure the correct volume was administered. One administration was started 10 minutes before incision, and the second during the fascial closure. The topical solution was applied to the wound by the surgical team after component placement and allowed to sit undisturbed for 5 minutes at which point it was removed by suction. TXA, IV, 2g, preop TXA, IA The patient was randomized to receive 2.0 g of either topical or IV TXA in 100 ml of 0.9% normal saline solution. Two solutions labelled “IV” and “Topical” accompanied the patient to the operating room (one solution contained the 2.0 g of TXA and the other contained saline placebo) The IV solution was administered by anaesthesia in two 50-ml doses, each over 20 minutes using a pump to ensure the correct volume was administered. One administration was started 10 minutes before incision, and the second during the fascial closure. The topical solution was applied to the wound by the surgical team after component placement and allowed to sit undisturbed for 5 minutes at which point it was removed by suction. TXA, IA, 2g, intraop
Outcomes	Primary outcome:

	Assessment of blood and hemoglobin loss Transfusion rates Secondary outcome: Transfusion cost analysis relative to historic controls Assessment of thromboembolic events
Notes	**Sponsorship source:** Non-pharmaceutical **Country:** USA **Setting:** Single-centre **Comments:** None **Authors name:** W. North **Institution:** Henry Ford Hospital **Email:** Not reported **Address:** Not reported **Native language of paper:** English **Reference type:** Full text (1) **Trial registration number:** NCT01683955 **Was it translated for this review:** No

B.1.4.66 Orpen 2006

Methods	**Study design:** RCT **Intention to treat analysis:** Not reported **Length of duration of study:** Not reported **Power calculation reached:** No **Transfusion strategy:** Blood transfusion was given to patients whose post-operative haemoglobin (Hb) was less than 9 g/dl, with 1 unit given for each g/dl (or part thereof) that the Hb was below 10 g/dl, with a minimum of 2 units being administered in the event of a transfusion being indicated. **Was the trial stopped early:** No
Participants	**Baseline Characteristics** Placebo *Age (years) (mean range)*: 69 (63-74)

	Ethnicity: Not reported *Gender (males, females)*: 3, 11 *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 15 *Number of participants receiving treatment*: 15 *Number of participants analysed*: 14 *Dropout rate*: 1/15 (6.7%) TXA *Age (years) (mean range)*: 73 (70-78) *Ethnicity*: Not reported *Gender (males, females)*: 8, 7 *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 15 *Number of participants receiving treatment*: 15 *Number of participants analysed*: 15 *Dropout rate*: 0/15 (0%) Overall *Age (years) (mean range)*: Not reported *Ethnicity*: Not reported

	Gender (males, females): Not reported *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 30 *Number of participants receiving treatment*: 30 *Number of participants analysed*: 29 *Dropout rate*: 1/30 (3.3%) **Included criteria:** All patients fit for a total knee replacement were considered eligible **Excluded criteria:** 1) History of thromboembolic disease, 2) Cerebrovascular disease, 3) Recent myocardial infarction or unstable angina, 4) A coagulation defect, 5) Those with an allergy to TA, 6) Not fit to undergo surgery under general anaesthetic. **Pre-treatment:** No **If TKR, is tourniquet used:** Yes **Indication for surgery:** Osteoarthritis, inflammatory arthritis **Type of anaesthetic:** General **Type of surgery:** Primary, unilateral TKR
Interventions	**Intervention Characteristics** Placebo 15 mg/kg of TXA, or an equivalent volume of normal saline, given intravenously at the time that cement mixing commenced. This time is reasonably constant in relation to the tourniquet release, as this is governed by the time taken for the cement to cure (10–12 min). Placebo saline mls, IV, intraop, single TXA 15 mg/kg of TXA, or an equivalent volume of normal saline, given intravenously at the time that cement mixing

	commenced. This time is reasonably constant in relation to the tourniquet release, as this is governed by the time taken for the cement to cure (10–12 min). TXA, IV, 15mg/kg, intraop, single
Outcomes	Primary outcome: Reductions in blood loss Clinical and sub-clinical DVT Secondary outcome: Not reported
Notes	**Sponsorship source:** Not reported **Country:** UK **Setting:** Single-centre **Comments:** None **Authors name:** E.J.P. Crawfurd **Institution:** Northampton General Hospital **Email:** edward.crawfurd@ngh.nhs.uk **Address:** Department of Orthopaedics and Department of Anaesthetics, Northampton General Hospital, Northampton NN1 5BD, UK **Native language of paper:** English **Reference type:** Full text (1) **Trial registration number:** Not applicable, but when checked trial registration number not found **Was it translated for this review:** No

B.1.4.67 Painter 2018

Methods	**Study design:** RCT **Intention to treat analysis:** Yes **Length of duration of study:** 37 months + 6 months = 43 months **Power calculation reached:** Yes **Transfusion strategy:** No red blood cell transfusion trigger was imposed, but clinicians were encouraged to adopt a haemoglobin (Hb) concentration threshold of 80 g/l before considering transfusion. **Was the trial stopped early:** No

Participants	**Baseline Characteristics** Placebo *Age (years) (mean SD)*: 68 (8.6) *Ethnicity*: Not reported *Gender (males, females)*: 37 M, 32 F *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: 8/ 69 (11.6%) *Incidence of preoperative anaemia*: Not reported *Co-morbidities (n/ N, %)*: Hypertension 47/ 69 (68.1%), Diabetes 17/ 69 (24.6%), Hypercholesterolaemia 25/ 69 (36.2%), Prior myocardial infarction 7/ 69 (10.1%) *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 69 *Number of participants receiving treatment*: 69 *Number of participants analysed*: 69 *Dropout rate*: 0/69, (0)% TXA *Age (years) (mean SD)*: 69 (9.1) *Ethnicity*: Not reported *Gender (males, females)*: 28 M, 43 F *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: 6/ 71 (8.5%) *Incidence of preoperative anaemia*: Not reported *Co-morbidities (n/ N, %)*: Hypertension 36/ 71 (50.7%), Diabetes 11/ 71 (15.5%), Hypercholesterolaemia 23/ 71 (32.4%), Prior myocardial infarction 6/ 71 (8.5%) *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 71

	Number of participants receiving treatment: 71 *Number of participants analysed*: 71 *Dropout rate*: 0/71, (0)% Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males, females)*: Not reported *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 140 *Number of participants receiving treatment*: 140 *Number of participants analysed*: 140 *Dropout rate*: 0 **Included criteria:** 1) Aged 45 years or older 2) undergoing primary or revision hip or knee joint replacement **Excluded criteria:** 1) Contraindications to the administration of TA including active thromboembolic disease or a history of venous (spontaneous or provoked) or arterial thromboembolic disease **Pre-treatment:** No **If TKR, is tourniquet used:** Yes **Indication for surgery:** Not reported **Type of anaesthetic:** Mixed (at discretion of treating clinician). **Type of surgery:** Mixed - primary and revision THR and TKR
Interventions	**Intervention Characteristics** Placebo No information given about placebo, except that saline

	was used. Placebo, IV, intraop (at incision for THR, at tourniquet deflation for TKR) AND Placebo, IV, 8+16 hours postop TXA TXA was prepared and administered per the product information—15mg/kg at skin incision (hip joint replacement) or at tourniquet deflation (knee joint replacement) with repeat dosing at eight- and 16-hours post–initial dosing. TXA, IV, 15mg/kg, intraop (at incision for THR, at tourniquet deflation for TKR) AND TXA, IV, 15mg/kg, 8+16 hours postop
Outcomes	Primary outcome: Proportion of patients receiving allogenic blood transfusion Feasibility of extending our trial methodology to a large trial of TA and placebo in this population. Secondary outcome: Change in Hb concentration and PCV, Incidence of adverse clinical events (mortality, myocardial infarction, MINS, non-fatal cardiac arrest, transient ischaemic attack/stroke, deep venous thrombosis, pulmonary embolism, acute kidney injury, atrial fibrillation, infection/sepsis, bleeding, congestive heart failure, peripheral arterial thrombosis or coronary intervention) Incidence of surgical complications (need for reoperation, hemarthrosis, haematoma, infection of wound or joint or wound ooze) Length of hospital stay Change in a range of quality of life (EQ-5D) Quality of recovery (QoR-15) Osteoarthritis severity (Western Ontario McMaster Osteoarthritis [WOMAC®] Index, under licence) Joint specific questionnaires (Oxford Hip or Knee score).
Notes	**Sponsorship source:** Non-pharmaceutical **Country:** Australia **Setting:** Multi-centre **Comments:** None **Authors name:** T.W. Painter **Institution:** University of Adelaide

	Email: thomas.painter@adelaide.edu.au **Address:** Senior Staff Anaesthetist, Department of Anaesthesia, Royal Adelaide Hospital; Clinical Senior Lecturer, Discipline of Acute Care Medicine, Adelaide Medical School, University of Adelaide; Adelaide, South Australia **Native language of paper:** English **Reference type:** Full text (1), trial registration (1) **Trial registration number:** ACTRN12613000323729 **Was it translated for this review:** No

B.1.4.68 Peng 2021

Methods	**Study design:** RCT **Intention to treat analysis:** Yes **Length of duration of study:** 18 months (January 2017 to July 2018) + 3 months follow-up = 21 months **Power calculation reached:** Yes **Transfusion strategy:** The criteria for the transfusion of blood products included a hemoglobin level of < 8 g/dl or a hemoglobin level of < 10 g/dl in a patient with symptomatic anemia, or a patient deemed at high risk because of notable underlying cardiac comorbidities **Was the trial stopped early:** No
Participants	**Baseline Characteristics** TXA, IV *Age (years) (mean SD)*: 68.13 ± 8.12 *Ethnicity*: Not reported *Gender (males, females)*: 6 M, 41 F *Length of surgery (minutes)*: 105.36 ± 4.54 *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: 0/ 47, 0% *Incidence of preoperative anaemia*: 0/ 47, 0% *Co-morbidities (n/ N, %)*: Not reported *ASA 1 (n/ N,%)*: 5/ 47, 10.6% *ASA 2 (n/ N,%)*: 21/ 47, 44.7% *ASA 3 (n/ N,%)*: 21/ 47, 44.7% *ASA 4 (n/ N,%)*: 0/ 47, 0%

	Number of participants randomised: 49 *Number of participants receiving treatment*: 47 *Number of participants analysed*: 47 *Dropout rate*: 2/ 49, 4.1% TXA, Peri-articular (PA) *Age (years) (mean SD)*: 68.65 ± 9.54 *Ethnicity*: Not reported *Gender (males, females)*: 7 M, 39 F *Length of surgery (minutes)*: 104.30 ± 3.52 *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: 0/ 46, 0% *Incidence of preoperative anaemia*: 0/ 46, 0% *Co-morbidities (n/ N, %)*: Not reported *ASA 1 (n/ N,%)*: 7/ 46, 15.2% *ASA 2 (n/ N,%)*: 27/ 46, 58.7% *ASA 3 (n/ N,%)*: 12/ 46, 26.1% *ASA 4 (n/ N,%)*: 0/ 46, 0% *Number of participants randomised*: 49 *Number of participants receiving treatment*: 46 *Number of participants analysed*: 46 *Dropout rate*: 3/ 49, 6.1% Overall *Age (years) (mean SD)*: 68.2 years (range, 48 to 80 years) *Ethnicity*: Not reported *Gender (males, females)*: 13 M, 80 F *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: 12/ 93, 12.9% *ASA 2 (n/ N,%)*: 48/ 93, 51.6% *ASA 3 (n/ N,%)*: 33/ 93, 35.5% *ASA 4 (n/ N,%)*: 0/ 93, 0% *Number of participants randomised*: 98

	Number of participants receiving treatment: 93 *Number of participants analysed*: 93 *Dropout rate*: 5/ 98, 5.1% **Included criteria:** Patients undergoing elective unilateral, primary TKA for end stage osteoarthritis or rheumatoid arthritis **Excluded criteria:** Patients were then excluded for any of the following reasons: (1) an allergy to TXA; (2) preoperative hepatic or renal dysfunction; (3) serious cardiac or respiratory disease, including coronary artery stent placement; (4) congenital or acquired coagulopathy, as evidenced by an international normalized ratio (INR) of > 1.4 or a partial thromboplastin time (PTT) of > 1.4 times normal; (5) thrombocytopenia, as identified by a preoperative platelet count of < 150,000/mm3; (6) a history of a pro-thrombotic condition; (7) pregnancy; (8) breastfeeding; (9) donated preoperative autologous blood; (10) an age of < 18 years or > 80 years; and/or (11) a preoperative hemoglobin level of < 10 g/dl **If TKR, is tourniquet used:** Yes time: TXA IV, 82.36 ± 4.54 , TXA PAI 82.93 ± 3.21 **Indication for surgery:** End stage osteoarthritis or rheumatoid arthritis **Type of anaesthetic:** Not reported **Type of surgery:** Primary unilateral TKA
Interventions	**Intervention Characteristics** TXA, IV In the IV group, a 60-ml multimodal cocktail periarticular injection (MCPI) with ropivacaine, 200 mg/20ml (AstraZeneca AB, Sweden); morphine, 10 mg/1 ml(domestic company); flurbiprofen axetil injection, 50 mg/5 ml (Beijing Tide Pharmaceutical Co., Ltd., China); adrenaline, 0.25 mg (1:1000); betamethasone, 7 mg/1 ml (Schering-Plow Labo NV, Belgium); and 34 ml of normal saline solution was prepared in three 20-ml syringes. Ten minutes before skin incision, patients received 1000mg of IV TXA (110 ml total volume) IV administration. TXA, IV, 1g, preop TXA, Peri-articular In the PAI group, the 60-ml MCPI was the same as that in the IV TXA group, except that TXA 1000 mg/10ml (Guangzhou Baiyunshan Pharmaceutical Co., Ltd.,China) was added. Before incision, patients received 110ml of saline IV administration as a placebo.

	TXA, PA, 1g, preop
Outcomes	Primary outcome: Total blood loss Hidden blood loss Hemoglobin drift Haematocrit drift Need for a blood transfusion Secondary outcome: Deep Vein Thrombosis. D-dimer levels Complications (including local soft tissue complications, skin necrosis, peroneal nerve palsies, superficial and deep surgical site infections, symptomatic VTEs, cerebrovascular accident, and myocardial infarction)
Notes	**Sponsorship source:** Non-Pharmaceutical (2016 Perioperative Orthopaedic Blood Management Research Project from the China International Medical Exchange Foundation) **Country:** China **Setting:** Single-centre **Comments:** None **Authors name:** H-M Peng **Institution:** Chinese Academy of Medical Sciences & Peking Union Medical College **Email:** penghuiming@139.com, or corresponding author: Jin Lin - lin_chaos@sina.com **Address:** Department of Orthopaedic Surgery, Peking Union Medical College Hospital, Chinese Academy of Medical Sciences & Peking Union Medical College, No.1, Shuaifuyuan Wangfujing, Dongcheng District, Beijing 100730, China **Native language of paper:** English **Reference type:** Full text (1), trial registration (1) **Trial registration number:** ChiCTR-INR-16010270 **Was it translated for this review:** No

B.1.4.69 Petsatodis 2006

Methods	**Study design:** RCT **Intention to treat analysis:** Yes **Length of duration of study:** Not reported **Power calculation reached:** Not reported **Transfusion strategy:** Not reported **Was the trial stopped early:** No
Participants	**Baseline Characteristics** Placebo *Age (years) (mean SD)*: 59.6 (10.9) *Ethnicity*: Not reported *Gender (males)*: Not reported *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 25 *Number of participants receiving treatment*: 25 *Number of participants analysed*: 25 *Dropout rate*: 0/25 (0%) Aprotinin *Age (years) (mean SD)*: 58.4 (12.5) *Ethnicity*: Not reported *Gender (males)*: Not reported *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported

	Co-morbidities: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 25 *Number of participants receiving treatment*: 25 *Number of participants analysed*: 25 *Dropout rate*: 0/25 (0%) Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males)*: Not reported *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 50 *Number of participants receiving treatment*: 50 *Number of participants analysed*: 50 *Dropout rate*: 0 **Included criteria:** 1) Patients with hip osteoarthritis necessitating THA **Excluded criteria:** 1) Suspected allergy to aprotinin or previous treatment with the drug. **Pre-treatment:** Unclear, no gender reported. **If TKR, is tourniquet used:** Not applicable **Indication for surgery:** Hip osteoarthritis **Type of anaesthetic:** Not reported **Type of surgery:** Primary THR

Interventions	**Intervention Characteristics** Placebo Same volume of normal saline Placebo, IV, intraop bolus at induction + Placebo, IV, infusion Aprotinin Bolus of 20,000 kIU/kg at the time of anaesthesia followed by an infusion of 50,000 kIU/hr Aprotinin, IV, 20,000 KIU/kg, intraop bolus at induction AND Aprotinin, IV, 50,000 KIU/hr, infusion
Outcomes	Primary outcome: Intra and postoperative blood loss Amount of transfusion units Secondary outcome: Clinical signs of DVT
Notes	**Sponsorship source:** Not reported **Country:** Greece **Setting:** Not reported **Comments:** None **Authors name:** G. Petsatodis **Institution:** Aristotle University **Email:** Not reported **Address:** 1st Orthopaedic Department, G. Papanikolaou Hospital, Aristotle University, Thessaloniki, Greece **Native language of paper:** English **Reference type:** Full text (1) **Trial registration number:** Not applicable, but when checked trial registration number not found **Was it translated for this review:** No

B.1.4.70 Ray 2005

Methods	**Study design:** RCT **Intention to treat analysis:** Yes **Length of duration of study:** Not reported

	Power calculation reached: No **Transfusion strategy:** Not reported **Was the trial stopped early:** Yes
Participants	**Baseline Characteristics** Placebo *Age (years) (median IQR)*: 69 (58-74) *Ethnicity*: Not reported *Gender (males, females)*: Not reported *Length of surgery (minutes) (median IQR)*: 104 (87-116) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: 3/15 (20%) *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 15 *Number of participants receiving treatment*: 15 *Number of participants analysed*: 15 *Dropout rate*: 0/15 (0%) EACA *Age (years) (median IQR)*: 72 (59-77) *Ethnicity*: Not reported *Gender (males, females)*: Not reported *Length of surgery (minutes) (median IQR)*: 111 (89-125) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: 2/15 (13.3%) *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported

	Number of participants randomised: 15 *Number of participants receiving treatment*: 15 *Number of participants analysed*: 15 *Dropout rate*: 0/15 (0%) Aprotinin *Age (years) (median IQR)*: 72 (65-81) *Ethnicity*: Not reported *Gender (males, females)*: Not reported *Length of surgery (minutes) (median IQR)*: 100 (75-120) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: 2/15 (13.3%) *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 15 *Number of participants receiving treatment*: 15 *Number of participants analysed*: 15 *Dropout rate*: 0/15 (0%) Overall *Age (years) (median IQR)*: Not reported *Ethnicity*: Not reported *Gender (males, females)*: Not reported *Length of surgery (minutes) (median IQR)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: Not reported

	Number of participants receiving treatment: Not reported *Number of participants analysed*: Not reported *Dropout rate*: Not reported **Included criteria:** 1) Undergoing primary, unilateral cemented THA under general anaesthesia, 2) Preoperative hemoglobin of <150 g L-1 for males and <140 g L-1 for female **Excluded criteria:** 1) Previous exposure to aprotinin (to avoid the increased likelihood of allergic response entailed with such exposure), 2) Abnormal preoperative coagulation profile (with the exception of platelet function as measured by whole blood platelet aggregometry employing collagen agonist at 1 micro grams mL-1), 3) Previous history of DVT, pulmonary embolus, stroke or transient ischemic attacks, 4) A strong family history of thrombosis, 5) Malignancy, 6) Renal failure (creatinine >0.15 mmol L-1), 7) Patients who would not consent to receive blood transfusion if required **Pre-treatment:** There was a significant difference in starting hemoglobin between EACA and placebo groups. **If TKR, is tourniquet used:** Not applicable **Indication for surgery:** Not reported **Type of anaesthetic:** General anaesthetic **Type of surgery:** Primary THR
Interventions	**Intervention Characteristics** Placebo Patients in the placebo group received saline only in the same way. Placebo, IV, intraop bolus over 30 mins AND Placebo, IV intraop infusion for 3 hours EACA Patients in the EACA group received 10 g of EACA in250 mL of IV saline given over 30 min after the induction of anaesthesia followed by 5 g in 250 mL of IV saline over 3 h EACA, IV, 10g, intraop bolus over 30 mins AND EACA, IV, 5g , intraop infusion for 3 hours Aprotinin Patients assigned to the aprotinin group received a 10 000 kallikrein inhibitor units (KIU) test dose of aprotinin (preservative free Trasylol, Bayer AG, Leverkusen, Germany) to test for any potential allergic reaction. Ten minutes later, aprotinin was administered as a bolus dose of 2 · 106 KIU given over 30 min after induction of

	anaesthesia followed by0.5 · 106 KIU h) 1 for 3 h Aprotinin, IV, 10,000 KIU, preop test dose AND Aprotinin, IV, 2 x 10^6, intraop bolus over 30 mins AND Aprotinin, IV, 0.5 x 10^6 KIU , intraop infusion for 3 hours
Outcomes	Primary outcome: Blood loss Transfusion requirements Complications Adverse events Secondary outcome: Not reported
Notes	**Sponsorship source:** Non-pharmaceutical **Country:** Australia **Setting:** Single-centre **Comments:** None **Authors name:** R. Crawford **Institution:** The Prince Charles Hospital **Email:** r.crawford@ qut.edu.au **Address:** Level 5, Clinical Science Building, The Prince Charles Hospital, Brisbane, Queensland 4032, Australia **Native language of paper:** English **Reference type:** Abstract (1) Full Text (1) **Trial registration number:** Not applicable, but when checked trial registration number not found **Was it translated for this review:** No

B.1.4.71 Schott 1995

Methods	**Study design:** RCT **Intention to treat analysis:** Yes **Length of duration of study:** Not reported **Power calculation reached:** No **Transfusion strategy:** (Erythrocyte volume fraction (EVF)) heterologous erythrocyte concentrate was transfused to correct EVF >27%. **Was the trial stopped early:** No

Participants	**Baseline Characteristics** Placebo *Age (years) (mean SD)*: 68 (7) *Ethnicity*: Not reported *Gender (males, females)*: 15, 25 *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: 0/40 (0%) *Incidence of preoperative anaemia (n/ N, %)*: 0/40 (0%) *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 40 *Number of participants receiving treatment*: 40 *Number of participants analysed*: 40 *Dropout rate*: 0/40 (0%) Desmopressin *Age (years) (mean SD)*: 71 (9) *Ethnicity*: Not reported *Gender (males, females)*: 20, 19 *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: 0, 0% *Incidence of preoperative anaemia (n/ N, %)*: 0/39 (0%) *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 40 *Number of participants receiving treatment*: 39 *Number of participants analysed*: 39 *Dropout rate*: 1/40 (2.5%)

	Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males, females)*: Not reported *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia (n/ N, %)*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 80 *Number of participants receiving treatment*: 79 *Number of participants analysed*: 79 *Dropout rate*: 1/79 **Included criteria:** 1) Normally haemostatic patients, scheduled for elective total hip replacement surgery for primary coxarthrosis. **Excluded criteria:** 1) Patients with secondary coxarthrosis were excluded, 2) Patients receiving acetylsalicylic acid or any other platelet inhibiting medication within 10 days prior to surgery, 3) Patients suffering from anaemia, diabetes mellitus, rheumatic disease or any disorder requiring steroid therapy, 4) Abnormal preoperative coagulation status and an abnormal bleeding time >580 s (Simplate II test, which was performed by the same person in all patients). **Pre-treatment:** No **If TKR, is tourniquet used:** Not applicable **Indication for surgery:** Primary coxarthrosis **Type of anaesthetic:** Spinal anaesthetic **Type of surgery:** Primary THR
Interventions	**Intervention Characteristics** Placebo Immediately after induction of spinal anaesthesia, the patient received in a double-blind fashion placebo or desmopressin, 0.3 micro g/kg BW. diluted in 50 ml NaCl

	and infused over 15 minutes. Six hours after the first dose (i.e. post-surgery, a second infusion was administered in an identical way). Placebo, IV, intraop (immediately after spinal) AND Placebo, IV, 6 hours post 1st dose Desmopressin Immediately after induction of spinal anaesthesia, the patient received in a double-blind fashion placebo or desmopressin, 0.3 pg/kg B\V. diluted in 50 ml NaCI and infused over 15 minutes. Six hours after the first dose (i.e. post-surgery), a second infusion was administered in an identical way. Desmopressin, IV, 0.3 micrograms/kg, intraop (immediately after spinal) AND Desmopressin, IV, 0.3 micrograms/kg, 6 hours post 1st dose
Outcomes	Primary outcome: Blood loss Transfusions and dextran infusions Haemostasis
Notes	**Sponsorship source:** Pharmaceutical **Country:** Sweden **Setting:** Not reported **Comments:** None **Authors name:** U. Schott **Institution:** Orebro Medical Center Hospital **Email:** Not reported **Address:** Departments of Anaesthesiology and Orthopedics, Regional Blood Centre, Orebro Medical Centre Hospital, Orebro, Sweden **Native language of paper:** English **Reference type:** Full text (1) **Trial registration number:** Not applicable, but when checked trial registration number not found **Was it translated for this review:** No

B.1.4.72 Sershon 2020

Methods	**Study design:** RCT

	Intention to treat analysis: No, per-protocol analysis done - report both ITT and per protocol **Length of duration of study:** 37 months (July 2016 to August 2019) + Follow-up (follow-up period not reported) **Power calculation reached:** Yes **Transfusion strategy:** Hemoglobin <7.0 g/dL or symptomatic anemia not responsive to IV fluid hydration, History of cardiac disease and hemoglobin <8.0 g/dL or symptomatic anemia not responsive to IV fluid hydration. Active arterial thromboembolic event and hemoglobin<10.0 g/dL, sepsis with hemoglobin <10.0 g/dL, or symptomatic anemia not responsive to IV fluid hydration **Was the trial stopped early:** No
Participants	**Baseline Characteristics** Single-dose IV group *Age (years) (mean SD)*: 66.8 (12.0) *Ethnicity*: Not reported *Gender (males, females)*: 23/ 43 M (53%), 20/ 43 F (47%) *Length of surgery (minutes) (mean SD)*: 134 (57) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Aspirin: 35/ 43 (81.4%); Warfarin: 4/ 43 (9.3%); Apixaban: 0/ 43 (0%); Enoxaparin: 4/ 43 (9.3%); Rivaroxaban: 0/ 43 (0%) *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Mean only: 2.5 ± 0.6 *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 47 *Number of participants receiving treatment*: 43 *Number of participants analysed*: 43 *Dropout rate*: 4/47 (8.5%) Double-dose IV group *Age (years) (mean SD)*: 67.8 (13.2) *Ethnicity*: Not reported *Gender (males, females)*: 18/ 40 M (45%), 22/ 40 F (55%)

	Length of surgery (minutes) (mean SD): 152 (66) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Aspirin: 31/ 40 (77.5%); Warfarin: 4/ 40 (10%); Apixaban: 0/ 40 (0%); Enoxaparin: 3/ 40 (7.5%); Rivaroxaban: 2/ 40 (5.0%) *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Mean only: 2.5 ± 0.6 *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 46 *Number of participants receiving treatment*: 40 *Number of participants analysed*: 40 *Dropout rate*: 6/ 46, 13% Combined IV and Topical group *Age (years) (mean SD)*: 66.5 (14.4) *Ethnicity*: Not reported *Gender (males, females)*: 19/ 46 M (41%), 27/ 46 F (59%) *Length of surgery (minutes) (mean SD)*: 155 ± 57 *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Aspirin: 37/ 46 (80.4%); Warfarin: 3/ 46 (6.5%); Apixaban: 1/ 46 (2.2%); Enoxaparin: 3/ 46 (6.5%); Rivaroxaban: 2/ 46 (4.4%) *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Mean only: 2.5 ± 0.6 *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 54 *Number of participants receiving treatment*: 46 *Number of participants analysed*:*46* *Dropout rate*: 8/ 54, 14.8% Multi-dose Oral group *Age (years) (mean SD)*: 64.0 (12.3)

	Ethnicity: Not reported *Gender (males, females)*: 26/ 46 M (56%), 20/ 46 F (44%) *Length of surgery (minutes) (mean SD)*: 148 (46) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Aspirin: 33/ 46 (71.7%); Warfarin: 5/ 46 (10.9%); Apixaban: 1/ 46 (2.2%); Enoxaparin: 4/ 46 (8.7%); Rivaroxaban: 3/ 46 (6.5%) *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Mean only: 2.4 ± 0.6 *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 54 *Number of participants receiving treatment*: 46 *Number of participants analysed*: 46 *Dropout rate*: 8/ 54, 14.8% Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males, females)*: 86/ 175 M (49%), 89/ 175 F (51%) *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 251 *Number of participants receiving treatment*: 175 *Number of participants analysed*: 175 *Dropout rate*: 76/ 251, 30.3% **Included criteria:** Patients indicated for a revision total hip

	arthroplasty were approached to participate. Revision total hip arthroplasty was defined as a both-component (femoral and acetabular) revision, femoral revision, acetabular revision, resection arthroplasty with antibiotic spacer insertion, or second-stage reimplantation **Excluded criteria:** Individuals indicated for a modular head and polyethylene liner revision were excluded. Patients were also excluded for any of the following health conditions: prior thromboembolic event, anticoagulant medication (excluding aspirin) within 5 days prior to the surgical procedure, New York Heart Association Class-III or IV heart failure, myocardial infarction or cardiac stenting within 6 months of the surgical procedure, hepatic failure, renal failure requiring dialysis, pulmonary disease requiring supplemental oxygen, documented allergy to TXA, acquired disturbances of colour vision, and the refusal to receive blood products **Pre-treatment:** **If TKR, is tourniquet used:** Not applicable **Indication for surgery:** Not reported **Type of anaesthetic:** General, General and nerve block, Spinal and epidural, Spinal, Spinal and nerve block, General and epidural, Epidural, Spinal and general **Type of surgery:** Revision THA
Interventions	**Intervention Characteristics** Single-dose IV group The single-dose IV group, was administered a single dose of 1-g IV TXA prior to incision and during preparing and draping. TXA, IV, 1g, preop Double-dose IV group The double dose IV group, was administered a double dose of IV TXA, in which the first dose of 1-g IV TXA was administered during preparing and draping with an additional 1-g IV TXA given at the time of skin closure TXA, IV, 1g, preop + IV, 1g, intraop Combined IV and Topical group The combined IV and topical dose group, was administered a dose of 1-g IV TXA during preparing and draping and a dose of 1-g intra-articular TXA was introduced immediately following arthrotomy closure TXA, IV, 1g, preop + IA, 1g, intraop

	Multi-dose Oral group The multidose oral group, was administered a total of 1,950 mg (3 tablets of 650 mg each) of oral TXA 2 hours prior to incision, 6 hours postoperatively, and on the morning of postoperative day 1. TXA, Oral, 1 x 650g, preop + 1 x 650g 6hrs postop + 1 x 650g day 1 postop am
Outcomes	Primary outcome: Postoperative hemoglobin value Secondary outcome: Deep vein thrombosis Venous thromboembolic complications Cerebrovascular events Transient ischemic attacks Calculated blood loss Rate of transfusion Need for transfusion Length of stay
Notes	**Sponsorship source:** Not reported but this information was given... ''Disclosure: The authors received partial financial support through a multipurpose resident grant from the Mid-America Orthopaedic Association. On the Disclosure of Potential Conflicts of Interest forms, which are provided with the online version of the article, one or more of the authors checked “yes” to indicate that the author had a relevant financial relationship in the biomedical arena outside the submitted work and “yes” to indicate that the author had other relationships or activities that could be perceived to influence, or have the potential to influence, what was written in this work'' **Country:** USA **Setting:** Multi-centre **Comments:** ASA given as an average, not individual grades (ASA I, ASA II, ASA III etc) **Authors name:** R.A. Sershon **Institution:** Anderson Orthopaedic Research Institute **Email:** bobsershon@gmail.com **Address:** Department of Orthopaedic Surgery, Anderson Orthopaedic Research Institute, Alexandria, Virginia, USA

	Native language of paper: English **Reference type:** Full text (2), trial registration (1) **Trial registration number:** NCT02877381 **Was it translated for this review:** No

B.1.4.73 Staniforth 2017

Methods	**Study design:** RCT **Intention to treat analysis:** Unclear **Length of duration of study:** 20 months (17 + 3 months follow-up) **Power calculation reached:** Not reported **Transfusion strategy:** Not reported **Was the trial stopped early:** No
Participants	**Baseline Characteristics** Placebo *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males)*: Not reported *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: 0/0 (0%) *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 70 *Number of participants receiving treatment*: Not reported *Number of participants analysed*: Not reported *Dropout rate*: Not reported TXA, IA *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported

	Gender (males): Not reported *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: 0/0 (0%) *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 70 *Number of participants receiving treatment*: Not reported *Number of participants analysed*: Not reported *Dropout rate*: Not reported Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males)*: Not reported *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 140 *Number of participants receiving treatment*: Not reported *Number of participants analysed*: Not reported *Dropout rate*: Not reported **Included criteria:** 1) 18 Years and older, 2) Osteoarthritis, 3) scheduled for elective primary unilateral THR or TKR, 4) provided informed consent, 5) can read, write and speak English **Excluded criteria:** 1) History of arterial or venous

	thromboembolic disease (myocardial infarction, symptomatic ischemic heart disease, atrial fibrillation, cerebrovascular accident, deep-vein thrombosis, pulmonary embolus, or thrombogenic cardiac valvular disease or rhythm disease), 2) pre-operative Hb of <120 g/L, 3) Known allergy to Tranexamic Acid, 4) Coagulation disorder, 5) Acquired disturbances of colour vision, 6) Hepatic insufficiency, any history of liver disease, 7) Renal insufficiency (on dialysis), 8) Preoperative prophylactic use of antiplatelet or anticoagulant therapy such as Clopidogrel, Warfarin, dabigatran or Rivaroxaban. This does not include low dose Aspirin (81mg), 9) Patients with a history of subarachnoid haemorrhage [20], 10) Simultaneous bilateral THA or TKA, 11) Any contra-indication for spinal anaesthesia, 12) Allergy to Celecoxib, which will be the only nonsteroidal anti-inflammatory drugs (NSAID) used in the multi-modal analgesia regime, 13) Retinal vein or retinal artery occlusion, 14) Female on oral contraceptive pills and/or premenopausal, 15) Concurrently taking hydrochlorothiazide, desmopressin, sulbactam-ampicillin, carbazochrome, ranitidine and/or nitroglycerin for the duration of the surgery **Pre-treatment:** Unclear **If TKR, is tourniquet used:** Not reported **Indication for surgery:** Osteoarthritis **Type of anaesthetic:** Spinal **Type of surgery:** Primary THR and primary TKR
Interventions	**Intervention Characteristics** Placebo They were randomized to either receive 0.5 G of TXA in 50 ml NS or 50 ml of NS injected intra-articularly after closure of the joint capsule during surgery Placebo, IA, intraop after closure through temporary catheter TXA, IA They were randomized to either receive 0.5 G of TXA in 50 ml NS or 50 ml of NS injected intra-articularly after closure of the joint capsule during surgery TXA, IA, 0.5g, intraop after closure through temporary catheter
Outcomes	Primary outcome: Blood loss Thromboembolic complications

	Blood transfusions Other postoperative complications
Notes	**Sponsorship source:** Non-pharmaceutical **Country:** Canada **Setting:** Single-centre **Comments:** None **Authors name:** C. Staniforth **Institution:** University of Manitoba **Email:** Not reported **Address:** Orthopaedic Innovation Centre Concordia Hip & Knee Institute Suite 320-1155 Concordia Avenue Winnipeg, Manitoba, Canada R2K 2M9 **Native language of paper:** English **Reference type:** Abstract (1) Trial Registration (1) **Trial registration number:** NCT02393963 **Was it translated for this review:** No

B.1.4.74 Stowers 2017

Methods	**Study design:** RCT **Intention to treat analysis:** Yes **Length of duration of study:** 16 months + Follow-up **Power calculation reached:** Yes **Transfusion strategy:** The criteria for transfusion of blood products was an Hb<80 g/L,or an Hb<100 g/L in a patient with ischemic heart disease or with symptomatic anemia. Intravenous fluids in the perioperative period were also measured to account for any differences in haemodilution effect on Hb recordings between the 3 groups **Was the trial stopped early:** No
Participants	**Baseline Characteristics** Placebo *Age (years) (mean SD)*: 70 (7.6) *Ethnicity*: Not reported *Gender (males, females)*: 4, 19 *Length of surgery (minutes)*: Not reported

	Proportion of participants on anticoagulants prior to surgery (n/ N, %): Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities (n/ N, %)*: Type 2 Diabetes - 4/ 23, 17%, Hypertension - 12/ 23, 52%, Cholesterol - 4/ 23, 17%, Chronic Obstructive Pulmonary Disease - 0/ 23, 0%, Ischemic Heart Disease - 0/ 23, 0% *ASA 1 (n/ N,%)*: 4/ 23, (17.39%) *ASA 2 (n/ N,%)*: 15/ 23, (65.22%) *ASA 3 (n/ N,%)*: 4/ 23, (17.39%) *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 30 *Number of participants receiving treatment*: Not reported *Number of participants analysed*: 23 *Dropout rate*: 7/ 30, (23.33) TXA, IA *Age (years) (mean SD)*: 70 (8.5) *Ethnicity*: Not reported *Gender (males, females)*: 28, 32 *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities (n/ N, %)*: Type 2 Diabetes - 14/ 60, 23%, Hypertension - 36/ 60, 60%, Cholesterol - 17/ 60, 28%, Chronic Obstructive Pulmonary Disease - 6/ 60, 10%, Ischemic Heart Disease - 4/ 60, 7% *ASA 1 (n/ N,%)*: 4/ 60, (6.67%) *ASA 2 (n/ N,%)*: 48/ 60, (80%) *ASA 3 (n/ N,%)*: 8/ 60, (13.33%) *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 60 *Number of participants receiving treatment*: Not reported *Number of participants analysed*: 60 *Dropout rate*: 0/ 60, (0%) TXA, IV *Age (years) (mean SD)*: 71 (8.6)

	Ethnicity: Not reported *Gender (males, females)*: 27, 24 *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities (n/ N,%)*: Type 2 Diabetes - 5/51, 10%, Hypertension - 29/ 51, 57%, Cholesterol - 15/ 51, 29%, Chronic Obstructive Pulmonary Disease - 7/ 51, 14%, Ischemic Heart Disease - 4/ 51, 8% *ASA 1 (n/ N,%)*: 10/ 51, (19.60%) *ASA 2 (n/ N,%)*: 28/ 51, (54.90%) *ASA 3 (n/ N,%)*: 13/ 51, (25.49%) *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 60 *Number of participants receiving treatment*: 60 *Number of participants analysed*: 51 *Dropout rate*: 9/ 60, (15%) Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males, females)*: Not reported *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 150 *Number of participants receiving treatment*: 150 *Number of participants analysed*: Not reported *Dropout rate*: Not reported **Included criteria:** Older than 18 years undergoing primary

	unilateral TKA were eligible to participate in the study **Excluded criteria:** 1) History or risk of thrombosis, 2) Active thromboembolic disease, 3) Refused blood products, 4) Known hypersensitivity to TXA or any of its ingredients, 5) Complex hematologic disorders requiring manipulation, 6) Pregnant and lactating women, 7) Taking anticoagulant therapy within 5 days of surgery (warfarin, dabigatran, heparin, rivaroxaban), 8) Severe renal failure (estimated glomerular filtration rate <29). **Pre-treatment:** Yes **If TKR, is tourniquet used:** Yes **Indication for surgery:** Not reported **Type of anaesthetic:** Spinal **Type of surgery:** Primary TKR
Interventions	**Intervention Characteristics** Placebo Intra-articular: 20 mL of normal saline intra-articularly after implantation of prosthesis and closure of arthrotomy followed by standard closure. Intravenous: administration of 20 mL of normal saline intravenously at the same time before release of tourniquet Placebo, IA, intraop (after implantation) + Placebo, IV, intraop (before tourniquet deflation) TXA, IA Intra-articular: 1.5 g TXA in 20 mL intra-articularly after implantation of prosthesis and closure of arthrotomy followed by standard closure. Intravenous: administration of 20 mL of normal saline (in a 20-mLsyringe) intravenously at the same time before release of tourniquet TXA, IA, 1.5g, intraop (after implantation) + Placebo, IV, intraop (before tourniquet deflation) TXA, IV Intra-articular: 20 mL of normal saline intra-articularly after implantation of prosthesis and closure of arthrotomy followed by standard closure. Intravenous: administration of 1.5 g TXA intravenously at the same time before release of tourniquet Placebo, IA, intraop (after implantation) + TXA, IV, 1.5g, intraop (before tourniquet deflation)
Outcomes	Primary outcome:

	Estimated perioperative blood loss. Secondary outcome: Functional measurements using patient self-reported questionnaires (Short-Form 12 survey and Oxford knee scores) Transfusion rates Median length of stay 30-day readmissions Complications (symptomatic deep vein thrombosis (DVT), pulmonary embolism (PE), and infection). Range of motion (both passive and active, was measured as a surrogate for postoperative swelling).
Notes	**Sponsorship source:** None **Country:** New Zealand **Setting:** Multi-centre **Comments:** None **Authors name:** M.D.J. Stowers **Institution:** Middlemore Hospital, Counties Manukau District Health Board (DHB) **Email:** Not reported **Address:** Marinus D. J. Stowers, MBChB, Department of Orthopaedics, Middlemore Hospital, Counties Manukau District Health Board (DHB), Hospital Rd, Auckland 1064, New Zealand **Native language of paper:** English **Reference type:** Full text (1), trial registration (1) **Trial registration number:** NCT02278263 **Was it translated for this review:** No

B.1.4.75 Tanaka 2001

Methods	**Study design:** RCT **Intention to treat analysis:** Not reported **Length of duration of study:** Not reported **Power calculation reached:** Not reported **Transfusion strategy:** In 1988, the National Institutes of Health Consensus Conference on perioperative transfusion suggested appropriate criteria and guidelines, which formed

	the basis for transfusion in our study. **Was the trial stopped early:** No
Participants	**Baseline Characteristics** Placebo *Age (years) (mean range)*: 65 (58-70) *Ethnicity*: Not reported *Gender (males, females)*: 9 M, 17 F *Length of surgery (minutes) (mean range)*: 125 (90-160) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: Not reported *Number of participants receiving treatment*: 26 *Number of participants analysed*: 26 *Dropout rate*: Not reported Pre-op TXA *Age (years) (mean range)*: 65 (59-70) *Ethnicity*: Not reported *Gender (males, females)*: 7 M, 17 F *Length of surgery (minutes) (mean range)*: 110 (80-150) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: Not reported

	Number of participants receiving treatment: 24 *Number of participants analysed*: 24 *Dropout rate*: Not reported Intra-op TXA *Age (years) (mean range)*: 65 (60-71) *Ethnicity*: Not reported *Gender (males, females)*: 7 M, 15 F *Length of surgery (minutes) (mean range)*: 120 (85-155) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: Not reported *Number of participants receiving treatment*: 22 *Number of participants analysed*: 22 *Dropout rate*: Not reported Pre and intra-op TXA *Age (years) (mean range)*: 65 (59-69) *Ethnicity*: Not reported *Gender (males, females)* : 8 M, 19 F *Length of surgery (minutes) (mean range)*: 110 (70-150) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: Not reported *Number of participants receiving treatment*: 27

	Number of participants analysed: 27 *Dropout rate*: Not reported Overall *Age (years) (mean range)*: Not reported *Ethnicity*: Not reported *Gender (males, females)*: Not reported *Length of surgery (minutes) (mean range)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: Not reported *Number of participants receiving treatment*: 99 *Number of participants analysed*: 99 *Dropout rate*: Not reported **Included criteria:** Rheumatoid arthritis or osteoarthritis patients who were to have a unilateral bicondylar cemented TKA **Excluded criteria:** 1) Known allergy to drug, 2) Preoperative hepatic or renal dysfunction, 3) Serious cardiac or respiratory disease, 4) Congenital or acquired coagulopathy, 5) History of thromboembolic disease. **Pre-treatment:** No **If TKR, is tourniquet used:** Yes **Indication for surgery:** Rheumatoid arthritis or osteoarthritis **Type of anaesthetic:** Not reported **Type of surgery:** Primary TKR
Interventions	**Intervention Characteristics** Placebo Pairs of ampoules, each containing 20 ml of either TNA (Rikavarin 100 mg/ml; Asahi Chemical Industry Co Ltd, Japan) or a placebo (physiological saline) were numbered

	and placed in envelopes at random by a pharmacologist. A slow intravenous injection of the contents of each ampoule, the constituents of which were known only to the pharmacologist, was given by the anaesthetist. The patients were given either: 1) saline twice, ten minutes before surgery and on deflation of the tourniquet (control group) Placebo, saline IV, 20ml, pre-op + intra-op (at tourniquet deflation) Pre-op TXA Pairs of ampoules, each containing 20 ml of either TNA (Rikavarin 100 mg/ml; Asahi Chemical Industry Co Ltd, Japan) or a placebo (physiological saline) were numbered and placed in envelopes at random by a pharmacologist. A slow intravenous injection of the contents of each ampoule, the constituents of which were known only to the pharmacologist, was given by the anaesthetist. The patients were given either: 2) 20 mg/kg of TXA ten minutes before surgery and saline ten minutes before deflation of the tourniquet (preop TXA group) TXA, IV, 20mg/kg, preop + placebo, IV, 20ml, intra-op (at tourniquet deflation) Intra-op TXA Pairs of ampoules, each containing 20 ml of either TNA (Rikavarin 100 mg/ml; Asahi Chemical Industry Co Ltd, Japan) or a placebo (physiological saline) were numbered and placed in envelopes at random by a pharmacologist. A slow intravenous injection of the contents of each ampoule, the constituents of which were known only to the pharmacologist, was given by the anaesthetist. The patients were given either: 3) saline ten minutes before surgery and 20 mg/kg of TXA ten minutes before deflation of the tourniquet (intraop TXA group) Placebo, saline IV, 20ml, pre-op + TXA, IV, 20mg/kg, intra-op (at tourniquet deflation) Pre and intra-op TXA Pairs of ampoules, each containing 20 ml of either TNA (Rikavarin 100 mg/ml; Asahi Chemical Industry Co Ltd, Japan) or a placebo (physiological saline) were numbered and placed in envelopes at random by a pharmacologist. A slow intravenous injection of the contents of each ampoule, the constituents of which were known only to the pharmacologist, was given by the anaesthetist. The patients were given either: 4) 10 mg/kg of TXA ten minutes before surgery and again ten minutes before deflation of the tourniquet (pre- and intraop TXA group). TXA, IV, 10mg/kg, preop + TXA, IV, 10mg/kg, intra-op (at

	tourniquet deflation)
Outcomes	Primary outcome: Blood loss Adverse events (thromboembolic and other complications) Secondary outcome: Not reported
Notes	**Sponsorship source:** None **Country:** Japan **Setting:** Single-centre **Comments:** None **Authors name:** N. Tanaka **Institution:** Sapporo Gorinbashi Orthopaedic Hospital **Email:** Not reported **Address:** Sapporo Gorinbashi Orthopaedic Hospital, Gorinbashi Health Care Facilities and Hospitals, 2-1 Kawazoe, Minami-ku, Sapporo, Hokkaido 005-0802, Japan. **Native language of paper:** English **Reference type:** Full text (1) **Trial registration number:** Not applicable, but when checked trial registration number not found **Was it translated for this review:** No

B.1.4.76 Tsukada 2019

Methods	**Study design:** RCT **Intention to treat analysis:** Yes **Length of duration of study:** 23 months + 3 months follow-up **Power calculation reached:** Yes **Transfusion strategy:** We planned additional allogenic blood transfusion for patients with a hemoglobin level of < 7.0 g/dL who were asymptomatic and those with a hemoglobin level of < 10.0 g/dL who had symptoms related to anemia **Was the trial stopped early:** No
Participants	**Baseline Characteristics**

	TXA, IV + Placebo, IA *Age (years) (mean SD)*: 77 (6) *Ethnicity*: Not reported *Gender (males, females)*: 6 M, 28 F *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n, %)*: 5, 14.7% *Incidence of preoperative anaemia*: Not reported *Co-morbidities (n/ N)*: 6/28 *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 34 *Number of participants receiving treatment*: 34 *Number of participants analysed*: 34 *Dropout rate*: 0/ 34, 0% TXA, IV + TXA, IA *Age (years) (mean SD)*: 75 (6) *Ethnicity*: Not reported *Gender (males, females)*: 10 M, 33 F *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n, %)*: 8, 16.6% *Incidence of preoperative anaemia*: Not reported *Co-morbidities (n/ N)*: 9/34 *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 43 *Number of participants receiving treatment*: 43 *Number of participants analysed*: 43 *Dropout rate*: 0/ 43, 0% Overall

	Age (years) (mean SD): Not reported *Ethnicity*: Not reported *Gender (males, females)*: Not reported *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities (n/ N)*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 77 *Number of participants receiving treatment*: 77 *Number of participants analysed*: 77 *Dropout rate*: 0/ 77, 0% **Included criteria:** 1) 20 years of age or older 2) medically fit for simultaneous bilateral TKA **Excluded criteria:** 1) known allergic reaction to TXA 2) patients with pre-operative hemoglobin level under 11.0 g/dL 3) patients who refused blood products 4) patients who were enrolled in another interventional clinical trial within 6 months prior to surgery **If TKR, is tourniquet used:** No **Indication for surgery:** Osteoarthritis **Type of anaesthetic:** General **Type of surgery:** Simultaneous bilateral TKA
Interventions	**Intervention Characteristics** TXA, IV + Placebo, IA In the intravenous TXA group, 1000 mg of TXA was similarly administered intravenously just before the skin incision in the first knee. After closing the capsule and retinaculum, 10 mL of normal saline was administered intra-articularly into each knee. For the patients allocated to the intravenous TXA group, 1000 mg of TXA was administered in the operating theatre. Six hours later, we administered another 1000 mg of TXA intravenously TXA, IV, 1g, pre-incision and Placebo, IA, intraop both knees and TXA, IV, 1g, intraop and TXA, IV, 1g, 6 hours

	postop TXA, IV + TXA, IA Combined TXA group, patients received 1000mg of TXA intravenously (Transamin; Daiichi-Sankyo,Tokyo, Japan) just before the skin incision in the first knee. After implantation of the prosthesis, we closed the capsule and retinaculum. Then, we injected 1000 mg of TXA (10 mL of 100 mg/mL TXA) intra-articularly into each knee through the medial patellar retinaculum using a 23-gauge needle. Thus, a total of 3000 mg of TXA was administered in the operating theatre for patients allocated to the combined TXA group. In the ward, an-other 1000 mg of TXA was given intravenously 6 h after the initial intravenous administration TXA, IV, 1g, pre-incision and TXA, IA, 1g, intraop both knees and TXA, IV, 1g, 6 hours postop
Outcomes	Primary outcome Perioperative blood loss calculated Change in hemoglobin from preoperative to postoperative day 3. Secondary outcome Calculated blood loss at 7 days after TKA Number of patients requiring allogeneic blood transfusion Major bleeding Thrombotic events up to 3 months after TKA
Notes	**Sponsorship source:** Non-pharmaceutical funding **Country:** Japan **Setting:** Single-centre **Comments:** Paper says patients were allowed to continue anticoagulant tablets but data not reported **Authors name:** S. Tsukada **Institution:** Hokusuikai Kinen Hospital **Email:** s8058@nms.ac.jp **Address:** Department of Orthopaedic Surgery, Hokusuikai Kinen Hospital, 3-2-1 Higashihara, Mito, Ibaraki 310-0035, Japan **Native language of paper:** English **Reference type:** Full text (1), trial registration (1) **Trial registration number:** UMIN000026137

	Was it translated for this review: No

B.1.4.77 Tsukada 2020

Methods	**Study design:** RCT **Intention to treat analysis:** Yes **Length of duration of study:** 13 months + 3 months (Follow-up) **Power calculation reached:** Yes **Transfusion strategy:** We used a standardized allogeneic transfusion protocol whereby red blood cells were transfused if the hemoglobin concentration was <7.0 g/dL or if it was <10.0 g/dL and associated with symptoms related to anemia. **Was the trial stopped early:** No
Participants	**Baseline Characteristics** TXA, IV and IA + postop Placebo *Age (years) (mean SD)*: 75 (6) *Ethnicity*: Not reported *Gender (males, females)*: 14 M, 40 F *Length of surgery (minutes) (mean SD)*: 96 (15) *Proportion of participants on anticoagulants prior to surgery (n, %)*: 12, 28% *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Diabetes 10/44 *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 54 *Number of participants receiving treatment*: 54 *Number of participants analysed*: 54 *Dropout rate*: 0/ 54, 0% TXA, IV and IA + postop TXA, IV *Age (years) (mean SD)*: 75 (7) *Ethnicity*: Not reported

	Gender (males, females): 9 M, 37 F *Length of surgery (minutes) (mean SD)*: 102 (16) *Proportion of participants on anticoagulants prior to surgery (n, %)*: 9, 24% *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Diabetes 7/39 *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 46 *Number of participants receiving treatment*: 46 *Number of participants analysed*: 46 *Dropout rate*: 0/ 46, 0% Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males, females)*: Not reported *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: Not reported *Number of participants receiving treatment*: Not reported *Number of participants analysed*: Not reported *Dropout rate*: Not reported **Included criteria:** 1) >20 years of age, 2) undergoing primary unilateral TKA, 3) medically fit for an operation, and suitable for TKA **Excluded criteria:** 1) Known allergic reaction to TXA

	If TKR, is tourniquet used: No **Indication for surgery:** Osteoarthritis of the knee, rheumatoid arthritis, avascular necrosis **Type of anaesthetic:** General **Type of surgery:** Primary TKR
Interventions	**Intervention Characteristics** TXA, IV and IA + postop Placebo In the placebo group, intravenous normal saline solution (100 mL) was administered 6 hours after the first intravenous administration of TXA and at 8:00A.M.and 8:00P.M.1 day after TKA. TXA, IV, 1g, pre-incision and TXA IA 1g, intraop and Placebo IV, 6 hours, 12 hours and 24 hours TXA, IV and IA + postop TXA, IV In both groups, patients received intravenous TXA (1,000 mg/100 mL) (Transamin; Daiichi Sankyo) just before skin incision. After implantation of the prosthesis and arthrotomy closure, we injected 1,000 mg of TXA into the knee joint with use of a 23-gauge needle that penetrated the medial patellar retinaculum and knee capsule in the TXA group, patients received intravenous TXA (1,000 mg/100 mL) 6 hours after the first intravenous administration of TXA and at 8:00A.M.and 8:00P.M.1 day after TKA. TXA, IV, 1g, pre-incision and TXA IA 1g, intraop and TXA IV 1g, 6 hours, 12 hours and 24 hours
Outcomes	Primary outcome Volume of perioperative blood loss Change in hemoglobin from preoperatively to 3 days postoperatively Secondary outcome Volume of perioperative blood loss at 7 days after TKA Range of knee motion Complications Major bleeding Thrombotic events Volume of perioperative blood loss at 1 day after TKA Number of patients requiring allogeneic blood transfusion
Notes	**Sponsorship source:** No external funding

	Country: Japan **Setting:** Single-centre **Comments:** Patients included taking anti-coagulants **Authors name:** S. Tsukada **Institution:** Hokusuikai Kinen Hospital **Email:** s8058@nms.ac.jp **Address:** Department of Orthopaedic Surgery, Hokusuikai Kinen Hospital, Mito, Japan **Native language of paper:** English **Reference type:** Full text (1), trial registration (1) **Trial registration number:** UMIN000030237 **Was it translated for this review:** No

B.1.4.78 Utada 1997

Methods	**Study design:** RCT **Intention to treat analysis:** Yes **Length of duration of study:** 18 months **Power calculation reached:** Not reported **Transfusion strategy:** Not reported **Was the trial stopped early:** No
Participants	**Baseline Characteristics** Placebo *Age (years) (mean SD)*: 64 (5) *Ethnicity*: Not reported *Gender (males, females)*: 2 M, 8 F *Length of surgery (minutes)*: 88 (29) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported

	ASA 4 (n/ N,%): Not reported *Number of participants randomised*: 10 *Number of participants receiving treatment*: 10 *Number of participants analysed*: 10 *Dropout rate*: 0/10 (0%) Aprotinin *Age (years) (mean SD)*: 63 (11) *Ethnicity*: Not reported *Gender (males, females)*: 1 M, 10 F *Length of surgery (minutes)*: 80 (28) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 11 *Number of participants receiving treatment*: 11 *Number of participants analysed*: 11 *Dropout rate*: 0/11 (0%) Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males, females)*: Not reported *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported

	Number of participants randomised: 21 *Number of participants receiving treatment*: Not reported *Number of participants analysed*: Not reported *Dropout rate*: Not reported **Included criteria:** 1) Undergoing primary total hip replacement, 2) ASA classification I or II **Excluded criteria:** 1) History of hip replacement surgery, 2) For whom bone cements were used **Pre-treatment:** No **If TKR, is tourniquet used:** Not applicable **Indication for surgery:** Not reported **Type of anaesthetic:** Combined spinal and general anaesthetic **Type of surgery:** Primary THR
Interventions	**Intervention Characteristics** Placebo After inducing anaesthesia, we started administration of ready-to-use third-party aprotinin or saline 200 mL. In the first 30 minutes, 100 mL was intravenously infused, and thereafter, the infusion speed was at 50 mL/hr until the end of surgery to complete administration of 200 mL in total (aprotinin 1 mL = 10,000 KIU). Placebo, IV, intraop, bolus, + fast intraop infusion (30 mins) + slow intraop infusion until surgery end Aprotinin After inducing anaesthesia, we started administration of ready-to-use third-party aprotinin or saline 200 mL. In the first 30 minutes, 100 mL was intravenously infused, and thereafter, the infusion speed was at 50 mL/hr until the end of surgery to complete administration of 200 mL in total (aprotinin 1 mL = 10,000 KIU). Aprotinin, IV, 2x10^6 KIU, intraop, bolus, + fast intraop infusion (30 mins) 1 x 10^6 KIU + slow intraop infusion 0.5x10^6 KIU until surgery end
Outcomes	Primary outcome: Blood loss Secondary outcome: Not reported
Notes	**Sponsorship source:** Not reported

	Country: Japan **Setting:** Single-centre **Comments:** Results reported mean and SD of transfusions intra op and post op but not total therefore calculated combined means as per Cochrane handbook section 7.7.3.8 **Authors name:** K. Utada **Institution:** Yamaguchi Prefectural Central Hospital **Email:** Not reported **Address:** Department of Anesthesia, Yamaguchi Prefectural Central Hospital, Hofu, 747 **Native language of paper:** Japanese **Reference type:** Full text (1) **Trial registration number:** Not applicable, but when checked trial registration number not found **Was it translated for this review:** Yes

B.1.4.79 Veien 2002

Methods	**Study design:** RCT **Intention to treat analysis:** Yes **Length of duration of study:** Not reported **Power calculation reached:** Yes **Transfusion strategy:** Blood transfusion was indicated when the haematocrit value was less than 28%. **Was the trial stopped early:** No
Participants	**Baseline Characteristics** Placebo *Age (years) (mean SD)*: 69.5 (9.0) *Ethnicity*: Not reported *Gender (males, females)*: 1 M, 14 F *Length of surgery (minutes) (mean SD)*: 70.4 (21.8) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: 0/15, 0% *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported

	ASA 1 (n/ N,%): Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 15 *Number of participants receiving treatment*: 15 *Number of participants analysed*: 15 *Dropout rate*: 0/15 (0%) TXA *Age (years) (mean SD)*: 70.5 (9.5) *Ethnicity*: Not reported *Gender (males, females)*: 4 M, 11 F *Length of surgery (minutes) (mean SD)*: 71.6 (10.4) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: 0/15, 0% *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 15 *Number of participants receiving treatment*: 15 *Number of participants analysed*: 15 *Dropout rate*: 0/15 (0%) Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males, females)*: Not reported *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported

	ASA 2 (n/ N,%): Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 30 *Number of participants receiving treatment*: 30 *Number of participants analysed*: 30 *Dropout rate*: 0/0 (0%) **Included criteria:** 1) Patients scheduled for primary cemented TKR surgery **Excluded criteria:** 1) Patient age less than 18 years, 2) Recent myocardial infarction (<6 months), 3) Unstable angina, 4) Severe aortic or mitral valve stenosis, 5) Previous stroke, 6) Unmedicated hypertension, 7) History of thromboembolic episodes, 8) Bleeding disorders or warfarin medication. **Pre-treatment:** No **If TKR, is tourniquet used:** Yes **Indication for surgery:** Not reported **Type of anaesthetic:** Spinal anaesthetic **Type of surgery:** Primary TKR
Interventions	**Intervention Characteristics** Placebo Randomized according to a computer-generated randomization table for either TXA or not TXA (non-TXA) (no other information given about this arm) ASSUMED not reported: Placebo, IV, intraop prior to tourniquet release AND Placebo, IV, 3 hours after 1st dose TXA The TXA dose of 10 mg kgª1 body weight was given just before the release of the tourniquet, and the same dose was again given 3 h later in the recovery room. Although a maximum of 1 g was given each time. TXA, IV, 10mg/kg, intraop prior to tourniquet release AND TXA, IV, 10mg/kg, 3 hours after 1st dose (Max 1g each time)
Outcomes	Primary outcome: Blood loss Blood transfusions

	Complications (intra-articular hematoma, thromboembolic episodes) Secondary outcome: Not reported
Notes	**Sponsorship source:** Not reported **Country:** Denmark **Setting:** Not reported **Comments:** None **Authors name:** M. Veien **Institution:** Aarhus University Hospital **Email:** mveien@dadlnet.dk **Address:** Department of Anesthesiology, Aarhus Amtssygehus, Aarhus University Hospital, Aarhus, Denmark **Native language of paper:** English **Reference type:** Full text (1) **Trial registration number:** Not applicable, but when checked trial registration number not found **Was it translated for this review:** No

B.1.4.80 Veien 2005

Methods	**Study design:** RCT **Intention to treat analysis:** Unclear **Length of duration of study:** Not reported **Power calculation reached:** Not reported **Transfusion strategy:** Not reported **Was the trial stopped early:** No
Participants	**Baseline Characteristics** TXA, IV, repeated dose *Age (years) (mean SD)*: 70.1 (10) *Ethnicity*: Not reported *Gender (males, females)*: 6 M, 11 F *Length of surgery (minutes)*: 65 (17.3) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: 0/17, (0%)

	Incidence of preoperative anaemia: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: Not reported *Number of participants receiving treatment*: Not reported *Number of participants analysed*: 17 *Dropout rate*: Not reported TXA, IV, single dose *Age (years) (mean SD)*: 67.8 (7.3) *Ethnicity*: Not reported *Gender (males, females)*: 8 M, 6 F *Length of surgery (minutes)*: 62.3 (11.7) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: 0/14, (0%) *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: Not reported *Number of participants receiving treatment*: Not reported *Number of participants analysed*: 14 *Dropout rate*: Not reported Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males, females)*: Not reported *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported

	Co-morbidities: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: Not reported *Number of participants receiving treatment*: Not reported *Number of participants analysed*: Not reported *Dropout rate*: Not reported **Included criteria:** 1) ≥18 years of age, 2) Able to be anaesthetised regionally, according to local guidelines, 3) Haematocrit value of > 0.3, 4) Scheduled to have total knee replacement (TKR) surgery. **Excluded criteria:** 1) Prior cardiac infarction (< 6 months), 2) Unstable angina pectoris, 3) Severe aortic- or mitral stenosis, 4) Former vascular disease in the CNS (stroke, haemorrhage, TCI), 5) Untreated hypertension (diastolic pressure > 105 mmHg, systolic > 10 mmHg), 6) Former thromboembolic episodes, 7) Haematologic disease, 8) Active anticoagulant treatment, 9) Intake of acetylic acid or NSAID 2 weeks prior to surgery **Pre-treatment:** No **If TKR, is tourniquet used:** No **Indication for surgery:** Not reported **Type of anaesthetic:** Spinal anaesthesia **Type of surgery:** Primary TKR
Interventions	**Intervention Characteristics** TXA, IV, repeated dose Group A: two doses of TXA (10 mg/kg body weight) with 3 hours intervals, TXA, IV, 10mg/kg, repeated dose (timepoint unclear) TXA, IV, single dose Group B: one dose (10 mg/kg body weight) TXA, IV, 10mg/kg, (timepoint unclear)
Outcomes	Primary outcome: Blood loss Transfusions

	Episodes of nausea Intraarticular haematomas Post-surgery thromboembolic episodes
Notes	**Sponsorship source:** Not reported **Country:** Denmark **Setting:** Not reported **Comments:** Further information on treatment arms provided by author **Authors name:** M. Veien **Institution:** Arhus Universiteit's hospital **Email:** mveien@dadlnet.dk **Address:** Anaestesiologisk, Arhus Universiteit's hospital Afdeling, Arhus Sygehus, DK-8000Arhus **Native language of paper:** Danish **Reference type:** Full Text (1) **Trial registration number:** Not applicable, but when checked trial registration number not found **Was it translated for this review:** Yes

B.1.4.81 Wang 2018

Methods	**Study design:** RCT **Intention to treat analysis:** Yes **Length of duration of study:** 11 (4+7) months **Power calculation reached:** Yes **Transfusion strategy:** According to the blood-transfusion protocol, based on the guidelines of Chinese Ministry of Health, an allogeneic transfusion was given if the Hb level was < 7 g/dl in asymptomatic patients or between 7 g/dl and 10 g/dl in symptomatic patients. **Was the trial stopped early:** No
Participants	**Baseline Characteristics** TXA 2g preop + placebo postop repeated dose *Age (years) (mean SD)*: 63.02 (14.14) *Ethnicity*: Not reported *Gender (males, females)*: 15 M, 35 F

	Length of surgery (minutes): 66.21 (10.40) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: 0/ 50 (0%) *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: 11/ 50, (22%) *ASA 2 (n/ N,%)*: 32/ 50, (64%) *ASA 3 (n/ N,%)*: 7/ 50, (14%) *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 50 *Number of participants receiving treatment*: 50 *Number of participants analysed*: 50 *Dropout rate*: 0/ 50 (0%) TXA 2g preop + 1g postop + placebo repeated dose *Age (years) (mean SD)*: 65.60 (8.55) *Ethnicity*: Not reported *Gender (males, females)*: 13 M, 37 F *Length of surgery (minutes)*: 67.56 (12.21) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: 0/ 50 (0%) *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: 12/ 50, (24%) *ASA 2 (n/ N,%)*: 30/ 50, (60%) *ASA 3 (n/ N,%)*: 8/ 50, (16%) *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 50 *Number of participants receiving treatment*: 50 *Number of participants analysed*: 50 *Dropout rate*: 0/ 50 (0%) TXA 2g preop + 1g postop repeated dose + placebo *Age (years) (mean SD)*: 64.10 (11.36) *Ethnicity*: Not reported *Gender (males, females)*: 17 M, 33 F *Length of surgery (minutes)*: 67.58 (13.25)

	Proportion of participants on anticoagulants prior to surgery (n/ N, %): 0/ 50 (0%) *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: 10/ 50, (20%) *ASA 2 (n/ N,%)*: 35/ 50, (70%) *ASA 3 (n/ N,%)*: 5/ 50, (10%) *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 50 *Number of participants receiving treatment*: 50 *Number of participants analysed*: 50 *Dropout rate*: 0/ 50 (0%) TXA 2g preop + 1g postop repeated dose *Age (years) (mean SD)*: 63.42 (11.72) *Ethnicity*: Not reported *Gender (males, females)*: 16 M, 34 F *Length of surgery (minutes)*: 68.56 (12.45) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: 0/ 50 (0%) *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: 12/ 50, (24%) *ASA 2 (n/ N,%)*: 31/ 50, (62%) *ASA 3 (n/ N,%)*: 7/ 50, (14%) *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 50 *Number of participants receiving treatment*: 50 *Number of participants analysed*: 50 *Dropout rate*: 0/ 50 (0%) Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males, females)*: Not reported *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to*

	surgery (n/ N, %): Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: Not reported *Number of participants receiving treatment*: 200 *Number of participants analysed*: 200 *Dropout rate*: Not reported **Included criteria:** All patients aged > 18 years who were scheduled for elective, unilateral, primary TKA **Excluded criteria:** 1) Diagnosis other than primary osteoarthritis (OA), absence of written informed consent, 2) The use of spinal anaesthesia, 3) Simultaneous bilateral TKAs, 4) A history of medical comorbidity including deep vein thrombosis (DVT) or pulmonary embolism (PE), haematological disorders, 5) Current anticoagulant therapy (warfarin or heparin) within one week, 6) A history of allergy to TXA **Pre-treatment:** No **If TKR, is tourniquet used:** No **Indication for surgery:** Primary osteoarthritis (OA) **Type of anaesthetic:** General anaesthetic **Type of surgery:** Primary TKA
Interventions	**Intervention Characteristics** TXA 2g preop + placebo postop repeated dose Those in group A were given an oral dose of 2 g of TXA (four tablets of 500 mg) approximately two hours preoperatively and then an oral form of 1 g of placebo pills (two tablets of 500 mg) identical in appearance, with no active ingredient, three, nine, and 15 hours postoperatively. TXA, 2g, oral, 2 hours preop AND TXA, 1.5g, IA, intraop, AND Placebo, oral, 3, 9, 15 hours postop. TXA 2g preop + 1g postop + placebo repeated dose Those in group B were given 2 g of oral TXA two hours preoperatively, 1 g of oral TXA three hours postoperatively, and 1 g of placebo nine and fifteen hours

	postoperatively. TXA, 2g, oral, 2 hours preop + TXA, 1g, oral, 3 hours postop AND TXA, 1.5, IA, intraop AND Placebo, oral, 9 + 15 hours postop. TXA 2g preop + 1g postop repeated dose + placebo Those in group C were given 2 g of oral TXA two hours preoperatively, 1 g of oral TXA three and nine hours postoperatively, and 1 g of placebo 15 hours postoperatively. TXA, 2g, 2 hours preop + TXA, 1g, oral, 3 + 9 hours postop AND TXA, 1.5, IA, intraop AND Placebo, oral, 15 hours postop. TXA 2g preop + 1g postop repeated dose Those in group D were given 2 g oral TXA two hours preoperatively and 1 g of oral TXA three, nine, and 15 hours postoperatively. All patients received an intra-articular dose of 1.5 g of TXA on the basis of our previous study. TXA, 2g, 2 hours preop + TXA, 1g, oral, 3 + 9 + 15 hours postop AND TXA, 1.5, IA, intraop
Outcomes	Primary outcome: Total blood loss Secondary outcome: Hidden blood loss Reduction in the level of haemoglobin Rate of transfusion Adverse events
Notes	**Sponsorship source:** Non-pharmaceutical **Country:** China **Setting:** Single-centre **Comments:** None **Authors name:** Z-K Zhou **Institution:** Sichuan University **Email:** zongkehx@163.com **Address:** W-N. Zeng, MD, Associated Professor Centre for Joint Surgery, Southwest Hospital, Third Military Medical University, Chongqing, China **Native language of paper:** English

	Reference type: Full text (1) **Trial registration number:** ChiCTR-IPR-17012265 **Was it translated for this review:** No

B.1.4.82 Wang 2019

Methods	**Study design:** RCT **Intention to treat analysis:** Yes **Length of duration of study:** 7 months (September 2017 and April 2018) + 90 days follow-up (3 months) = 10 months **Power calculation reached:** Yes **Transfusion strategy:** Based on the guidelines of the Chinese Ministry of Health, an allogeneic transfusion was given if Hb was <70 g/L in asymptomatic patients or between 70 g/L and 100 g/L in symptomatic patients (i.e. fatigue, poor appetite, anemia, or myocardial ischemia) in hospital **Was the trial stopped early:** No
Participants	**Baseline Characteristics** TXA, IV + TXA, Oral *Age (years) (mean SD)*: 63.0 (13.9) *Ethnicity*: Not reported *Gender (males, females)*: 15/ 60 M (25%), 45/ 60 F (75%) *Length of surgery (minutes)*: 62.9 (13.1) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported separately: overall 2.1 ± 0.3 *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 60 *Number of participants receiving treatment*: 60 *Number of participants analysed*: 60 *Dropout rate*: 0/ 60, 0%

	TXA, IV + Placebo, Oral *Age (years) (mean SD)*: 64.1 (9.3) *Ethnicity*: Not reported *Gender (males, females)*: 11/ 58 M (18.96%), 47/ 58 F (81.03%) *Length of surgery (minutes)*: 63.6 (12.4) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported separately: overall 2.1 ± 0.4 *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 60 *Number of participants receiving treatment*: 58 *Number of participants analysed*: 58 *Dropout rate*: 2/ 60, 3.3% Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males, females)*: 26 M, 92F *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 120 *Number of participants receiving treatment*: 118 *Number of participants analysed*: 118 *Dropout rate*: 2/ 120, 1.6%

	Included criteria: Patients with primary osteoarthritis undergoing primary unilateral TKA **Excluded criteria:** The exclusion criteria were secondary osteoarthritis, allergy to this medicine, a history of coexisting diseases that cannot tolerate surgery or general anaesthesia, and active cancer. **If TKR, is tourniquet used:** A tourniquet was not used **Indication for surgery:** Primary osteoarthritis **Type of anaesthetic:** General **Type of surgery:** Primary TKA
Interventions	**Intervention Characteristics** TXA, IV + TXA, Oral The patients in Group A were given TXA (20 mg/kg) intravenously 10 min before the surgery and 3 h after the operation, and then the patients received 1 g TXA orally from postoperative day (POD) 1 to POD 14. TXA, IV, 20mg, preop and postop + TXA, Oral, 1g, postop day 1-14 TXA, IV + Placebo, Oral Patients in the Group B received IV TXA (20 mg/kg) intravenously 10 min before the surgery and 3 h after the operation, and then the patients received placebo pills identical in quantity to oral TXA from POD 1 to POD 14 TXA, IV, 20mg, preop and postop + Placebo, Oral, 1g, postop day 1-14
Outcomes	Primary outcome: Total blood loss Estimated blood loss Secondary outcome: Subcutaneous ecchymosis morbidity Area of ecchymosis Patients requiring transfusion Units transfused Postoperative laboratory values (i.e. hemoglobin, haematocrit, FDP, and D-Dimer) Postoperative knee function Knee circumference VAS pain score

	Length of hospital stay
Notes	**Sponsorship source:** Non-pharmaceutical (This research was funded by the China Health Ministry Program (201302007), who is not involved in study design, data collection, analysis and interpretation or manuscript preparation.) **Country:** China **Setting:** Single-centre **Comments:** None **Authors name:** H-Y Wang **Institution:** Sichuan University **Email:** Dr Xin Tang: tangxin9388@163.com; Dr Zong-Ke Zhou: zongkehx@163.com **Address:** Department of Orthopedics, West China Hospital/ West China School of Medicine, Sichuan University, 37# Wuhou Guoxue Road, Chengdu 610041, People's Republic of China **Native language of paper:** English **Reference type:** Full text (1), trial registration (1) **Trial registration number:** ChiCTR-IPR-17012264 **Was it translated for this review:** No

B.1.4.83 Wang 2019a

Methods	**Study design:** RCT **Intention to treat analysis:** Yes **Length of duration of study:** 4 months (June 2017 to October 2017) + 3 months (follow-up) = 7 months **Power calculation reached:** Yes **Transfusion strategy:** A standardized blood-transfusion protocol was followed for all patients (consistent with the perioperative transfusion guidelines of the Chinese Ministry of Health), whereby blood transfusion was indicated for a hemoglobin (Hb) level of <7.0 g/dL in asymptomatic patients or an Hb level of <10.0 g/dL in patients who developed any anemia-related organ dysfunction, intolerable symptoms of anemia, or ongoing blood loss **Was the trial stopped early:** No
Participants	**Baseline Characteristics** TXA, oral, 2g, 2 hrs pre-incision + placebo, oral, postop 3, 9

	and 15hrs + TXA, IA, 1g *Age (years) (mean SD)*: 64.41 (13.94) *Ethnicity*: Not reported *Gender (males, females)*: 13 M (26%) 37 F (74%) *Length of surgery (minutes) (mean SD)*: 69.67 ± 11.17 *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Treatment with anticoagulant therapy (warfarin or heparin) within 1 week prior to surgery - excluded *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: 13/ 50, 26% *ASA 2 (n/ N,%)*: 30/ 50, 60% *ASA 3 (n/ N,%)*: 7/ 50, 14% *ASA 4 (n/ N,%)*: 0/ 50, 0% *Number of participants randomised*: 50 *Number of participants receiving treatment*: Not reported *Number of participants analysed*: 50 *Dropout rate*: 0/ 50, 0% TXA, oral, 2g, 2 hrs pre-incision + TXA, oral, 1g, 3 hrs post + placebo, oral, 9, 15hrs post +TXA, IA, 1g *Age (years) (mean SD)*: 66.98 (9.71) *Ethnicity*: Not reported *Gender (males, females)*: 15 M (30%) 35 F (70%) *Length of surgery (minutes) (mean SD)*: 70.54 ± 12.63 *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Treatment with anticoagulant therapy (warfarin or heparin) within 1 week prior to surgery - excluded *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: 11/ 50, 22% *ASA 2 (n/ N,%)*: 34/ 50, 68% *ASA 3 (n/ N,%)*: 5/ 50, 10% *ASA 4 (n/ N,%)*: 0/ 50, 0% *Number of participants randomised*: 50

	Number of participants receiving treatment: Not reported *Number of participants analysed*: 50 *Dropout rate*: 0/ 50, 0% TXA, oral, 2g, 2hrs pre-incision + TXA, oral, 1g, 3, 9 hrs post + placebo, oral, 15 hrs postop + TXA, IA, 1g *Age (years) (mean SD)*: 66.76 (9.87) *Ethnicity*: Not reported *Gender (males, females)*: 17 M (34%) 33 F (66%) *Length of surgery (minutes) (mean SD)*: 67.48 ± 12.67 *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Treatment with anticoagulant therapy (warfarin or heparin) within 1 week prior to surgery - excluded *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: 15/ 50, 30% *ASA 2 (n/ N,%)*: 28/ 50, 56% *ASA 3 (n/ N,%)*: 7/ 50, 14% *ASA 4 (n/ N,%)*: 0/ 50, 0% *Number of participants randomised*: 50 *Number of participants receiving treatment*: Not reported *Number of participants analysed*: 50 *Dropout rate*: 0/ 50, 0% TXA, oral, 2g, 2 hours pre-incision + TXA, oral, 1g, 3, 9, 15 hrs post + TXA, IA, 1g *Age (years) (mean SD)*: 63.94 ± 12.37 *Ethnicity*: Not reported *Gender (males, females)*: 14 M (28%) 36 F (72%) *Length of surgery (minutes) (mean SD)*: 67.07 ± 11.64 *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Treatment with anticoagulant therapy (warfarin or heparin) within 1 week prior to surgery - excluded *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: 11/ 50, 22% *ASA 2 (n/ N,%)*: 30/ 50, 60%

	ASA 3 (n/ N,%): 9/ 50, 18% *ASA 4 (n/ N,%)*: 0/ 50, 0% *Number of participants randomised*: 50 *Number of participants receiving treatment*: Not reported *Number of participants analysed*: 50 *Dropout rate*: 0/ 50, 0% Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males, females)*: Not reported *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 200 *Number of participants receiving treatment*: Not reported *Number of participants analysed*: 200 *Dropout rate*: 0/ 200, 0% **Included criteria:** Consecutive adult patients (18 years of age and over) who were scheduled for primary unilateral total hip arthroplasty **Excluded criteria:** Exclusion criteria included a diagnosis other than osteoarthritis or osteonecrosis of the femoral head, a known allergy to TXA, use of spinal anaesthesia, a history of a hematopoietic or haemorrhagic disorder, a history of deep venous thrombosis (DVT) or pulmonary embolism (PE), treatment with anticoagulant therapy (warfarin or heparin) within 1 week prior to surgery, and refusal of participation or blood products. **If TKR, is tourniquet used:** Not applicable **Indication for surgery:** Osteoarthritis or osteonecrosis of the femoral head **Type of anaesthetic:** General (97% received this),

	assumed the rest had spinal **Type of surgery:** Primary THA
Interventions	**Intervention Characteristics** TXA, oral, 2g, 2 hrs pre-incision + placebo, oral, postop 3, 9 and 15hrs + TXA, IA, 1g 2.0 g of oral TXA (4 tablets, 0.5 g each) at 2 hours preoperatively and 1.0 g of placebo (2 tablets, 0.5 g each) at 3, 9, and 15 hours postoperatively (Group A, control) TXA, oral, 2g, 2 hrs pre-incision + TXA, oral, 1g, 3 hrs post + placebo, oral, 9, 15hrs post +TXA, IA, 1g 2.0 g of oral TXA at 2 hours preoperatively, 1.0 g of oral TXA at 3 hours postoperatively, and 1.0 g of placebo at 9 and 15 hours postoperatively TXA, oral, 2g, 2hrs pre-incision + TXA, oral, 1g, 3, 9 hrs post + placebo, oral, 15 hrs postop + TXA, IA, 1g 2.0 g of oral TXA at 2 hours preoperatively, 1.0 g of oral TXA at 3 and 9 hours postoperatively, and 1.0 g of placebo at 15 hours postoperatively TXA, oral, 2g, 2 hours pre-incision + TXA, oral, 1g, 3, 9, 15 hrs post + TXA, IA, 1g 2.0 g of oral TXA at 2 hours preoperatively and 1.0 g of oral TXA at 3, 9, and 15 hours postoperatively
Outcomes	Primary outcome: Total blood loss Secondary outcome: Hb reduction Intra-operative blood loss Operative time Hospital stay Transfusion rate Thromboembolic complications Adverse events
Notes	**Sponsorship source:** Not reported (but No external funding was received in support of this study). **Country:** China **Setting:** Single-centre **Comments:** None

	Authors name: D. Wang **Institution:** Sichan University **Email:** zongke@126.com; weinanzeng@163.com **Address:** Department of Orthopedics, West China Hospital/ West China School of Medicine, Sichuan University, Chengdu, People's Republic of China **Native language of paper:** English **Reference type:** Full text (1), trial registration (1) **Trial registration number:** ChiCTR-IPR-17012266 **Was it translated for this review:** No

B.1.4.84 Wang 2019b

Methods	**Study design:** RCT **Intention to treat analysis:** Per protocol **Length of duration of study:** 6 months (October 2017 to April 2018 - recruitment) + 3 months follow-up = 9 months **Power calculation reached:** Yes **Transfusion strategy:** Allogeneic red cell transfusion was given if the Hb level was < 7 g/dL in patients who were asymptomatic or if a patient with intolerable symptom of anaemia (dyspnoea, palpitation, pallor or tachycardia) or any organ dysfunction that was attributable to anaemia regardless of the Hb level. **Was the trial stopped early:** No
Participants	**Baseline Characteristics** TXA IA 1g intra *Age (years) (mean SD)*: 68.7 (9.8) *Ethnicity*: Not reported *Gender (males, females)*: 22 M (36.7%), 38 F (63.3%) *Length of surgery (minutes) (mean SD)*: 69.8 (14.1) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Patients excluded if full dose of warfarin or heparin consumed within one week of surgery *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: ASA 1/ 2 - 52 (86.7)

	ASA 3 (n/ N,%): ASA 3 and greater - 8 (13.3) *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 60 *Number of participants receiving treatment*: 60 *Number of participants analysed*: 60 *Dropout rate*: 0/ 60, 0% TXA oral IA 4g prel intra post *Age (years) (mean SD)*: 67.3 (8.3) *Ethnicity*: Not reported *Gender (males, females)*: 23 M (38.3%), 37 F (61.7%) *Length of surgery (minutes) (mean SD)*: 70.3 (10.7) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Patients excluded if full dose of warfarin or heparin consumed within one week of surgery *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: ASA 1/ 2 - 50 (83.3) *ASA 3 (n/ N,%)*: ASA 3 and greater - 10 (16.7) *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 60 *Number of participants receiving treatment*: 60 *Number of participants analysed*: 60 *Dropout rate*: 0/ 60, 0% TXA oral IA 5g prel intra post b6-24hr *Age (years) (mean SD)*: 68.9 (7.7) *Ethnicity*: Not reported *Gender (males, females)*: 22 M (36.7%), 38 F (63.3%) *Length of surgery (minutes) (mean SD)*: 68.3 (9.8) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Patients excluded if full dose of warfarin or heparin consumed within one week of surgery *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported

	ASA 2 (n/ N,%): ASA 1/ 2 - 52 (86.7) *ASA 3 (n/ N,%)*: ASA 3 and greater - 8 (13.3) *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 60 *Number of participants receiving treatment*: 60 *Number of participants analysed*: 60 *Dropout rate*: 0/ 60, 0% TXA oral IA 6g preI intra post b6-24hr *Age (years) (mean SD)*: 67.2 (9.6) *Ethnicity*: Not reported *Gender (males, females)*: 24 M (38.7%), 36 F (60%) *Length of surgery (minutes) (mean SD)*: 69.2 (9.9) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Patients excluded if full dose of warfarin or heparin consumed within one week of surgery *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: ASA 1/ 2 - 51 (85.0) *ASA 3 (n/ N,%)*: ASA 3 and greater - 9 (15.0) *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 60 *Number of participants receiving treatment*: 60 *Number of participants analysed*: 60 *Dropout rate*: 0/ 60, 0% TXA oral IA 7g preI intra post b6-24hr *Age (years) (mean SD)*: 68.5 (9.5) *Ethnicity*: Not reported *Gender (males, females)*: 21 M (35.1%), 39 F (65%) *Length of surgery (minutes) (mean SD)*: 71.5 (11.6) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Patients excluded if full dose of warfarin or heparin consumed within one week of surgery *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported

	ASA 1 (n/ N,%): Not reported *ASA 2 (n/ N,%)*: ASA 1/ 2 - 53 (88.3) *ASA 3 (n/ N,%)*: ASA 3 and greater - 7 (11.7) *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 60 *Number of participants receiving treatment*: 60 *Number of participants analysed*: 60 *Dropout rate*: 0/ 60, 0% Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males, females)*: 112 M (37.3%), 188 F (62.7%) *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Patients excluded if full dose of warfarin or heparin consumed within one week of surgery *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 300 *Number of participants receiving treatment*: 300 *Number of participants analysed*: 300 *Dropout rate*: 0/ 300, 0% **Included criteria:** All patients (age > 18 years) with hip osteoarthritis or osteonecrosis of the femoral head, scheduled for elective, unilateral, primary THA, **Excluded criteria:** Patients were excluded in the following circumstances: known allergy to TXA; a haemoglobin (Hb) level of < 11 g/dL; a history of arrhythmia, pulmonary embolism (PE), deep venous thrombosis (DVT) or severe ischaemic heart disease; an acquired or congenital coagulopathy; previous vascular or cardiac bypass surgery; a history of high-risk medical co-morbidities (severe renal insufficiency, hepatic failure or severe pulmonary disease); current full dose anticoagulant therapy (warfarin or heparin) within 1 week; refusal of blood products or participation; or

	participation in another clinical trial during the last year. **If TKR, is tourniquet used:** Not applicable **Indication for surgery:** Patients with hip osteoarthritis or osteonecrosis of the femoral head **Type of anaesthetic:** General **Type of surgery:** Elective, unilateral, primary THA
Interventions	**Intervention Characteristics** TXA IA 1g intra Group A received an oral form of 2 g of matching placebo (4 tablets of 500 mg) approximately2 hours pre-operatively, followed by an oral administration of 1-g placebo 3, 7, 11 and 15 hours post-operatively TXA, IA, 1g, intraop TXA oral IA 4g preI intra post Group B received an oral dose of 2 g of TXA (4 tablets of 500 mg) approximately 2 hours pre-operatively, 1-g oral TXA 3 hours post-operatively and 1-g placebo 7, 11 and 15 hours post operatively TXA oral IA 4g preI intra post TXA oral IA 5g preI intra post b6-24hr Group C received 2-g oral TXA 2 hours pre-operatively, 1-g oral TXA 3 and 7 hours post-operatively and 1-g placebo 11 and 15 hours post-operatively TXA oral IA 5g preI intra post b6-24hr TXA oral IA 6g preI intra post b6-24hr Group D received 2-g oral TXA 2 hours pre-operatively, 1-g oral TXA 3, 7 and 11 hours post-operatively and 1-g placebo15 hours post-operatively TXA oral IA 6g preI intra post b6-24hr TXA oral IA 7g preI intra post b6-24hr Group E received 2-g oral TXA 2 hours pre-operatively and 1-g oral TXA 3, 5, 11 and15 hours post-operatively TXA oral IA 7g preI intra post b6-24hr
Outcomes	Primary outcome: Total blood loss Secondary outcome: Hb drop

	Intra-operative blood loss Allogeneic red cell transfusion rates Number of blood units transfused Length of hospital stay Post-operative changes in joint function (range of motion) Severity of hip pain Thromboembolic and other complications
Notes	**Sponsorship source:** Not reported **Country:** China **Setting:** Single-centre **Comments:** None **Authors name:** D.Wang **Institution:** Sichuan University **Email:** zongke@126.com **Address:** Department of Orthopedics, West China School of Medicine, West China Hospital, Sichuan University, Chengdu, China **Native language of paper:** English **Reference type:** Full text (1), trial registration (1) **Trial registration number:** ChiCTR-IPR-17011669 **Was it translated for this review:** No

B.1.4.85 Wu 2018

Methods	**Study design:** RCT **Intention to treat analysis:** Yes **Length of duration of study:** 13 months (7+6) **Power calculation reached:** Yes **Transfusion strategy:** Blood transfusions were applied using the guidelines of the Chinese Ministry of Health if the Hb level was<70g/L or 70–100g/L with symptoms of anaemia (e.g., change in mental status and palpitations). **Was the trial stopped early:** No
Participants	**Baseline Characteristics** TXA, IV

	Age (years) (mean SD): 65.1 (63.8 - 66.5) *Ethnicity*: Not reported *Gender (males, females)*: 30, 20 *Length of surgery (minutes)*: 66.6 (4.6) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities (n/ N, %)*: Hypertension 7/50 (14%), Type 2 Diabetes 4/50 (8%) *ASA 1 (n/ N,%)*: 25/ 50 (50%) *ASA 2 (n/ N,%)*: 17/ 50 (34%) *ASA 3 (n/ N,%)*: 8/ 50 (16%) *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 50 *Number of participants receiving treatment*: 50 *Number of participants analysed*: 50 *Dropout rate*: 0/50 (0%) TXA, Oral *Age (years) (mean SD)*: 66.5 (65.1-67.9) *Ethnicity*: Not reported *Gender (males, females)*: 29, 21 *Length of surgery (minutes)*: 68.2 (4.5) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities (n/ N, %)*: Hypertension 5/50 (10%), Type 2 Diabetes 3/50 (6%) *ASA 1 (n/ N,%)*: 23/ 50 (46%) *ASA 2 (n/ N,%)*: 20/ 50 (40%) *ASA 3 (n/ N,%)*: 7/ 50 (14%) *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 50 *Number of participants receiving treatment*: 50 *Number of participants analysed*: 50 *Dropout rate*: 0/50 (0%)

	Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males, females)*: Not reported *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 100 *Number of participants receiving treatment*: Not reported *Number of participants analysed*: Not reported *Dropout rate*: Not reported **Included criteria:** Patients with a diagnosis of osteoarthritis (OA) or osteonecrosis of the femoral head (ONFH) undergoing unilateral THA were eligible for inclusion in the study. **Excluded criteria:** 1) Developmental dysplasia of the hip, 2) Rheumatoid arthritis, 3) Revision surgery, 4) History of thrombosis, 5) Patients with infection, 6) Allergy to TXA, 7) Uncontrolled hypertension, 8) Body mass index (BMI) > 35 kg/m2, 9) Preoperative anaemia (hemoglobin [Hb] level < 12 g/dL for women and < 13 g/dL for men). **Pre-treatment:** No **If TKR, is tourniquet used:** NA **Indication for surgery:** Osteoarthritis (OA) or Osteonecrosis of the femoral head (ONFH) **Type of anaesthetic:** General **Type of surgery:** Primary THR
Interventions	**Intervention Characteristics** TXA, IV In the IV TXA group, 1g of TXA was administered 10min before the incision, and the same dose was repeated 3h and 6h postoperatively. Patients in the IV TXA group were

	given 2 placebo tablets (with no active component) orally 2h before the incision, and the same dose was repeated 3h and 6h postoperatively. TXA, IV, 1g, intraop (10 min before incision) + TXA, IV, 3 + 6 hours postop + Placebo, oral, 2 hours preop + Placebo, oral, 3 + 6 hours postop TXA, Oral In the oral TXA group, 1g of TXA (2 tablets of 500mg) was given 2h before the incision, and the same dose was repeated 3h and 6h postoperatively. Additionally, to support this double-blind study, patients in the oral TXA group were given 100mL of normal saline solution intravenously 10min before the incision, and the same dose was repeated 3h and 6h postoperatively. Placebo, IV, intraop (10 min before incision) + Placebo, IV, 3 + 6 hours postop + TXA, oral, 1g, 2 hours preop + TXA, oral, 1g, 3 + 6 hours postop
Outcomes	Primary outcome: Total blood loss Maximum Hb drop TXA cost (¥, RMB) Transfusion rates Transfusion units. Secondary outcome: Hb level on postoperative days 1 and 3 Operating time Hospital length of stay DVT and/or PE Wound complications.
Notes	**Sponsorship source:** Non-pharmaceutical **Country:** China **Setting:** Single-centre **Comments:** None **Authors name:** B. Shen **Institution:** Sichuan University **Email:** shenbin_1971@163.com **Address:** Department of Orthopaedics, West China hospital, Sichuan University, 37# Guoxue Road, Chengdu,

	610041, China. **Native language of paper:** English **Reference type:** Full text (1), trial registration (1) **Trial registration number:** ChiCTR1800015265 **Was it translated for this review:** No

B.1.4.86 Xie 2017 - hips

Methods	**Study design:** RCT **Intention to treat analysis:** Yes **Length of duration of study:** 5 + 3 months FU = 8 months **Power calculation reached:** Yes **Transfusion strategy:** Criteria for a blood transfusion were: Hb < 70 g/L or between 70g/L and100 g/L in the presence of symptomatic anaemia, defined as light-headedness, fatigue that precluded participation in treatment, palpitations or shortness of breath not due to other causes. **Was the trial stopped early:** No
Participants	**Baseline Characteristics** TXA, IV pre-op + placebo, IV, post-op, repeated dose *Age (years) (mean SD)*: 57.24 (13.05) *Ethnicity*: Not reported *Gender (males, females)*: 22 M, 28 F *Length of surgery (minutes) (mean SD)*: 66.72 (7.45) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)* : 33/50 (66%) *ASA 2 (n/ N,%)* : 17/50 (34%) *ASA 3 (n/ N,%)* : 0/50 (0%) *ASA 4 (n/ N,%)* : 0/50 (0%) *Number of participants randomised*: 50 *Number of participants receiving treatment*: 50

	Number of participants analysed: 50 *Dropout rate*: 0/50 (0%) TXA, IV pre-op + TXA, IV, post-op + placebo, IV, post-op *Age (years) (mean SD)*: 54.96 (12.57) *Ethnicity*: Not reported *Gender (males, females)*: 18 M, 32 F *Length of surgery (minutes) (mean SD)*: 72.72 (13.59) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: 28/50 (56%) *ASA 2 (n/ N,%)*: 22/50 (44%) *ASA 3 (n/ N,%)*: 0/50 (0%) *ASA 4 (n/ N,%)*: 0/50 (0%) *Number of participants randomised*: 50 *Number of participants receiving treatment*: 50 *Number of participants analysed*: 50 *Dropout rate*: 0/50 (0%) TXA, IV pre-op + TXA, IV, post-op, repeated dose *Age (years) (mean SD)*: 54.38 (11.80) *Ethnicity*: Not reported *Gender (males, females)*: 20 M, 30 F *Length of surgery (minutes) (mean SD)*: 69.99 (12.52) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: 30/50 (60%) *ASA 2 (n/ N,%)*: 20/50 (40%) *ASA 3 (n/ N,%)*: 0/50 (0%) *ASA 4 (n/ N,%)*: 0/50 (0%) *Number of participants randomised*: 50 *Number of participants receiving treatment*: 50 *Number of participants analysed*: 50

	Dropout rate: 0/50 (0%) Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males, females)*: Not reported *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 150 *Number of participants receiving treatment*: 150 *Number of participants analysed*: 150 *Dropout rate*: 0/150 (0%) **Included criteria:** 1) Aged > 18 years, 2) Scheduled for primary unilateral THA for osteoarthritis or osteonecrosis of the femoral head **Excluded criteria:** 1) Cardiovascular disease (including myocardial infarction, angina or atrial fibrillation), 2) Cerebrovascular pathology (a history of stroke), 3) Thromboembolic disorders (a history of deep-vein thrombosis (DVT) or pulmonary embolism (PE)), 4) An allergy to TXA **Pre-treatment:** No **If TKR, is tourniquet used:** Not applicable **Indication for surgery:** Osteoarthritis or osteonecrosis of the femoral head **Type of anaesthetic:** General anaesthesia **Type of surgery:** Primary THR
Interventions	**Intervention Characteristics** TXA, IV pre-op + placebo, IV, post-op, repeated dose Group A, the control group, received a bolus of 20 mg/kg intravenous (IV) -TXA before the incision and 100 ml of normal saline was injected intravenously three and six

	hours later. TXA, IV, 20mg/kg preop, AND TXA IA, 1.5g, intraop AND Placebo, IV, 3 + 6 hours later TXA, IV pre-op + TXA, IV, post-op + placebo, IV, post-op Group B received 20 mg/kg IV-TXA before the incision, 1 g/ 100 ml TXA three hours later and 100 ml of normal saline six hours later TXA, IV, 20mg/kg preop, AND TXA IA, 1.5g, intraop AND TXA, IV, 1g, 3 hours later AND Placebo, IV, 6 hours later TXA, IV pre-op + TXA, IV, post-op, repeated dose Group C received 20 mg/kg IV-TXA before the incision and 1 g/100 ml TXA three and six hours later. All patients received 1.5 g topical TXA intra-operatively, based on previous work. TXA, IV, 20mg/kg preop, AND TXA IA, 1.5g, intraop AND TXA, IV, 1g, 3 + 6 hours later
Outcomes	Primary outcome: Hidden blood loss Level of haemoglobin (Hb) Levels of C-reactive protein (CRP) and interleukin-6 (IL-6) Secondary outcome: Length of stay in hospital Incidence of venous thromboembolism (VTE) Total blood loss Rate of transfusion Pain score using a visual analogue scale (VAS) from 1 to 10. Wound complications, including infection, persistent discharge, periprosthetic infection and other adverse events
Notes	**Sponsorship source:** Non-pharmaceutical **Country:** China **Setting:** Single-centre **Comments:** None **Authors name:** J. Xie **Institution:** Sichuan University **Email:** peifuxinghuaxi@126.com

	Address: West China Hospital, Sichuan University, Chengdu, China **Native language of paper:** English **Reference type:** Full Text (1) Trial registration (1) **Trial registration number:** ChiCTR-INR-16009288 **Was it translated for this review:** No

B.1.4.87 Xie 2017 - knees

Methods	**Study design:** RCT **Intention to treat analysis:** Yes **Length of duration of study:** 8 months **Power calculation reached:** Yes **Transfusion strategy:** The criterion for a blood transfusion was set as a hemoglobin level of <70 g/L or 70-100 g/L with symptomatic anemia (defined as light-headedness, fatigue precluding participation in the therapy, palpitations, or shortness of breath not due to other causes) according to the guidelines by the National Ministry of Health. **Was the trial stopped early:** No
Participants	**Baseline Characteristics** TXA, IV pre-op + placebo, IV, post-op, repeated dose *Age (years) (mean SD)*: 66.2 (9.1) *Ethnicity*: Not reported *Gender (males, females)*: 17 M, 33 F *Length of surgery (minutes) (mean SD)*: 69.6 (10.1) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n,%)*: 1.7 (0.6) *ASA 2 (n,%)*: Not reported *ASA 3 (n,%)*: Not reported *ASA 4 (n,%)*: Not reported *Number of participants randomised*: 50 *Number of participants receiving treatment*: 50

	Number of participants analysed: 50 *Dropout rate*: 0/50 (0%) TXA, IV pre-op + TXA, IV, post-op + placebo, IV, post-op *Age (years) (mean SD)*: 65.3 (8.8) *Ethnicity*: Not reported *Gender (males, females)*: 14 M, 36 F *Length of surgery (minutes) (mean SD)*: 72.6 (12.1) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n,%)*: 1.9 (0.4) *ASA 2 (n,%)*: Not reported *ASA 3 (n,%)*: Not reported *ASA 4 (n,%)*: Not reported *Number of participants randomised*: 50 *Number of participants receiving treatment*: 50 *Number of participants analysed*: 50 *Dropout rate*: 0/50 (0%) TXA, IV pre-op + TXA, IV, post-op, repeated dose *Age (years) (mean SD)*: 61.5 (7.6) *Ethnicity*: Not reported *Gender (males, females)*: 10 M, 41 F *Length of surgery (minutes) (mean SD)*: 72.4 (8.4) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n,%)*: 1.7 (0.5) *ASA 2 (n,%)*: Not reported *ASA 3 (n,%)*: Not reported *ASA 4 (n,%)*: Not reported *Number of participants randomised*: 51 *Number of participants receiving treatment*: 51 *Number of participants analysed*: 51

	Dropout rate: 0/51 (0%) Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males, females)*: Not reported *Length of surgery (minutes) (mean SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n,%)*: Mean reported only *ASA 2 (n,%)*: Not reported *ASA 3 (n,%)*: Not reported *ASA 4 (n,%)*: Not reported *Number of participants randomised*: 151 *Number of participants receiving treatment*: 151 *Number of participants analysed*: 151 *Dropout rate*: 0/151 (0%) **Included criteria:** 1) Aged 18 years or older, 2) Scheduled to have primary unilateral TKA for osteoarthritis or rheumatoid arthritis **Excluded criteria:** 1) Patients with anemia (<120 g/L for female, <130 g/L for male), 2) Cardiovascular problems (history of myocardial infraction, angina, and atrial fibrillation), 3) Cerebrovascular conditions (history of previous stroke), 4) Thromboembolic disorders (history of deep vein thrombosis [DVT] or pulmonary embolism [PE]), 5) Clotting disorders, 6) Known allergy to TXA, 7) Flexion deformity 30, varus and/or valgus deformity 30 **Pre-treatment:** No **If TKR, is tourniquet used:** No **Indication for surgery:** Osteoarthritis or rheumatoid arthritis **Type of anaesthetic:** Mixed general and spinal **Type of surgery:** Primary TKR
Interventions	**Intervention Characteristics** TXA, IV pre-op + placebo, IV, post-op, repeated dose *TXA, IV, 2g, preop* : group A: the patients received 1 bolus

	of 20 mg/kg IV-TXA before skin incision, and 10 mg/kg of normal saline was intravenously injected 3 and 6 hours later; *TXA, IA, 2g, intraop* : TXA, IV, 20mg/kg, intraop (5-10 mins prior to skin incision) AND TXA, IA, 1g, intraop, (irrigated after cementing) AND Placebo, IV, post op (3 + 6 hours after 1st dose) TXA, IV pre-op + TXA, IV, post-op + placebo, IV, post-op *TXA, IV, 2g, preop* : group B: a dosage of 20 mg/kg IV-TXA was administered 5-10 minutes before skin incision, and 10 mg/kg of TXA was administered 3 hours later, another 10 mg/kg of normal saline was administered 6 hours later; *TXA, IA, 2g, intraop* : TXA, IV, 20mg/kg, intraop (5-10 mins prior to skin incision) AND TXA, IA, 1g, intraop, (irrigated after cementing) AND TXA, IV, 10mg/kg, post op (3 hours 1st dose) AND Placebo, IV, post op (6 hours after 1st dose) TXA, IV pre-op + TXA, IV, post-op, repeated dose *TXA, IV, 2g, preop* : group C: a dosage of 20 mg/kg of IV-TXA was administered 5-10 minutes before skin incision, and 10 mg/kg of TXA was administered 3 and 6 hours later *TXA, IA, 2g, intraop* : TXA, IV, 20mg/kg, intraop (5-10 mins prior to skin incision) AND TXA, IA, 1g, intraop, (irrigated after cementing) AND TXA, IV, 10mg/kg, post op (3 + 6 hours after 1st dose)
Outcomes	Primary outcome: Hidden blood loss Maximum hemoglobin drop Secondary outcome: Total blood loss Transfusion rate Inflammation markers (C-reactive protein, interleukin 6) Visual analog scale pain score Limb swelling ratio Hospital for Surgery Score Range of motion Length of hospital stay (LOH) Deep venous thrombosis
Notes	**Sponsorship source:** Non-pharmaceutical **Country:** China

	Setting: Single-centre **Comments:** None **Authors name:** J. Xie **Institution:** Schian University **Email:** Not reported **Address:** : Fuxing Pei, MD, Department of Orthopaedic Surgery, WestChina Hospital, Sichuan University, 37# Guoxue Road, Chengdu, Sichuan 610041, People's Republic of China **Native language of paper:** English **Reference type:** Full Text (1) Trial registration (1) **Trial registration number:** ChiCTR-INR-16009288 **Was it translated for this review:** No

B.1.4.88 Yamasaki 2004

Methods	**Study design:** RCT **Intention to treat analysis:** Yes **Length of duration of study:** 4 months (3 months + 1 months FU) **Power calculation reached:** Not reported **Transfusion strategy:** Not reported **Was the trial stopped early:** No
Participants	**Baseline Characteristics** Placebo *Age (years) (mean SD)*: 61.2 (6.9) *Ethnicity*: Not reported *Gender (males, females)*: 18 M, 2 F *Length of surgery (minutes)*: 70.0 (14.8) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported

	ASA 4 (n/ N,%): Not reported *Number of participants randomised*: 20 *Number of participants receiving treatment*: 20 *Number of participants analysed*: 20 *Dropout rate*: 0/20 (0%) TXA (whole body) *Age (years) (mean SD)*: 55.5 (14.2) *Ethnicity*: Not reported *Gender (males, females)*: 19 M, 1 F *Length of surgery (minutes)*: 68.8 (15.1) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 20 *Number of participants receiving treatment*: 20 *Number of participants analysed*: 20 *Dropout rate*: 0/20 (0%) Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males, females)*: Not reported *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported

	Number of participants randomised: 40 *Number of participants receiving treatment*: Not reported *Number of participants analysed*: Not reported *Dropout rate*: Not reported **Included criteria:** 1) Primary THA with osteoarthritis of the hip **Excluded criteria:** 1) Femoral head osteonecrosis, 2) Rheumatoid arthritis **Pre-treatment:** No **If TKR, is tourniquet used:** Not applicable **Indication for surgery:** Osteoarthritis **Type of anaesthetic:** Spinal anaesthetic **Type of surgery:** Primary THR
Interventions	**Intervention Characteristics** Placebo The other 20 patients served as a control group and were operated on without tranexamic acid. ASSUMED, no text: Placebo, IV, 5 mins preop TXA (whole body) In 20 patients, 1,000 mg of whole-body tranexamic acid (Transamin, Daiichi Pharmaceutical Co. Ltd., Japan) was administrated intravenously 5 min before the operation started TXA, IV, 1g, 5 mins preop
Outcomes	Primary outcome: Perioperative and postoperative bleeding Need for transfusion Thromboembolic complications Secondary outcome: Not reported
Notes	**Sponsorship source:** Not reported **Country:** Japan **Setting:** Single-centre **Comments:** None **Authors name:** S. Yamasaki

	Institution: Osaka Kosei-Nenkin Hospital **Email:** ys8483@okn.gr.jp **Address:** Department of Orthopaedic Surgery, Osaka Kosei-Nenkin Hospital,4–2-78, Fukushima, 553–0003 Fukushimaku, Osaka, Japan **Native language of paper:** English **Reference type:** Full text (1) **Trial registration number:** Not applicable, but when checked trial registration number not found **Was it translated for this review:** No

B.1.4.89 Yang 2020

Methods	**Study design:** RCT **Intention to treat analysis:** Yes **Length of duration of study:** 13 months + follow-up (length of follow-up not stated) **Power calculation reached:** No **Transfusion strategy:** Allogeneic transfusion was performed when hemoglobin levels were <7.0 g/dL or when hemoglobin was 7.0–9.0 g/dL combined with a poor mental status, palpitation, or pallor. **Was the trial stopped early:** No
Participants	**Baseline Characteristics** Placebo *Age (years) (mean SD)*: 64.4 (5.8) *Ethnicity*: Not reported *Gender (males, females)*: 13 M, 34 F *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported

	Number of participants randomised: 48 *Number of participants receiving treatment*: 48 *Number of participants analysed*: 47 *Dropout rate*: 1/ 48, 2.08% TXA *Age (years) (mean SD)*: 65.2 (6.2) *Ethnicity*: Not reported *Gender (males, females)*: 11 M, 36 F *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 48 *Number of participants receiving treatment*: 48 *Number of participants analysed*: 47 *Dropout rate*: 1/ 48, 2.08% Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males, females)*: Not reported *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: Not reported

	Number of participants receiving treatment: Not reported *Number of participants analysed*: Not reported *Dropout rate*: Not reported **Included criteria:** (1) diagnosis of moderate or severe knee OA (grade 3 or 4, based on the degree of erosion); (2) ineffective conservative treatment before undergoing primary TKA **Excluded criteria:** (1) <55 years of age; (2) any haemorrhagic blood disease; (3) hemoglobin levels<10 g/dL; (4) history of thromboembolic disease; (5) rheumatoid arthritis; (6) traumatic arthritis; (7) any disorder of the hips; (8) preoperative use of anticoagulants; or (9) TXA contraindications. **If TKR, is tourniquet used:** Yes **Indication for surgery:** Osteoarthritis **Type of anaesthetic:** Spinal anaesthetic **Type of surgery:** Primary TKR
Interventions	**Intervention Characteristics** Placebo The patients in the control group had the same volume of physiological saline injected as a placebo, and the affected limb was fully extended. A high-elasticity bandage was applied to compress the wound in all patients Placebo, IA, intraop TXA (whole body) In the TXA group, 500 mg of TXA mixed with 50 mL of physiological saline was injected into the knee joint before tourniquet release and after the closure of surgical wounds. Then, the affected knee and hip were flexed at 45 using a folding hospital bed after transporting the patients to the recovery ward; the position was retained for 4 h TXA, IA, 0.5g, intraop
Outcomes	Primary outcome: Postoperative hemoglobin reduction Secondary outcome: Calculated blood loss (CBL) at 3 days Transfusion rate Range of motion (ROM) VAS pain score

	Knee circumference increment
Notes	**Sponsorship source:** Not mentioned in full text, but trial registration says it was 'self-financed' **Country:** China **Setting:** Single-centre **Comments:** None **Authors name:** J-Q Yang **Institution:** The Third Affiliated Hospital of Southern Medical University **Email:** daozhangcai@163.com **Address:** Department of Orthopaedics, The Third Affiliated Hospital of Southern Medical University, 183 Zhongshan Avenue West, Tianhe District, Guangzhou, China 510630 **Native language of paper:** English **Reference type:** Full text (1), trial registration (1) **Trial registration number:** ChiCTR-INR-16010287 **Was it translated for this review:** No

B.1.4.90 Yasli 2019

Methods	**Study design:** RCT **Intention to treat analysis:** Unclear **Length of duration of study:** 4 months (taken from trial registration) + Follow-up (not reported) **Power calculation reached:** Yes **Transfusion strategy:** A HgB level of less than 8 g/ dL -1 was considered a transfusion trigger except in patients who could have a poor tolerance to these levels because of associated conditions such as chronic obstructive pulmonary disease (COPD), cerebral arterial insufficiency, or patients who presented signs, symptoms or both of hypoxia such as tachycardia, dyspnoea, or syncope. The transfusion trigger was placed at less than 10g/ dL for these patients. **Was the trial stopped early:** No
Participants	**Baseline Characteristics** Placebo *Age (years) (mean SD)*: 54.6 +/- 14.9 *Ethnicity*: Not reported

	Gender (males, females): 19 M, 11 F *Length of surgery (minutes) (median, min-max)*: 135 (60-210) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: 0/ 30, 0% *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: 17/ 30, 56.7% *ASA 2 (n/ N,%)*: 12/ 30, 40% *ASA 3 (n/ N,%)*: 1/ 30, 3.3% *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: Not reported *Number of participants receiving treatment*: 30 *Number of participants analysed*: 30 *Dropout rate*: 0/ 30, 0% TXA *Age (years) (mean SD)*: 53.5 +/- 12.7 *Ethnicity*: Not reported *Gender (males, females)*: 21 M, 9 F *Length of surgery (minutes) (median, min-max)*: 135 (60-225) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: 0/ 30, 0% *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: 10/ 30, 33.3% *ASA 2 (n/ N,%)*: 18/ 30, 60% *ASA 3 (n/ N,%)*: 2/ 30, 6.7% *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 30 *Number of participants receiving treatment*: 30 *Number of participants analysed*: 30 *Dropout rate*: 0/ 30, 0% Overall *Age (years) (mean SD)*: Not reported

	Ethnicity: Not reported *Gender (males, females)*: Not reported *Length of surgery (minutes) (median, min-max)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: Not reported *Number of participants receiving treatment*: Not reported *Number of participants analysed*: Not reported *Dropout rate*: Not reported **Included criteria:** 1) ASA 1-3, 2) 18-75 age, 3) total hip arthroplasty surgery, 4) regional anaesthesia **Excluded criteria:** 1) History of drug sensitivity, 2) liver and kidney failure 3) DVT or embolism 4) coagulopathy 5) severe aortic or mitral valve stenosis, 6) neurologic or CVA disease 7) Aspirin or platelet antiaggregant in the week before surgery 8) or NSAIDS in the 2 days before surgery **If TKR, is tourniquet used:** Not applicable **Indication for surgery:** Primary OA (n=51), femoral neck fracture (n=4) and rheumatoid arthritis (n=5) **Type of anaesthetic:** Spinal-epidural anaesthetic **Type of surgery:** Primary THA
Interventions	**Intervention Characteristics** Placebo Group C received normal saline in place of TXA, in the same manner and same volume Placebo, IV, pre-incision and intraop, infusion. TXA The TA group received a total dose of 50mg/kg TA mixed in normal saline, which started 15 minutes prior to the skin incision and took a total time of 30 minutes, meaning that it continued during part of the surgery.

	TXA, IV, 50mg/kg, pre-incision and intraop, infusion
Outcomes	Primary outcome Amount of intraoperative bleeding Number of given packed red blood cells Secondary outcome Length of hospital stay Thromboembolic events
Notes	**Sponsorship source:** Non-pharmaceutical **Country:** Turkey **Setting:** Not reported **Comments:** None **Authors name:** S.O. Yasli **Institution:** Erciyes University **Email:** syasli@erciyes.edu.tr **Address:** Department of Oral and Maxillofacial Surgery, Faculty of Denistry Erciyes University Kayseri Turkey **Native language of paper:** English **Reference type:** Full text (1), trial registration (1) **Trial registration number:** NCT02094066 **Was it translated for this review:** No

B.1.4.91 Yen 2017

Methods	**Study design:** Randomized controlled trial **Intention to treat analysis:** Yes **Length of duration of study:** 11 (8 months + 3 months follow-up) **Power calculation reached:** Yes **Transfusion strategy:** The trigger for allogenic transfusion of red blood cells was set at a Hb level of 8 g/dl in healthy patients, or between 8 and 9 g/dl in patients with clinical symptoms and signs of acute anemia. In patients with cardiovascular disease, the transfusion threshold was set at a Hb level of 9 g/dl. **Was the trial stopped early:** No
Participants	**Baseline Characteristics**

	Placebo *Age (years) (mean SD)*: 70.87 (6.05) *Ethnicity*: Not reported *Gender (males, females)*: 6 M, 24 F *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: 0/ 30, (0%) *Incidence of preoperative anaemia (n/ N, %)*: 0 *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: 1/ 30, (3.3%) *ASA 2 (n/ N,%)*: 24/ 30, (80%) *ASA 3 (n/ N,%)*: 4/ 30, (13.3%) *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 33 *Number of participants receiving treatment*: 30 *Number of participants analysed*: 30 *Dropout rate*: 3/ 33, (9.09%) TXA, IV *Age (years) (mean SD)*: 69.13 (7.94) *Ethnicity*: Not reported *Gender (males, females)*: 4 M, 27 F *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: 0/ 31, (0%) *Incidence of preoperative anaemia (n/ N, %)*: 0 *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: 1/31, 3.2% *ASA 2 (n/ N,%)*: 22/ 31, (71%) *ASA 3 (n/ N,%)*: 8/ 31, (25.8%) *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 32 *Number of participants receiving treatment*: 31 *Number of participants analysed*: 31 *Dropout rate*: 1/ 32, (3.13%)

	TXA, IA *Age (years) (mean SD)*: 69.66 (5.53) *Ethnicity*: Not reported *Gender (males, females)*: 13 M, 19 F *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: 0/ 32, (0%) *Incidence of preoperative anaemia (n/ N, %)*: 0 *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: 0/ 32, (0%) *ASA 2 (n/ N,%)*: 19/ 32, (59.4%) *ASA 3 (n/ N,%)*: 13/ 32, (40.6%) *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 33 *Number of participants receiving treatment*: 32 *Number of participants analysed*: 32 *Dropout rate*: 1/ 33, (3.03%) Overall *Age (years) (mean SD)*: (range available) *Ethnicity*: Not reported *Gender (males, females)*: Not reported *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia (n/ N, %)*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 98 *Number of participants receiving treatment*: Not reported *Number of participants analysed*: Not reported *Dropout rate*: Not reported **Included criteria:** 1) Aged 40 years or more 2) Underwent

	unilateral primary minimally invasive TKA **Excluded criteria:** 1) Patients with a documented history of thromboembolic disease, cardiovascular disease (myocardial infarction or angina), stroke, coagulopathy, 2) Lifelong warfarin treatment for thromboembolic prophylaxis, 3) Impaired hepatic or renal function (impaired hepatic function was defined as liver enzyme level, AST or ALT, which is more than twice normal range, history of liver cirrhosis, elevated total bilirubin level, or coagulopathy (INR < 1.3); and impaired renal function was defined as GFR < 55 ml/min/1.73 m2, which is relative contraindicated for chemical venous thromboembolism and venography), 4) Patients with an allergy history to tranexamic acid, 5) Concomitant use of protease inhibitors of human immunodeficiency virus, 6) Fibrinolytic agent that contraindicated the use of rivaroxaban, 7) Preoperative anemia (a hemoglobin level of ≤10 g/dl) **Pre-treatment:** No except gender distribution **If TKR, is tourniquet used:** Yes **Indication for surgery:** Not reported **Type of anaesthetic:** General anaesthetic **Type of surgery:** Primary TKR
Interventions	**Intervention Characteristics** Placebo Patients in the placebo group received saline twice, 20 mL intravenously 10 minutes before skin closure and 160 mL intra-articularly via the drain after capsule closure before deflation of the tourniquet. Placebo, IV, intraop (10 mins before closure) AND Placebo, IA, intraop before tourniquet deflation TXA, IV Patients in the IV group received 1 g (20 mL) TXA intravenously 10 minutes before skin closure and 160 mL saline intra-articularly via the drain after capsule closure TXA, IV, 1g, intraop (10 mins before closure) AND Placebo, IA, intraop before tourniquet deflation TXA, IA Patients in the topical TXA group received 10 mL of saline intravenously 10 minutes before skin closure and 3 g(60 mL) TXA (Transamin 50 mg/mL Placebo, IV, intraop (10 mins before closure) AND TXA, IA, 3g, intraop before tourniquet deflation

Outcomes	Primary outcome: Estimated total blood loss Secondary outcome: Rate of perioperative blood transfusion Rate of deep-vein thrombosis (DVT) Wound complications Visual analogue scale (VAS) on POD 1 Length of hospital stay Range of motion of the knee
Notes	**Sponsorship source:** Non-pharmaceutical **Country:** Taiwan **Setting:** Single-centre **Comments:** None **Authors name:** J-W Wang **Institution:** Chang Gung University **Email:** wangjw@adm.cgmh.org.tw **Address:** Department of Orthopaedic Surgery, Kaohsiung Chang Gung Memorial Hospital, Chang Gung University, College of Medicine, Taoyuan, Taiwan **Native language of paper:** English **Reference type:** Abstract (1) Full text (1) Trial Registration (1) **Trial registration number:** NCT02453802 **Was it translated for this review:** No

B.1.4.92 Yen 2021

Methods	**Study design:** RCT **Intention to treat analysis:** Per-protocol **Length of duration of study:** 11 months (January 2017 and December 2017) + 3 months follow-up = 14 months **Power calculation reached:** Yes **Transfusion strategy:** The trigger for allogenic transfusion of red blood cells was set at an Hb level of 8 g/dL in healthy patients and between 8 and 9 g/dL in patients with clinical symptoms and signs of anaemia

	Was the trial stopped early: No
Participants	**Baseline Characteristics** TXA, IA *Age (years) (mean SD)*: 69.35 (7.11) *Ethnicity*: Not reported *Gender (males, females)*: 6/ 34 M (17.6%) 28/34 F (82.4%) *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: 0/34, 0% *Incidence of preoperative anaemia*: 0/ 34, 0% *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: 2/34 (5.9%) *ASA 2 (n/ N,%)*: 23/34 (67.6%) *ASA 3 (n/ N,%)*: 9/34 (26.5%) *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 35 *Number of participants receiving treatment*: Not reported *Number of participants analysed*: 34 *Dropout rate*: 1/ 35, 2.9% Floseal, IA *Age (years) (mean SD)*: 69.71 (6.79) *Ethnicity*: Not reported *Gender (males, females)*: 6/ 34 M (17.6%) 28/34 F (82.4%) *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: 0/ 34, 0% *Incidence of preoperative anaemia*: 0/ 34, 0% *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: 1/34 (2.9%) *ASA 2 (n/ N,%)*: 19/34 (55.9%) *ASA 3 (n/ N,%)*: 14/34 (41.2%) *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 34 *Number of participants receiving treatment*: Not reported

	Number of participants analysed: 34 *Dropout rate*: 0/ 34, 0% Placebo, IA *Age (years) (mean SD)*: 69.71 (5.94) *Ethnicity*: Not reported *Gender (males, females)*: 3/ 35 M (8.6%) 32/35 F (91.4%) *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: 0/ 35, 0% *Incidence of preoperative anaemia*: 0/ 35, 0% *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: 1/35 (2.9%) *ASA 2 (n/ N,%)*: 23/35 (65.7%) *ASA 3 (n/ N,%)*: 11/35 (31.4%) *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 35 *Number of participants receiving treatment*: Not reported *Number of participants analysed*: 35 *Dropout rate*: 0/ 35, 0% Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males, females)*: Not reported *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: 0/103, 0% *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 104 *Number of participants receiving treatment*: Not reported *Number of participants analysed*: 103

	Dropout rate: 1/ 104, 0.96% **Included criteria:** The inclusion criteria were patients who were aged 50 years or older with a preoperative Hb level of ≥11 g/dL and a history of thromboembolic disease, cardiovascular disease (myocardial infarction or angina, stroke), or risk factors related to venous thromboembolism, such as old age (≥70 years), obesity(body mass index ½BMI ≥ 25), a history of cancer, or varicose veins of the leg **Excluded criteria:** The exclusion criteria were patients who had preoperative anaemia (an Hb level of <11 g/dL), a history of infection or intra-articular fracture of the affected knee, or impaired hepatic or renal function. The impaired hepatic function was defined as liver enzyme levels of AST or ALT that were more than twice the normal range, or a history of liver cirrhosis, while the impaired renal function was defined as a glomerular filtration rate eGFR < 30 mL/min/1:73 m2, which is contraindicated for chemical thromboprophylaxis. Patient use of lifelong anticoagulant therapy, allergy to tranexamic acid, Floseal, enoxaparin or rivaroxaban, or preoperative evaluation as being at high risk during surgery by a cardiologist or neurologist were also exclusion criteria in this study. **Pre-treatment:** No **If TKR, is tourniquet used:** Yes **Indication for surgery:** Osteoarthritis **Type of anaesthetic:** General **Type of surgery:** Unilateral primary TKR
Interventions	**Intervention Characteristics** TXA, IA Patients in the topical TXA group received 3 g (30 mL) intraarticular TXA (Transamin 100 mg/mL; China Chemical and Pharmaceutical Co, Taiwan) in 100 mL of saline via the drain after capsule closure. TXA, IA, 3g, intraop Floseal, IA Patients in the topical Floseal® group received intra-articular 10 mL Floseal® (Baxter, Deerfield, IL, USA), which was applied to the exposed bone surfaces of the femoral and tibial condyles after cutting and soft tissue release, as well as to the bleeding points of the soft tissue and tibial pinholes after cementing of the implant and before insertion of the tibial polyethylene liner. Floseal, IA, 10ml, intraop

	Placebo, IA Patients in the placebo group received a 130 mL saline injection intra-articularily via the drain after capsule closure. Placebo, IA, 130ml, intraop
Outcomes	Primary outcome: Calculated Total Blood Loss Hb level Secondary outcome: Rate of perioperative blood transfusion Rate of deep-vein thrombosis (DVT) Pulmonary embolism (PE) Wound complications Length of hospital stay.
Notes	**Sponsorship source:** Non-pharmaceutical (supported by the Ministry of Science and Technology (NMRPG8F0191)) **Country:** Taiwan **Setting:** Single-centre **Comments:** None **Authors name:** S-H Yen **Institution:** Kaohsiung Chang Gung Memorial Hospital and Chang Gung University **Email:** J-W Wang: wangjw@adm.cgmh.org.tw **Address:** Department of Orthopaedic Surgery, Kaohsiung Chang Gung Memorial Hospital and Chang Gung University, College of Medicine, Taiwan **Native language of paper:** English **Reference type:** Full text (1), trial registration (1) **Trial registration number:** NCT02865174 **Was it translated for this review:** No

B.1.4.93 Zeng 2017

Methods	**Study design:** RCT **Intention to treat analysis:** Yes **Length of duration of study:** 5 months and 3 Weeks

	follow-up **Power calculation reached:** Not reported **Transfusion strategy:** A transfusion protocol based on the guidelines for perioperative transfusion by the Chinese Ministry of Health was utilized to standardize the application of blood transfusions. Blood transfusion was indicated when the hemoglobin concentration was <7 g/dL; blood transfusion was indicated when the hemoglobin concentration was <8 g/dL in a patient who tolerated anemia poorly, and was indicated when the hemoglobin concentration was <10 g/dL in a patient who developed any anemia-related organ dysfunction. **Was the trial stopped early:** No
Participants	**Baseline Characteristics** Placebo *Age (years) (mean SD)*: 56.1 (11.2) *Ethnicity*: Not reported *Gender (males, females)*: 29 M, 21 F *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: 0/ 50 (0%) *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: 0, 0% *ASA 2 (n/ N,%)*: 35/ 50 (70%) *ASA 3 (n/ N,%)*: 15/ 50 (30%) *ASA 4 (n/ N,%)*: 0/0 (0%) *Number of participants randomised*: 50 *Number of participants receiving treatment*: 50 *Number of participants analysed*: 50 *Dropout rate*: 0/ 50, (0%) TXA *Age (years) (mean SD)*: 51.1 (14.9) *Ethnicity*: Not reported *Gender (males, females)*: 31 M, 19 F *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to*

	surgery (n/ N, %): 0/ 50 (0%) *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: 0/0 (0%) *ASA 2 (n/ N,%)*: 38/ 50 (76%) *ASA 3 (n/ N,%)*: 12/ 50 (24%) *ASA 4 (n/ N,%)*: 0/0 (0%) *Number of participants randomised*: 50 *Number of participants receiving treatment*: 50 *Number of participants analysed*: 50 *Dropout rate*: 0/ 50, (0%) Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males, females)*: Not reported *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: Not reported *Number of participants receiving treatment*: Not reported *Number of participants analysed*: Not reported *Dropout rate*: Not reported **Included criteria:** 1) all adult patients (aged between 18 and 90 years), 2) Undergoing primary unilateral THA, 3) End-stage joint disease and the treating surgeon believed their pre-morbid activity profile and general condition made them suitable for a THA **Excluded criteria:** 1) Allergy to TXA, 2) Preoperative hepatic or renal dysfunction, 3) Preoperative use of anticoagulant medication 7 days prior to surgery, 4) History of fibrinolytic disorder or blood dyscrasia, 5) History of

	cerebrovascular accident or myocardial infarction, 6) New York heart association class III or IV heart failure, 7) Atrial fibrillation, 8) History of deep vein thrombosis or pulmonary embolus, 9) Preoperative international normalized ratio (INR) >1.4, activated partial thromboplastin time (aPTT) >1.4× normal **Pre-treatment:** No **If TKR, is tourniquet used:** Not applicable **Indication for surgery:** End stage joint disease (Osteoarthritis, osteonecrosis of the femoral head, rheumatoid arthritis) **Type of anaesthetic:** General anaesthetic **Type of surgery:** Primary THR
Interventions	**Intervention Characteristics** Placebo The TXA group received i.v. (15 mg/kg, 15 mg TXA) in 1.5 mL normal saline (NS) combined with topical administration (1000 mg TXA in 100 mL NS) of TXA during THA procedure, and the placebo group received the same dosage of NS (100 mL NS i.v. combined with 100 mL NS topical). For patients in the TXA group, 15 mg/kg TXA was applied i.v. 5 min before the skin incision. Placebo, 100mls IV, intraop (5 mins before incision) AND Placebo, 20mls, IA, intraop to acetabular cup (bathed) + 20mls to femoral canal + 60mls to open joint surface TXA The TXA group received i.v. (15 mg/kg, 15 mg TXA) in 1.5 mL normal saline (NS) combined with topical administration (1000 mg TXA in 100 mL NS) of TXA during THA procedure, and the placebo group received the same dosage of NS (100 mL NS i.v. combined with 100 mL NS topical). For patients in the TXA group, 15 mg/kg TXA was applied i.v. 5 min before the skin incision. TXA, 15mg/kg IV, intraop (5 mins before incision) AND TXA, 1g, IA, intraop broken into 20mls to acetabular cup (bathed) + 20mls to femoral canal + 60mlsto open joint surface
Outcomes	Primary outcome: Total blood loss Hemoglobin Haematocrit Platelet concentration changes

	Amount of drainage Amount of intraoperative blood loss Frequency of transfusion Number of blood units transfused Secondary outcome: Length of postoperative stay Range of hip motion Harris hip scores (HHS) Perioperative complications or events such as infection, DVT, or PE.
Notes	**Sponsorship source:** Non-pharmaceutical **Country:** China **Setting:** Single-centre **Comments:** None **Authors name:** Y. Zeng **Institution:** Sichuan University **Email:** zengyigd@126.com **Address:** Department of Orthopaedics, West China Hospital, Sichuan University, 37# Guoxue Road, Chengdu,China 610041 **Native language of paper:** English **Reference type:** Full Text (1) Trial Registration (1) **Trial registration number:** ChiCTR-TRC-14004474 **Was it translated for this review:** No

B.1.4.94 Zeng 2018

Methods	**Study design:** RCT **Intention to treat analysis:** Yes **Length of duration of study:** 11 months (8 months +3 months follow-up) **Power calculation reached:** Not reported **Transfusion strategy:** The use of blood transfusions was standardized according to a protocol based on the guidelines for peri-operative transfusion provided by the Chinese Ministry of Health. According to the protocol, a blood transfusion was indicated when the hemoglobin concentration was <70 g/L or when a patient developed any

	anaemia-related organ dysfunction, such as an alteration in mental status or palpitation **Was the trial stopped early:** No
Participants	**Baseline Characteristics** Extension + TXA, IV + TXA, Topical *Age (years) (mean SD)*: 69.68 (6.34) *Ethnicity*: Not reported *Gender (males, females)*: 10 M, 20 F *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: 1/ 30, (3.33%) *ASA 2 (n/ N,%)*: 24/ 30, (80%) *ASA 3 (n/ N,%)*: 5/ 30, (16.67%) *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 30 *Number of participants receiving treatment*: 30 *Number of participants analysed*: 30 *Dropout rate*: 0/ 30, (0%) Control + TXA, IV *Age (years) (mean SD)*: 72.15 (7.24) *Ethnicity*: Not reported *Gender (males, females)*: 13 M, 17 F *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N%)*: 4/ 30, (13.33%) *ASA 2 (n/ N,%)*: 17/ 30, (56.67%) *ASA 3 (n/ N,%)*: 9/ 30, (30%) *ASA 4 (n/ N,%)*: Not reported

	Number of participants randomised: 30 *Number of participants receiving treatment*: 30 *Number of participants analysed*: 30 *Dropout rate*: 0/ 30, (0%) Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported *Gender (males, females)*: Not reported *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: Not reported *Number of participants receiving treatment*: Not reported *Number of participants analysed*: Not reported *Dropout rate*: Not reported **Included criteria:** 1) Patients undergoing primary unilateral TKA **Excluded criteria:** 1) Allergic to TXA, 2) Treatment with warfarin, heparin, or oestrogen before surgery, 3) A history of hypercoagulation, haemophilia, deep vein thrombosis (DVT), pulmonary embolism (PE), 4) Previous surgery to the knee, 5) Bleeding disorders, platelet of bone marrow disorders **Pre-treatment:** No **If TKR, is tourniquet used:** Yes **Indication for surgery:** Not reported **Type of anaesthetic:** Not reported **Type of surgery:** Primary TKR
Interventions	**Intervention Characteristics** Extension + TXA, IV + TXA, Topical

	The patients in the flexion group and extension group received 1 g (100 ml) of intravenous TXA five minutes before inflation of the tourniquet, and 1 g (100 ml) TXA was irrigated in the wound after implantation of the components. TXA, IV, 1g, intraop (5 min before tourniquet) + TXA, IA, 1g, intraop (after implantation) Control + TXA, IV For the controlled group, a single dose of 1 g(100 ml) TXA was applied intravenously before tourniquet inflation and knee was completely extended after surgery, combined with 100 ml normal saline applied topically without TXA TXA, IV, 1g, intraop (5min before tourniquet) + Placebo, IA, intraop (after implantation)
Outcomes	Primary outcome: Total blood loss Changes in haemoglobin and haematocrit Amount of drainage Transfusion frequency Number of blood units transfused Secondary outcome: Knee flexion motion Rates of DVT and PE Length of the post-operative hospital stay Hospital and surgery costs
Notes	**Sponsorship source:** Non-pharmaceutical **Country:** China **Setting:** Single-centre **Comments:** None **Authors name:** B.Shen **Institution:** Sichuan University **Email:** shenbin_1971@163.com **Address:** Department of Orthopaedic Surgery, West China Hospital, West China Medical School, Sichuan University, 37# Guoxue Road, Chengdu 610041, People's Republic of China **Native language of paper:** English

	Reference type: Full text (1) **Trial registration number:** ChiCTR-INR-17010951 **Was it translated for this review:** No

B.1.4.95 Zhang 2007

Methods	**Study design:** RCT **Intention to treat analysis:** Unclear **Length of duration of study:** 24 months (12 months + 12 months follow-up) **Power calculation reached:** Not reported **Transfusion strategy:** Blood transfusion was less than 10 g/dL **Was the trial stopped early:** No
Participants	**Baseline Characteristics** Placebo *Age (years) (mean range)*: Not reported *Ethnicity*: Not reported *Gender (males, females)*: Not reported *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 51 *Number of participants receiving treatment*: 51 *Number of participants analysed*: 51 *Dropout rate*: 0/51 (0%) TXA *Age (years) (mean range)*: Not reported *Ethnicity*: Not reported

	Gender (males, females): Not reported *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 51 *Number of participants receiving treatment*: 51 *Number of participants analysed*: 51 *Dropout rate*: 0/51 (0%) Overall *Age (years) (mean range)*: 68 (59-77) *Ethnicity*: Not reported *Gender (males, females)*: 43 M, 59 F *Length of surgery (minutes)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 102 *Number of participants receiving treatment*: 102 *Number of participants analysed*: 102 *Dropout rate*: Not reported **Included criteria:** Patients who underwent TKA **Excluded criteria:** Not reported **Pre-treatment:** Not reported **If TKR, is tourniquet used:** Yes

	Indication for surgery: Osteoarthritis, rheumatoid arthritis, traumatic arthritis. **Type of anaesthetic:** Not reported **Type of surgery:** Primary TKR
Interventions	**Intervention Characteristics** Placebo In Group B, only 250ml of normal saline was infused intravenously Placebo, IV, intraop (prior to tourniquet deflation) AND Placebo, IV, 3 hours later TXA In Group A, 1g of tranexamic acid dissolved in 250ml of normal saline was intravenously infused before deflation of the tourniquet; another intravenous administration of the same drug of the same dosage was given 3 hours later. TXA, IV, 1g, intraop (prior to tourniquet deflation) AND TXA, IV, 1g, 3 hours later
Outcomes	Primary outcome: Blood loss Blood transfusion Venous thrombosis Secondary outcome: Not reported
Notes	**Sponsorship source:** Not reported **Country:** China **Setting:** Not reported **Comments:** Mean units calculated from ml in paper. Assumed 525ml as 1 unit. **Authors name:** F. Zhang **Institution:** Tianjin Hospital **Email:** zhang656696@yahoo.com.cn **Address:** Department of Joint Surgery, Tianjin Hospital, Tianjin Medical University,Tianjin300211, P.R. China **Native language of paper:** Chinese **Reference type:** Full Text (1) **Trial registration number:** Not applicable, but when

	checked trial registration number not found **Was it translated for this review:** Yes

B.1.4.96 Zhao 2018

Methods	**Study design:** RCT **Intention to treat analysis:** Yes **Length of duration of study:** 10 **Power calculation reached:** Not reported **Transfusion strategy:** Perioperative blood transfusions were given based on guidelines of the Chinese Ministry of Health, which indicate transfusions when hemoglobin concentration < 70 g/L or when symptoms of anemia are present, such as altered mental state or palpitation (regardless of haemoglobin concentration). **Was the trial stopped early:** No
Participants	**Baseline Characteristics** Placebo *Age (years) (mean SD)*: 59.86 (10.68) *Ethnicity*: Not reported *Gender (males, females)*: 25 M, 15 F *Length of surgery (minutes) mean (SD)*: 66.3 (6.2) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: 19/ 40 (47.5%) *ASA 2 (n/ N,%)*: 9/ 40 (22.5%) *ASA 3 (n/ N,%)*: 2/ 40 (5%) *ASA 4 (n/ N,%)*: 0/ 40 (0%) *Number of participants randomised*: 40 *Number of participants receiving treatment*: 40 *Number of participants analysed*: 40 *Dropout rate*: 0/ 40 (0%) TXA, IV *Age (years) (mean SD)*: 59.50 (11.42)

	Ethnicity: Not reported *Gender (males, females)*: 23 M, 17 F *Length of surgery (minutes) mean (SD)*: 62.1 (9.1) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: 18/ 40 (45%) *ASA 2 (n/ N,%)*: 8/ 40 (20%) *ASA 3 (n/ N,%)*: 4/ 40 (10%) *ASA 4 (n/ N,%)*: 0/ 40 (0%) *Number of participants randomised*: 40 *Number of participants receiving treatment*: 40 *Number of participants analysed*: 40 *Dropout rate*: 0/ 40 (0%) TXA, Oral *Age (years) (mean SD)*: 60.47 (10.35) *Ethnicity*: Not reported *Gender (males, females)*: 22 M, 18 F *Length of surgery (minutes) mean (SD)*: 64.9 (13.4) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: 16/ 40 (40%) *ASA 2 (n/ N,%)*: 10/ 40 (25%) *ASA 3 (n/ N,%)*: 4/ 40 (10%) *ASA 4 (n/ N,%)*: 0/ 40 (0%) *Number of participants randomised*: 40 *Number of participants receiving treatment*: 40 *Number of participants analysed*: 40 *Dropout rate*: 0/ 40 (0%) Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported

	Gender (males, females): Not reported *Length of surgery (minutes) mean (SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: 120 *Number of participants receiving treatment*: 120 *Number of participants analysed*: 120 *Dropout rate*: Not reported **Included criteria:** All patients had been diagnosed with hip osteoarthritis or femoral head necrosis (Ficat III or IV) **Excluded criteria:** 1) Body weight index (BMI) > 30 kg/m2, 2) Crowe type 3 or 4 dysplasia, 3) Previous hardware, 4) Prior hip surgery, 5) Inability to tolerate general anaesthesia, 6) Bilateral arthroplasty, 7) Allergy to TXA, 8) History of renal failure, 9) Kidney transplant, 10) Recent arterial thromboembolic event such as myocardial infarction or stroke, hypercoagulation, haemophilia, deep vein thrombosis, or pulmonary embolism, 11) Declined to participate or to receive blood products **Pre-treatment:** No **If TKR, is tourniquet used:** Not applicable **Indication for surgery:** Hip osteoarthritis or femoral head necrosis (Ficat III or IV). **Type of anaesthetic:** General **Type of surgery:** Primary THR
Interventions	**Intervention Characteristics** Placebo Patients in the control group received ascorbic acid tablets and intravenous injections of saline as in the other groups, but no TXA Placebo, IV + oral, 10mins preop + 3 hours postop AND Placebo, oral, 2 hours preop and 3 hours postop.

	TXA, IV TXA in the intravenous group was administered at a dose of 15 mg/kg at ten minutes before skin incision and again at three hours after THA. In order to support the double-blind nature of the study, patients in this group also received four tablets of ascorbic acid (250 mg, so 1000 mg total) at two hours before and three hours after THA. TXA, 15mg/kg, IV 10 mins preop, + 3 hours postop, AND Placebo, oral 2 hours preop and 3 hours postop. TXA, Oral TXA in the oral group was administered at a dose of 20 mg/kg at two hours before and three hours after THA. In order to support the double-blind nature of the study, patients in this group also received intravenous injections of saline ten minutes before skin incision and again three hours after THA. TXA, 20mg/kg, oral, 2 hours preop and 3 hours postop AND Placebo, IV 10 mins preop + 3 hours postop.
Outcomes	Primary outcome: Reduction in haemoglobin concentration (defined as pre-operative haemoglobin minus lowest post-operative haemoglobin), Total blood loss Intra-operative blood loss Transfusion rates Number of blood units transfused Secondary outcome: Thromboembolic events Wound complications
Notes	**Sponsorship source:** None **Country:** China **Setting:** Single-centre **Comments:** None **Authors name:** P-D Kang **Institution:** Sichuan University **Email:** kangpd@163.com **Address:** Department of Orthopedics, West China Hospital, West China School of Medicine, Sichuan University, 37# Wuhou Guoxue Road,Chengdu 610041, People’s Republic of

	China **Native language of paper:** English **Reference type:** Full text (1) **Trial registration number:** ChiCTR-INR17013110 **Was it translated for this review:** No

B.1.4.97 Zohar 2004

Methods	**Study design:** RCT **Intention to treat analysis:** Yes **Length of duration of study:** Not reported **Power calculation reached:** Yes **Transfusion strategy:** In all cases, a haematocrit 28% constituted the postoperative transfusion trigger. **Was the trial stopped early:** No
Participants	**Baseline Characteristics** TXA, IV long *Age (years) (mean SD)*: 73 (8) *Ethnicity*: Not reported *Gender (males, females)*: 6 M, 14 F *Length of surgery (minutes) mean (SD)*: 118 (19) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: 0/20 (0%) *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: 4/20 (20%) *ASA 2 (n/ N,%)*: 16/20 (80%) *ASA 3 (n/ N,%)*: 0/20 (0%) *ASA 4 (n/ N,%)*: 0/20 (0%) *Number of participants randomised*: 20 *Number of participants receiving treatment*: 20 *Number of participants analysed*: 20 *Dropout rate*: 0/20 (0%) TXA, IV short *Age (years) (mean SD)*: 69 (7)

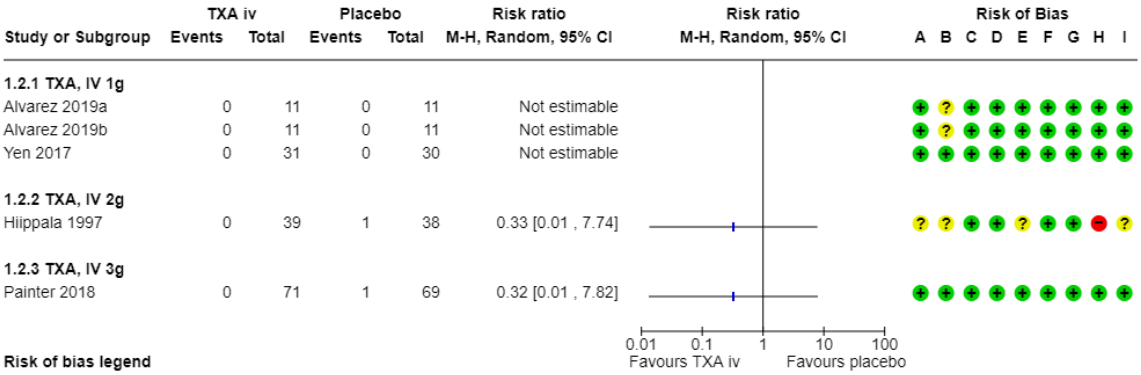
	Ethnicity: Not reported *Gender (males, females)*: 4 M, 16 F *Length of surgery (minutes) mean (SD)*: 124 (14) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: 0/20 (0%) *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: 2/20 (10%) *ASA 2 (n/ N,%)*: 17/20 (85%) *ASA 3 (n/ N,%)*: 1/20 (5%) *ASA 4 (n/ N,%)*: 0/20 (0%) *Number of participants randomised*: 20 *Number of participants receiving treatment*: 20 *Number of participants analysed*: 20 *Dropout rate*: 0/20 (0%) TXA, Oral *Age (years) (mean SD)*: 69 (10) *Ethnicity*: Not reported *Gender (males, females)*: 8M, 12 F *Length of surgery (minutes) mean (SD)*: 122 (17) *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: 0/20 (0%) *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: 5/20 (25%) *ASA 2 (n/ N,%)*: 15/20 (75%) *ASA 3 (n/ N,%)*: 0/20 (0%) *ASA 4 (n/ N,%)*: 0/20 (0%) *Number of participants randomised*: 20 *Number of participants receiving treatment*: 20 *Number of participants analysed*: 20 *Dropout rate*: 0/20 (0%) Overall *Age (years) (mean SD)*: Not reported *Ethnicity*: Not reported

	Gender (males, females): Not reported *Length of surgery (minutes) mean (SD)*: Not reported *Proportion of participants on anticoagulants prior to surgery (n/ N, %)*: Not reported *Incidence of preoperative anaemia*: Not reported *Co-morbidities*: Not reported *ASA 1 (n/ N,%)*: Not reported *ASA 2 (n/ N,%)*: Not reported *ASA 3 (n/ N,%)*: Not reported *ASA 4 (n/ N,%)*: Not reported *Number of participants randomised*: Not reported *Number of participants receiving treatment*: Not reported *Number of participants analysed*: Not reported *Dropout rate*: Not reported **Included criteria:** 1) ASA physical status I–III 2) Undergoing elective TKR **Excluded criteria:** 1) Patients with a history of severe ischemic heart disease (New York Heart Association Class III and IV) 2) Chronic renal failure 3) Cirrhosis 4) Bleeding disorders 5) Current anticoagulant therapy **If TKR, is tourniquet used:** Yes **Indication for surgery:** Not reported **Type of anaesthetic:** General **Type of surgery:** Primary TKR
Interventions	TXA, IV long In group TXA-long, 30 min before the limb tourniquet was deflated, an IV bolus dose of TA (TEVA™; Biogal Pharmaceutical Works Ltd., Debrecen, Hungary) 15 mg/kg was administered over 30 min. Thereafter, a constant IV infusion of 10 mg · kg1 · h1 was administered until 12 h after final deflation of the limb tourniquet TXA, IV short In group TXA-short, 30 min before deflation of the limb tourniquet, an IV bolus dose of TA 15 mg/kg was administered over 30 min, followed by a constant IV infusion of 10 mg · kg1 · h1 until 2 h after final deflation of the limb tourniquet (time of discharge from the PACU). Thereafter, oral TA 1 g was administered after 6 and 12 h. TXA, Oral

	In group TA-oral, 60 min before surgery, an oral dose of TA 1 g was administered. After surgery, the same dose of TA was administered every 6 h for the next 18 h.
Outcomes	Primary outcome: Allogeneic blood transfusion Blood accumulation in surgical drain Thromboembolic events
Notes	**Sponsorship source:** Not reported **Country:** Israel **Setting:** Not reported **Comments:** Mean and SD worked out from table in paper. **Authors name:** E. Zohar **Institution:** Tel Aviv University **Email:** Fredman.Brian@clalit.org.il. **Address:** Department of Anesthesiology and Intensive Care, Meir Hospital, Kfar Saba 44281, The Sackler School of Medicine, Tel Aviv University, Tel Aviv, Israel. **Native language of paper:** English **Reference type:** Full text (1), Abstract (1) **Trial registration number:** Not applicable, but when checked trial registration number not found **Was it translated for this review:** No

B.1.5 Forest plot pairwise analysis for primary outcome mortality

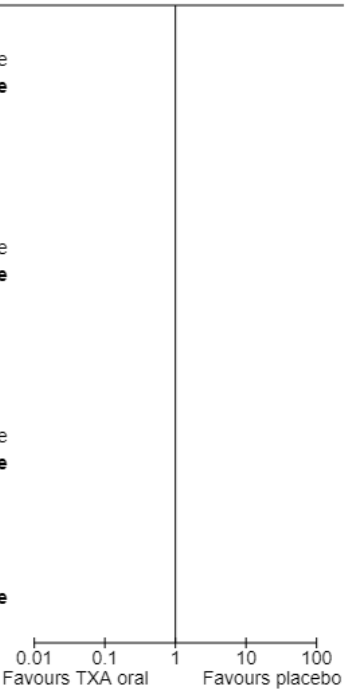
B.1.5.1 TXA IV versus Placebo pairwise



Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias) Subjective outcomes
(D) Blinding of participants and personnel (performance bias) Objective outcomes
(E) Blinding of outcome assessment (detection bias) Subjective outcomes
(F) Blinding of outcome assessment (detection bias) Objective outcomes
(G) Incomplete outcome data (attrition bias)
(H) Selective reporting (reporting bias)
(I) Other bias

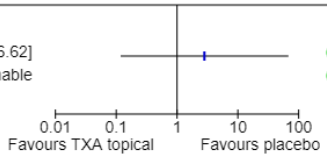
B.1.5.2 TXA oral versus placebo

Study or Subgroup	TXA oral Events	Total	Placebo Events	Total	Weight	Risk ratio M-H, Random, 95% CI
2.2.1 TXA, Oral 1g						
Wang 2019a	0	50	0	50		Not estimable
Subtotal (95% CI)		**50**		**50**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.2.2 TXA, Oral 2g						
Wang 2019a	0	50	0	50		Not estimable
Subtotal (95% CI)		**50**		**50**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
2.2.3 TXA, Oral 3g						
Wang 2019a	0	50	0	50		Not estimable
Subtotal (95% CI)		**50**		**50**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**150**		**150**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



B.1.5.3 TXA topical versus placebo

Study or Subgroup	TXA topical Events	Total	Placebo Events	Total	Risk ratio M-H, Random, 95% CI
3.2.1 TXA, Topical 3g					
Yen 2017	1	32	0	30	2.82 [0.12 , 66.62]
Yen 2021	0	34	0	35	Not estimable

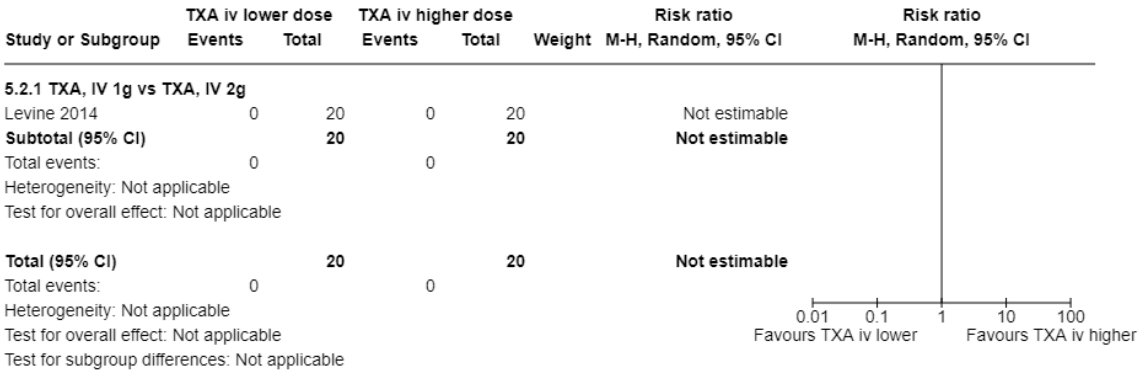




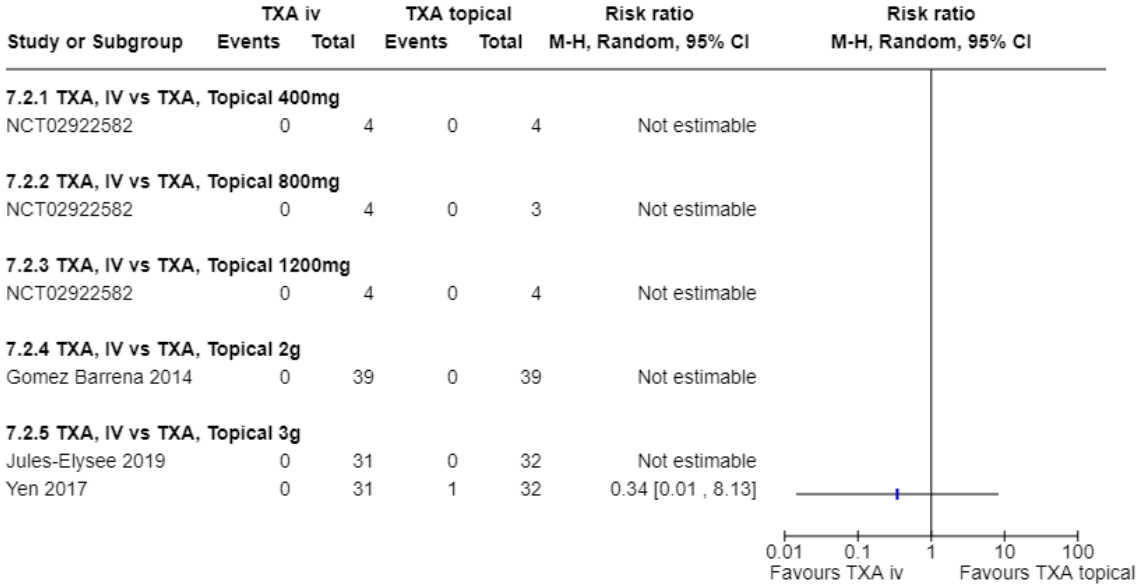
Risk of bias legend

(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias) Subjective outcomes
(D) Blinding of participants and personnel (performance bias) Objective outcomes
(E) Blinding of outcome assessment (detection bias) Subjective outcomes
(F) Blinding of outcome assessment (detection bias) Objective outcomes
(G) Incomplete outcome data (attrition bias)
(H) Selective reporting (reporting bias)
(I) Other bias

B.1.5.4 TXA IV lower dose versus TXA IV higher dose

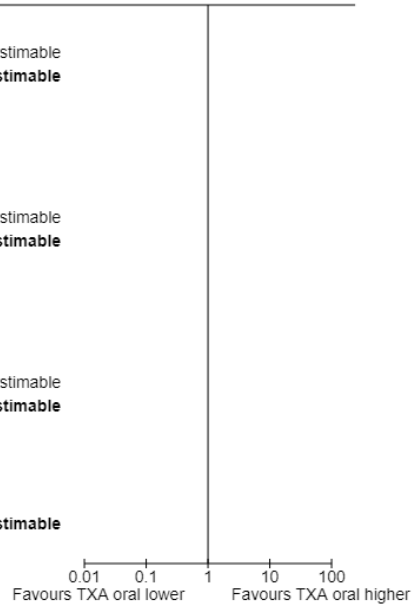


B.1.5.5 TXA IV versus TXA topical



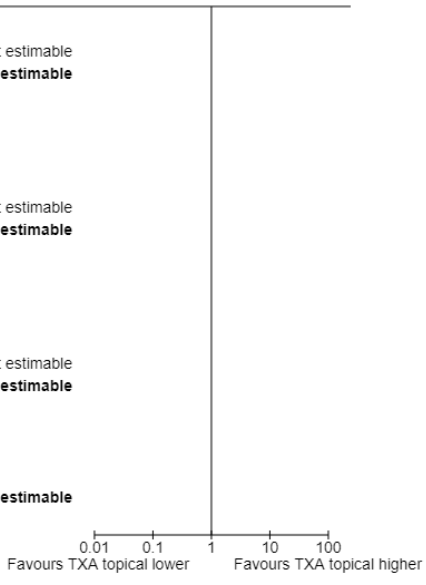
B.1.5.6 TXA oral lower dose versus TXA oral higher dose

Study or Subgroup	TXA oral lower dose Events	Total	TXA oral higher dose Events	Total	Weight	Risk ratio M-H, Random, 95% CI
8.2.1 TXA, Oral 1g vs TXA, Oral 2g						
Wang 2019a	0	50	0	50		Not estimable
Subtotal (95% CI)		**50**		**50**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
8.2.2 TXA, Oral 1g vs TXA, Oral 3g						
Wang 2019a	0	50	0	50		Not estimable
Subtotal (95% CI)		**50**		**50**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
8.2.3 TXA, Oral 2g vs TXA, Oral 3g						
Wang 2019a	0	50	0	50		Not estimable
Subtotal (95% CI)		**50**		**50**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**150**		**150**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						

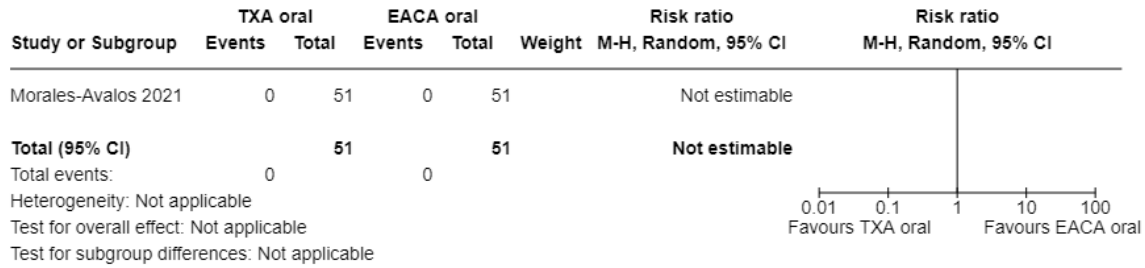


B.1.5.7 TXA topical lower dose versus TXA topical higher dose

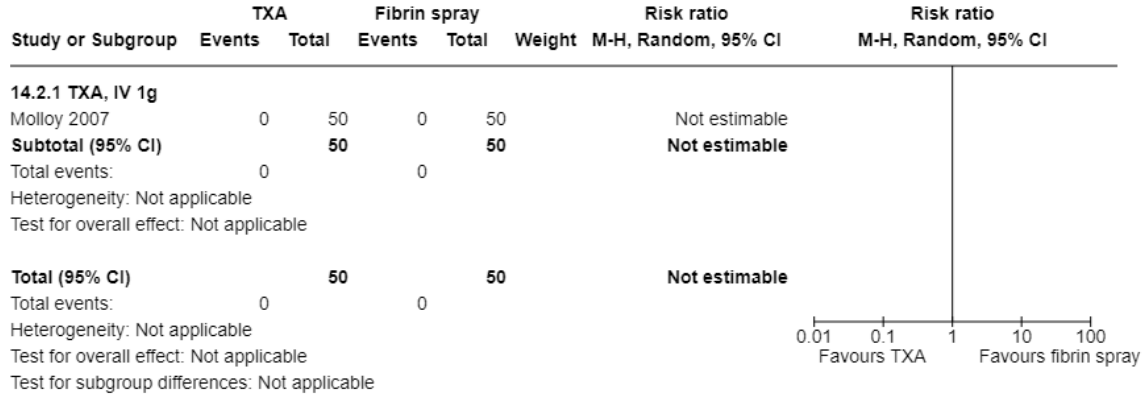
Study or Subgroup	TXA topical lower dose Events	Total	TXA topical higher dose Events	Total	Weight	Risk ratio M-H, Random, 95% CI
9.2.1 TXA, Topical 400mg vs TXA, Topical 800mg						
NCT02922582	0	4	0	3		Not estimable
Subtotal (95% CI)		**4**		**3**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
9.2.2 TXA, Topical 400mg vs TXA, Topical 1200mg						
NCT02922582	0	4	0	4		Not estimable
Subtotal (95% CI)		**4**		**4**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
9.2.3 TXA, Topical 800mg vs TXA, Topical 1200mg						
NCT02922582	0	3	0	4		Not estimable
Subtotal (95% CI)		**3**		**4**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**11**		**11**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



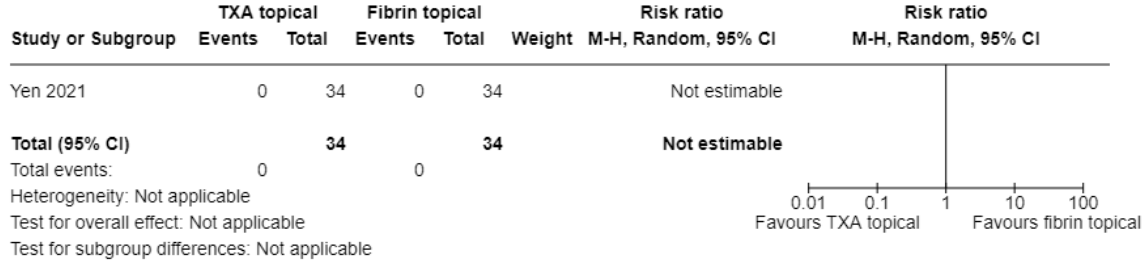
B.1.5.8 TXA oral versus EACA oral



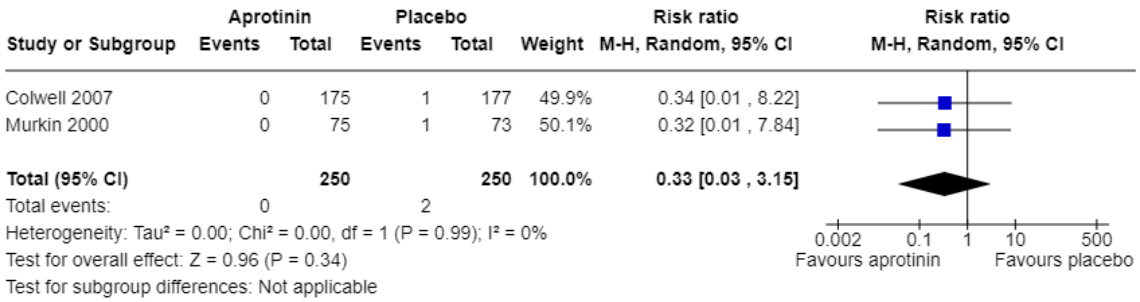
B.1.5.9 TXA iv versus Fibrin topical



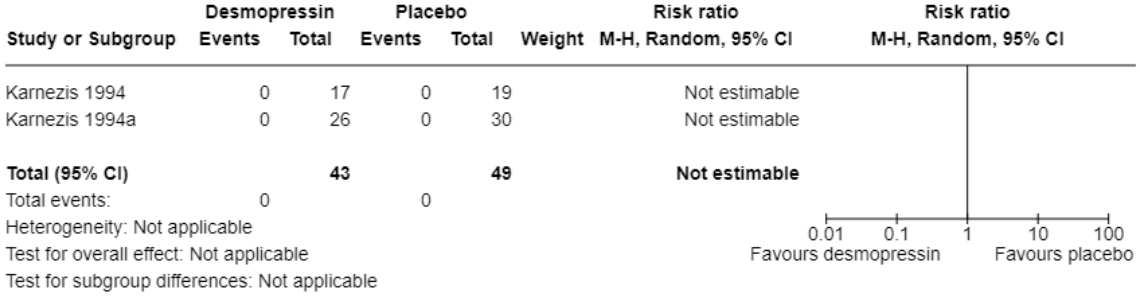
B.1.5.10 TXA topical versus Fibrin topical



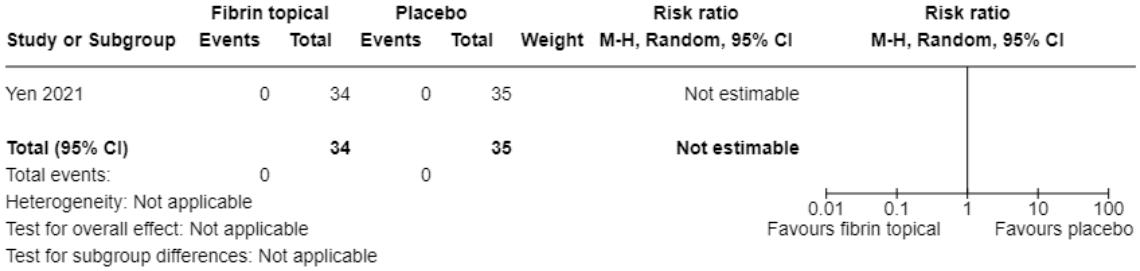
B.1.5.11 Aprotinin versus placebo



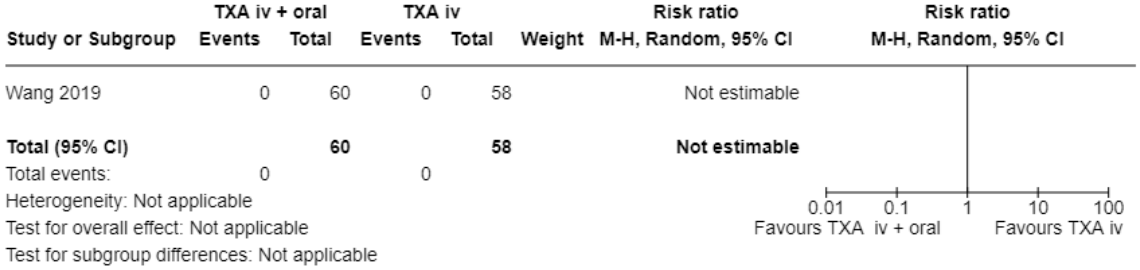
B.1.5.12 Desmopressin versus placebo



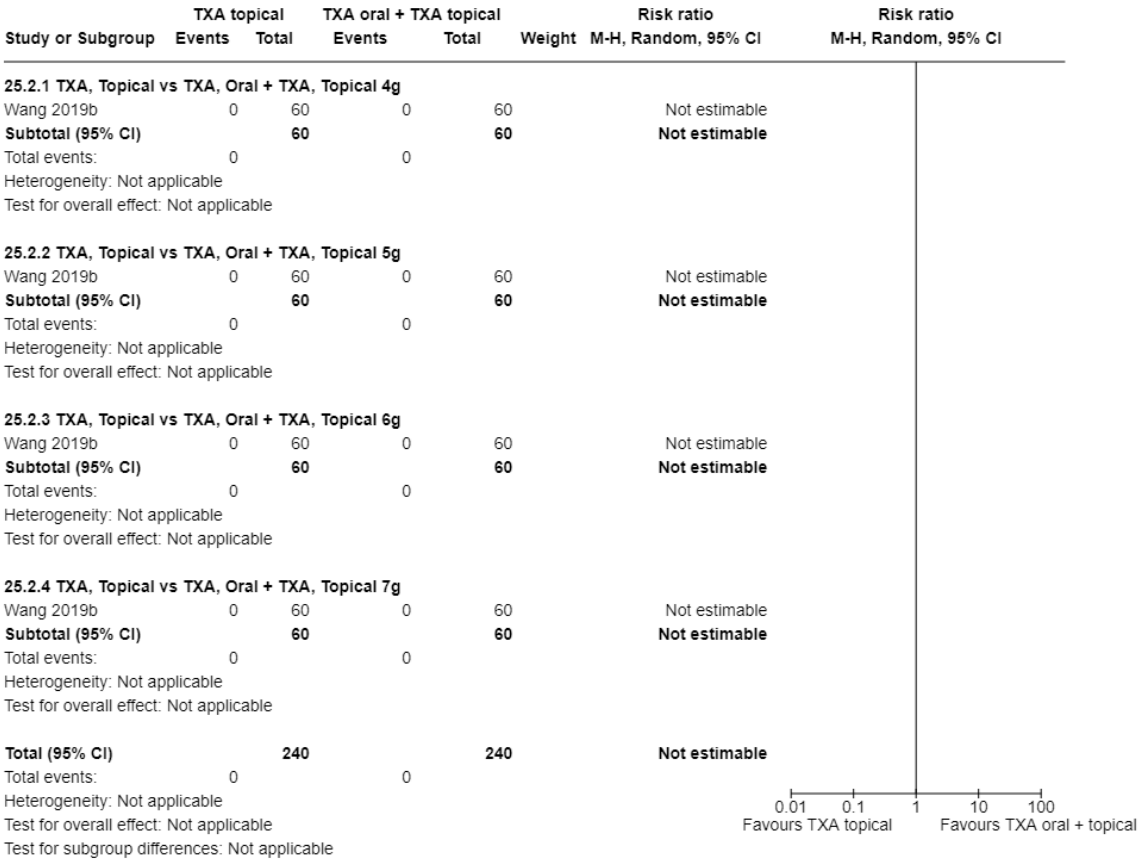
B.1.5.13 Fibrin topical versus placebo



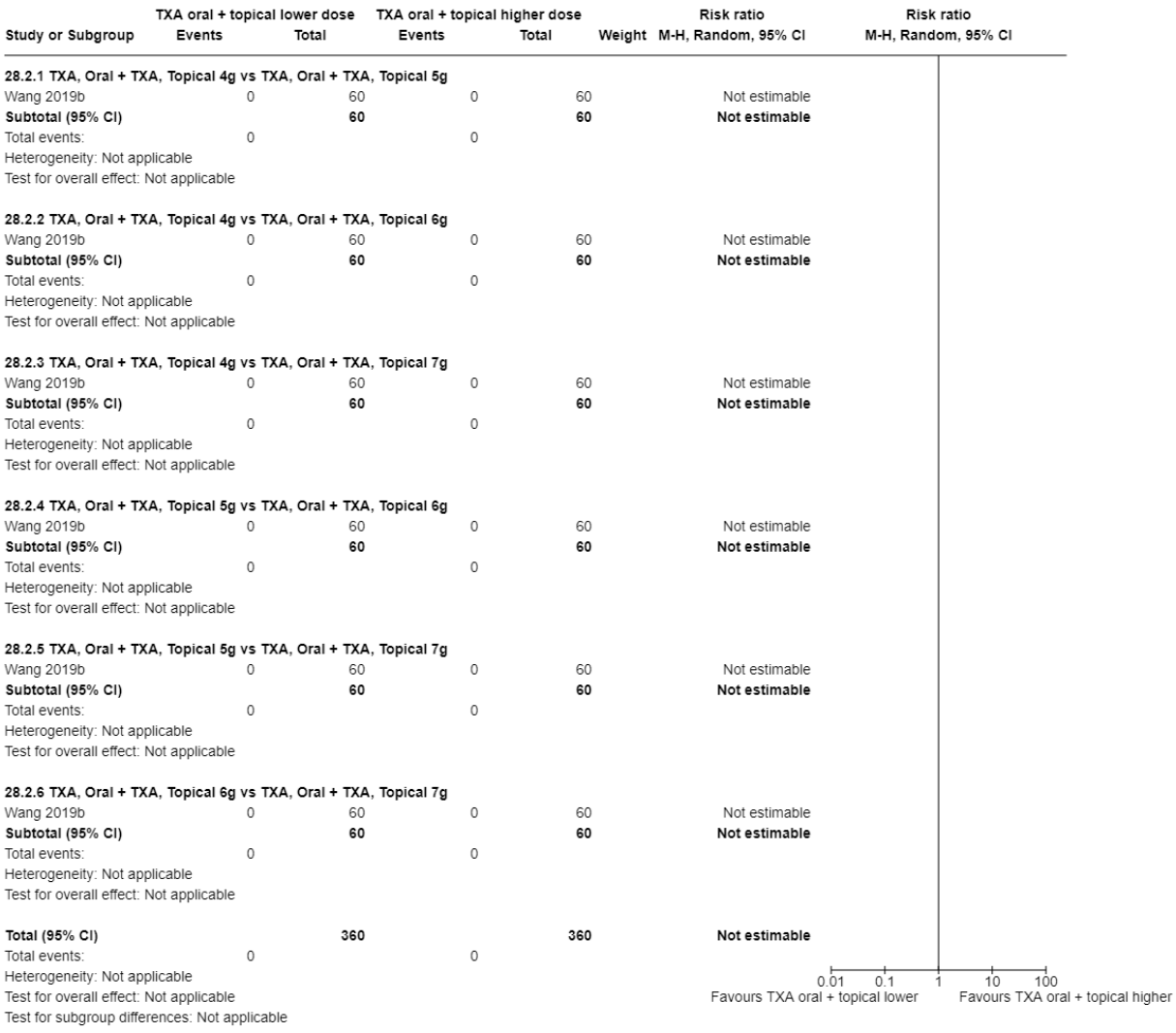
B.1.5.14 TXA IV and TXA oral versus TXA IV



B.1.5.15 TXA topical versus TXA oral and TXA topical

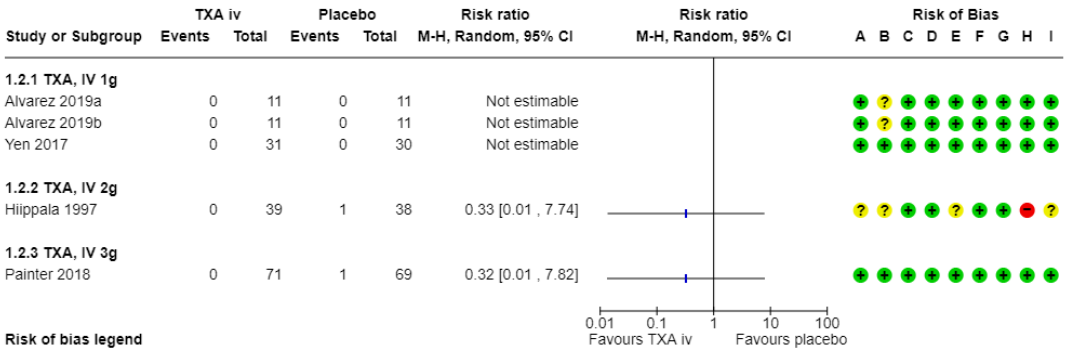


B.1.5.16 TXA oral and topical lower dose versus TXA oral and topical higher dose



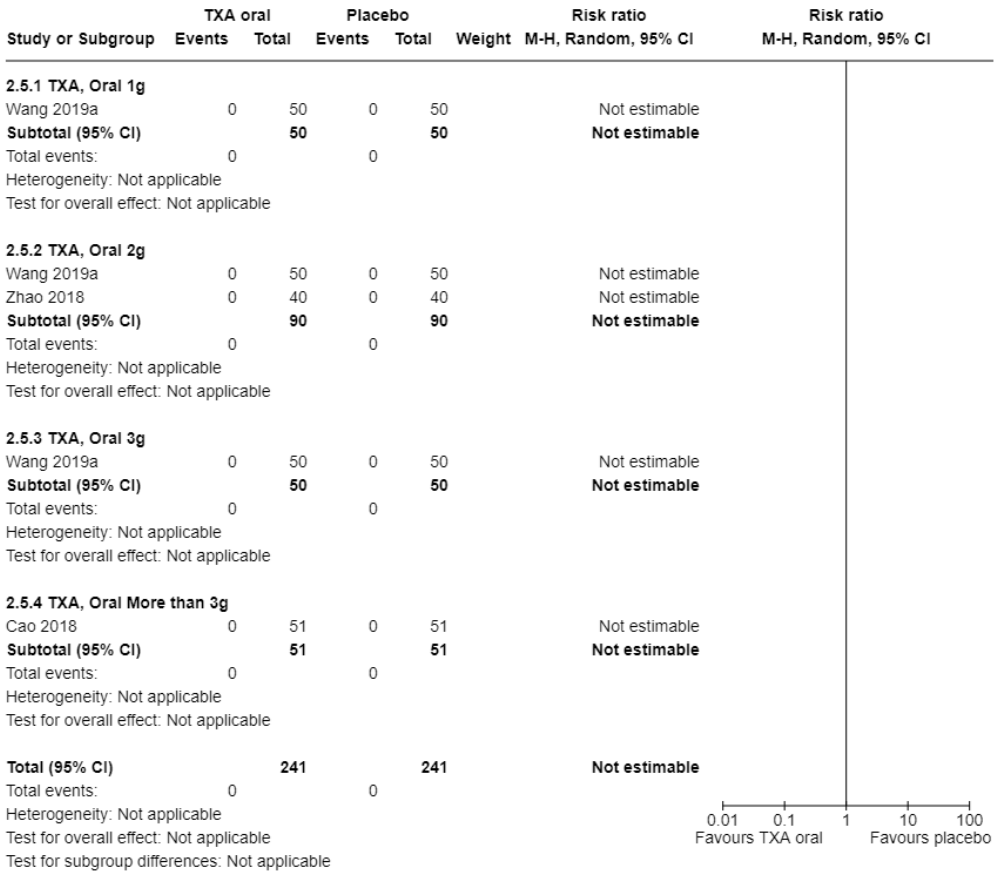
B.1.6 Pairwise comparisons for pulmonary embolism

B.1.6.1 TXA iv versus placebo

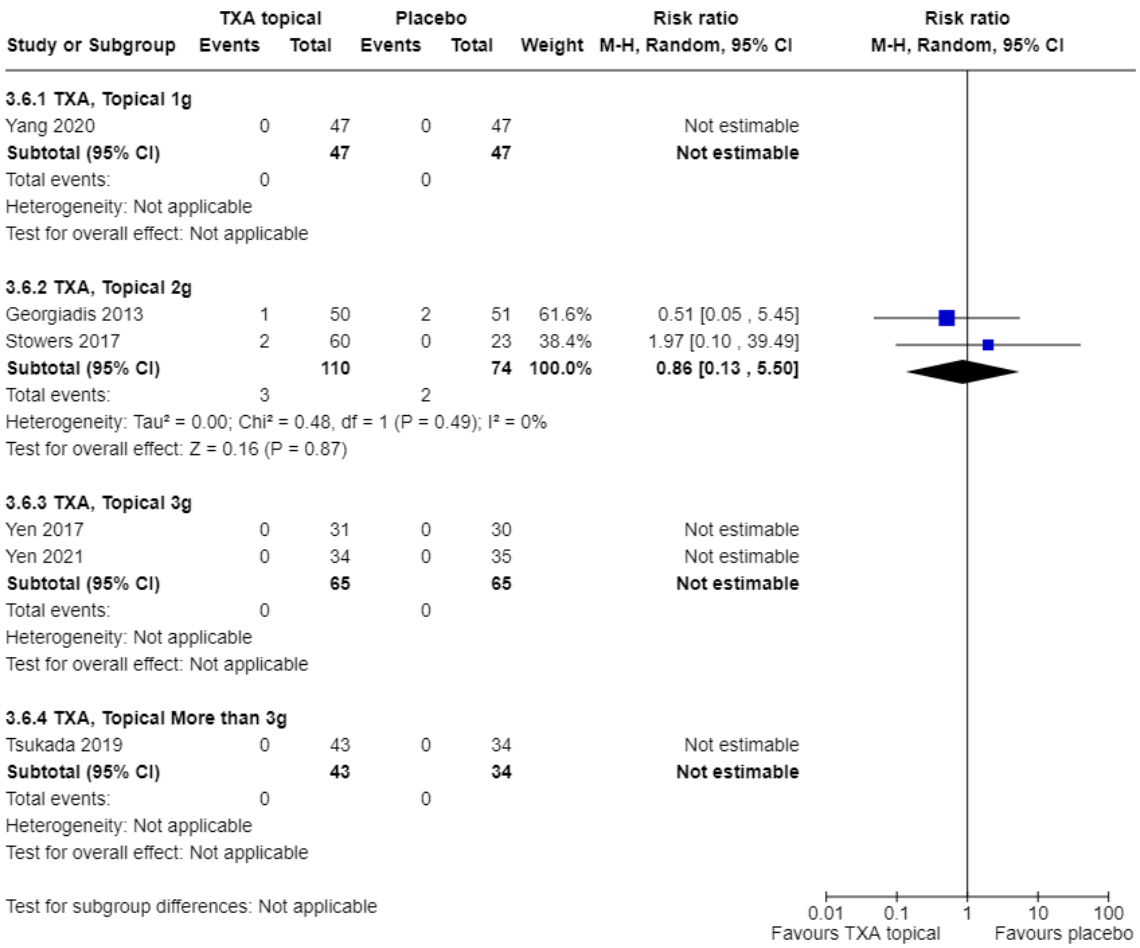


Risk of bias legend
(A) Random sequence generation (selection bias)
(B) Allocation concealment (selection bias)
(C) Blinding of participants and personnel (performance bias) Subjective outcomes
(D) Blinding of participants and personnel (performance bias) Objective outcomes
(E) Blinding of outcome assessment (detection bias) Subjective outcomes
(F) Blinding of outcome assessment (detection bias) Objective outcomes
(G) Incomplete outcome data (attrition bias)
(H) Selective reporting (reporting bias)
(I) Other bias

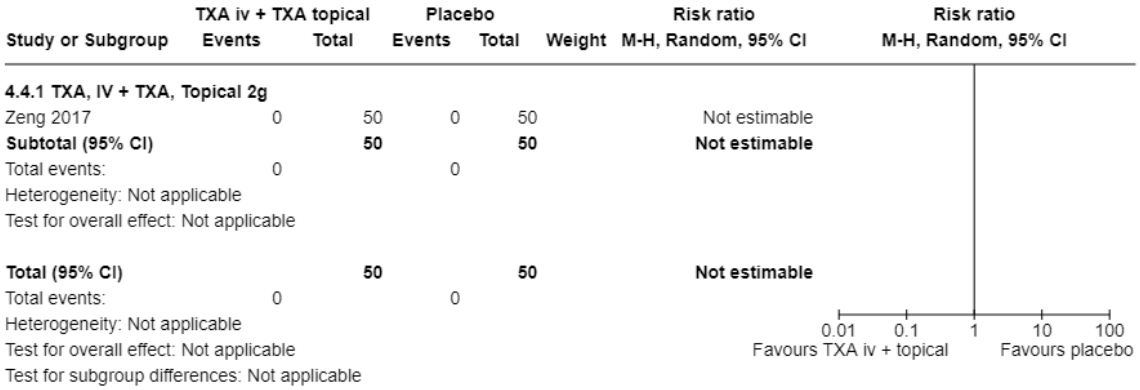
B.1.6.2 TXA oral versus placebo



B.1.6.3 TXA topical versus placebo



TXA IV and TXA topical versus placebo



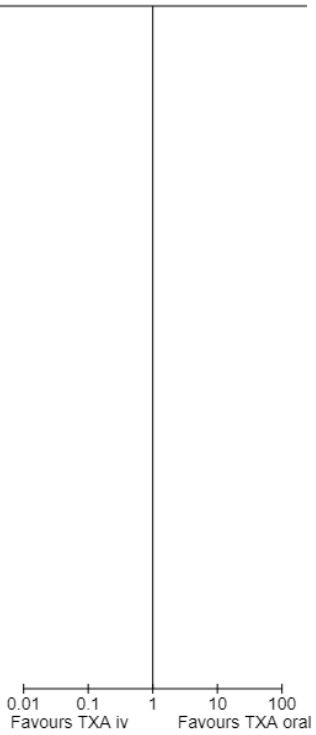
B.1.6.4 TXA IV lower dose versus TXA IV higher dose

Study or Subgroup	TXA iv lower dose Events	Total	TXA iv higher dose Events	Total	Risk ratio M-H, Random, 95% CI
5.7.1 TXA, IV 1g vs TXA, IV 2g					
Cui 2019	0	36	0	36	Not estimable
Levine 2014	1	20	0	20	3.00 [0.13 , 69.52]
Sershon 2020	0	43	0	40	Not estimable
Veien 2005	0	14	0	17	Not estimable
5.7.2 TXA, IV 1g vs TXA, IV 3g					
Kang 2021	0	48	0	49	Not estimable
Zohar 2004	0	20	0	20	Not estimable
5.7.3 TXA, IV 2g vs TXA, IV More than 3g					
Clave 2019	0	76	0	78	Not estimable
Lei 2017a	0	53	0	57	Not estimable
Xie 2016a	0	50	0	51	Not estimable
5.7.4 TXA, IV 2g vs TXA, IV 3g					
Lei 2017a	0	53	0	49	Not estimable
Xie 2016a	0	50	0	50	Not estimable
5.7.5 TXA, IV 3g vs TXA, IV More than 3g					
Lei 2017a	0	49	0	57	Not estimable
Xie 2016a	0	50	0	51	Not estimable
5.7.6 TXA, IV 3g vs TXA, IV 4g					
Lei 2018b	0	50	0	50	Not estimable
5.7.7 TXA, IV 3g vs TXA, IV 5g					
Lei 2018b	0	50	0	50	Not estimable
5.7.8 TXA, IV 4g vs TXA, IV 5g					
Lei 2018b	0	50	0	50	Not estimable
Lei 2020	0	50	0	50	Not estimable
5.7.9 TXA, IV 5g vs TXA, IV More than 5g					
Lei 2020	0	50	0	50	Not estimable
5.7.10 TXA, IV 4g vs TXA, IV More than 5g					
Lei 2020	0	50	0	50	Not estimable
5.7.11 TXA, IV 3.5g vs TXA, IV 5.5g					
Kang 2021a	0	100	0	100	Not estimable
5.7.12 TXA, IV 3.5g vs TXA, IV 6.5g					
Kang 2021a	0	100	0	100	Not estimable
5.7.13 TXA, IV 5.5g vs TXA, IV 6.5g					
Kang 2021a	0	100	0	100	Not estimable

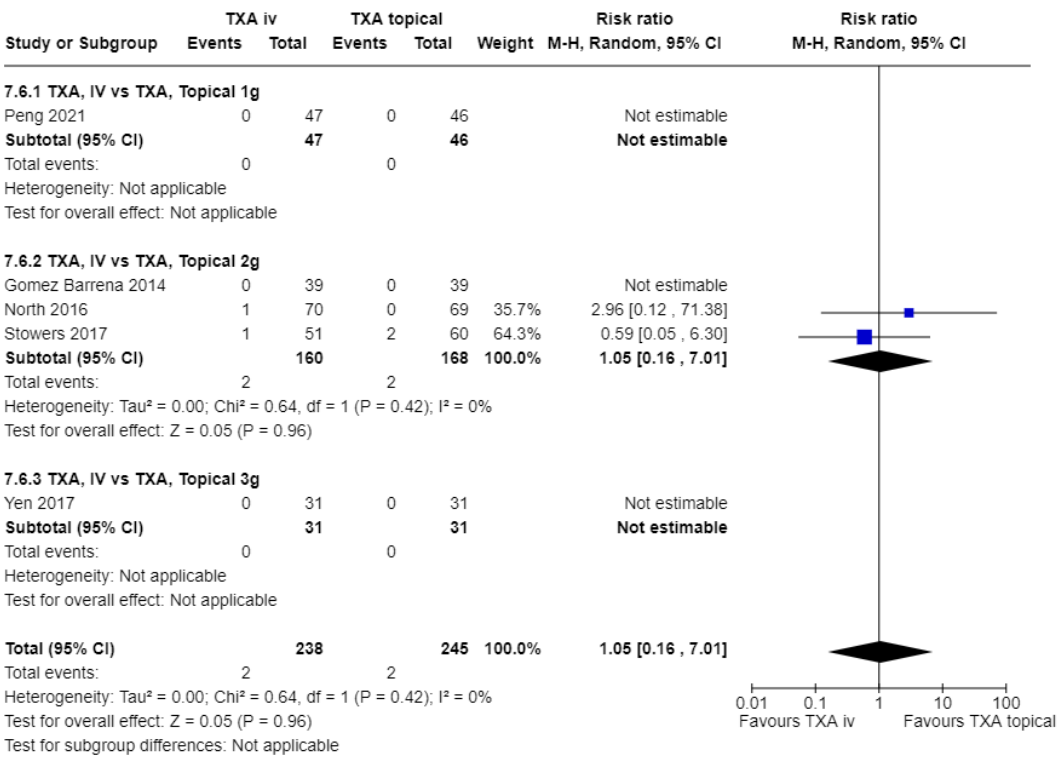


B.1.6.5 TXA IV versus TXA oral

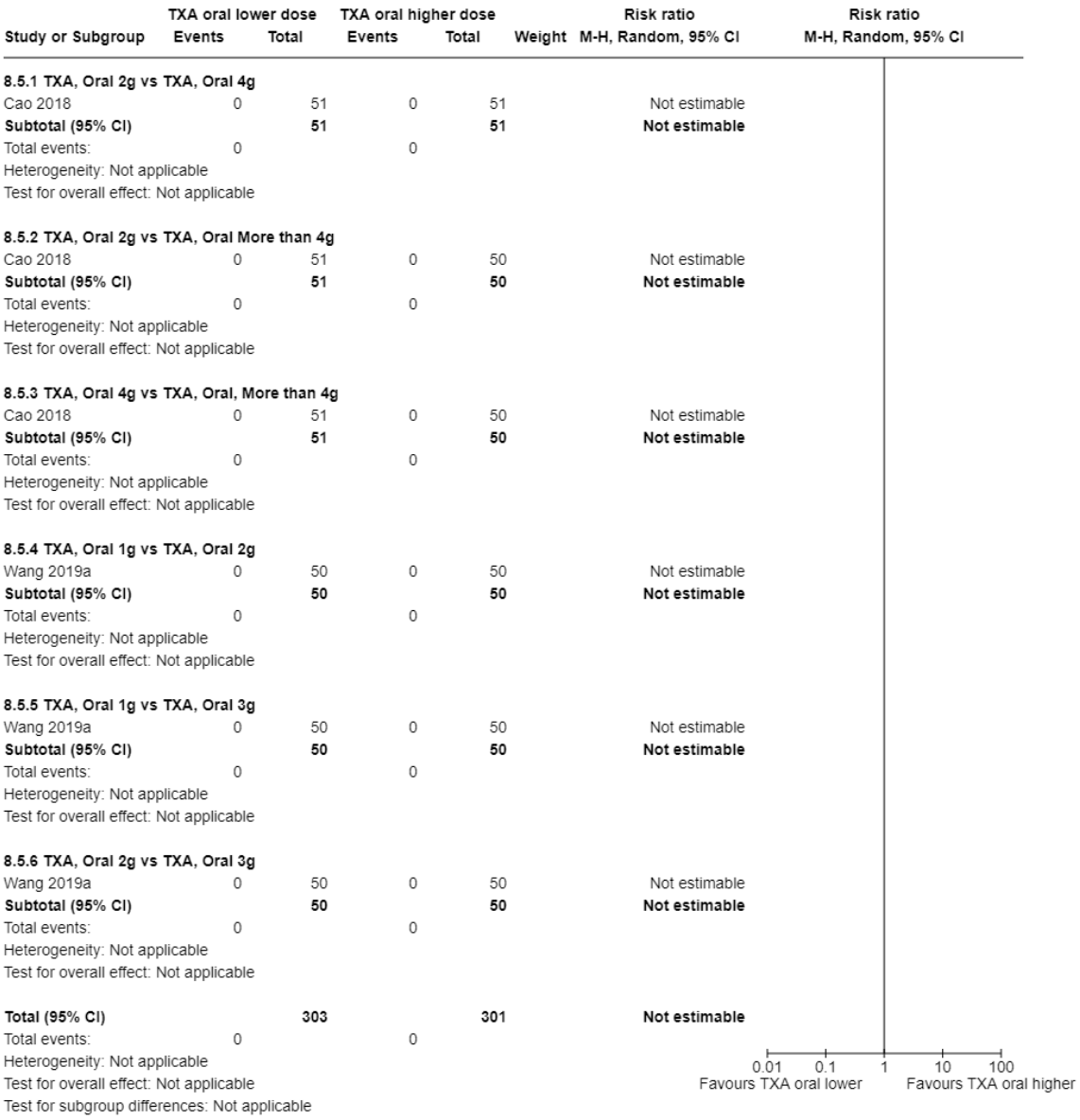
Study or Subgroup	TXA iv Events	TXA iv Total	TXA oral Events	TXA oral Total	Weight	Risk ratio M-H, Random, 95% CI
6.5.1 TXA, IV 1g						
Kayupov 2017	0	37	0	34		Not estimable
Kayupov 2017a	0	43	0	40		Not estimable
Sershon 2020	0	43	0	46		Not estimable
Zohar 2004	0	20	0	20		Not estimable
Subtotal (95% CI)		**143**		**140**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
6.5.2 TXA, IV 2g						
Sershon 2020	0	40	0	46		Not estimable
Zhao 2018	0	40	0	40		Not estimable
Subtotal (95% CI)		**80**		**86**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
6.5.3 TXA, IV 3g						
Wu 2018	0	50	0	50		Not estimable
Subtotal (95% CI)		**50**		**50**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**273**		**276**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



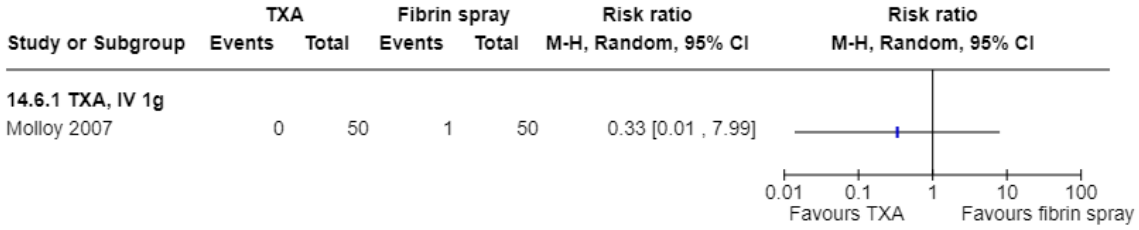
B.1.6.6 TXA IV versus TXA topical



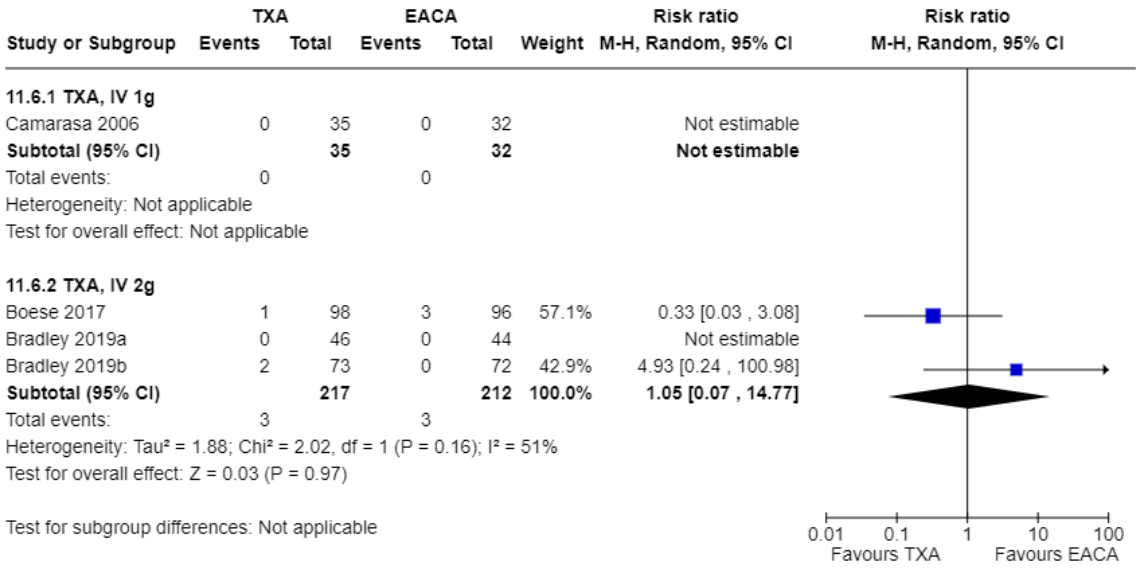
B.1.6.7 TXA oral lower dose versus TXA oral higher dose



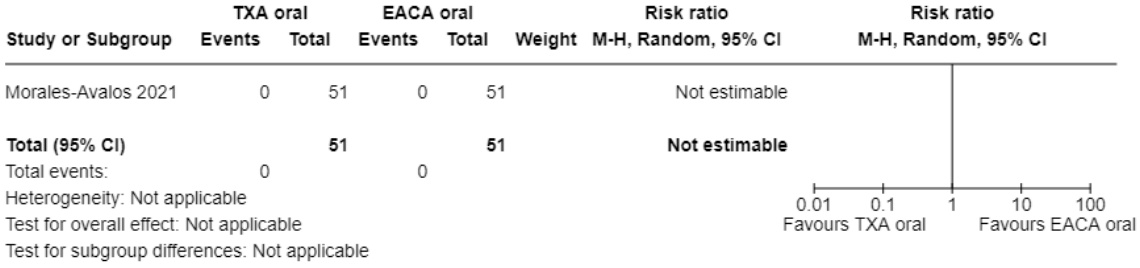
B.1.6.8 TXA IV versus fibrin topical



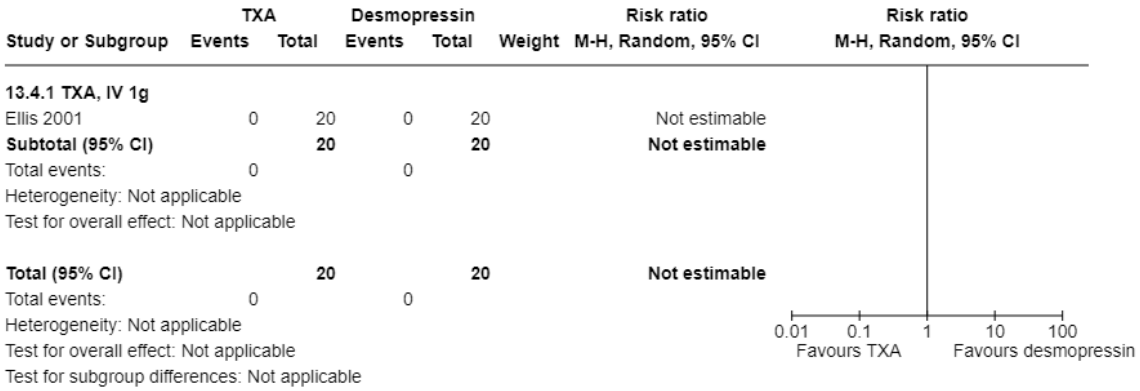
B.1.6.9 TXA IV versus EACA



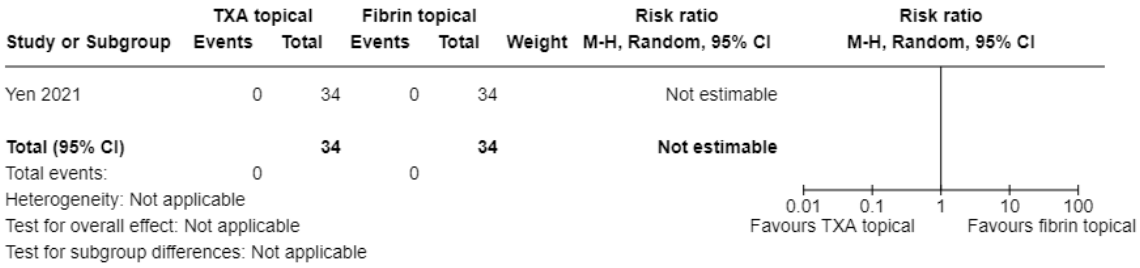
B.1.6.10 TXA oral versus EACA oral



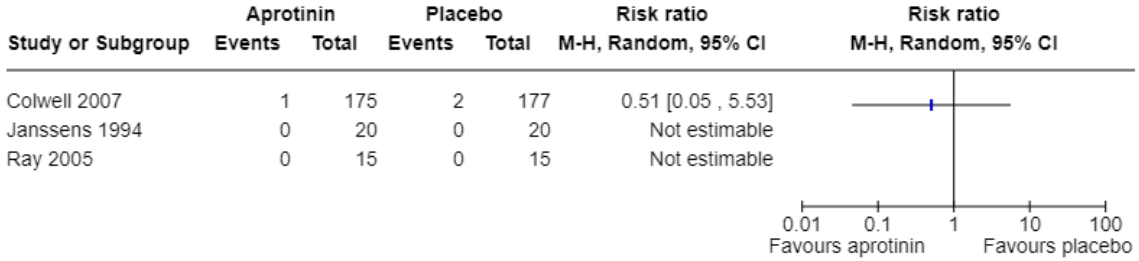
B.1.6.11 TXA IV versus desmopressin



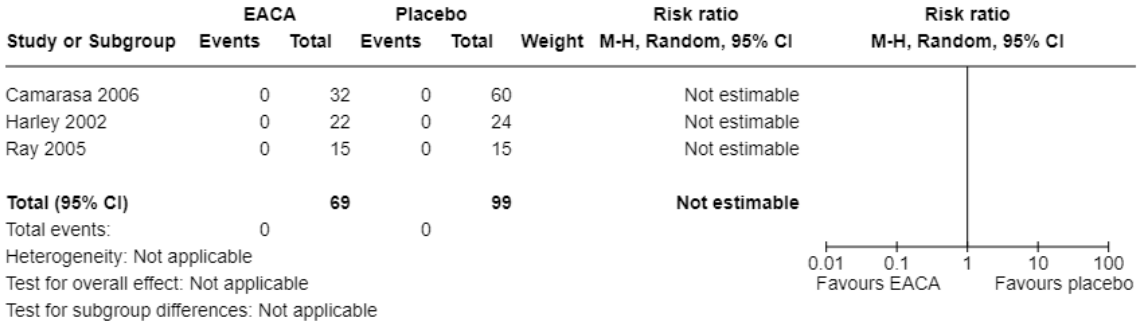
B.1.6.12 TXA topical versus fibrin topical



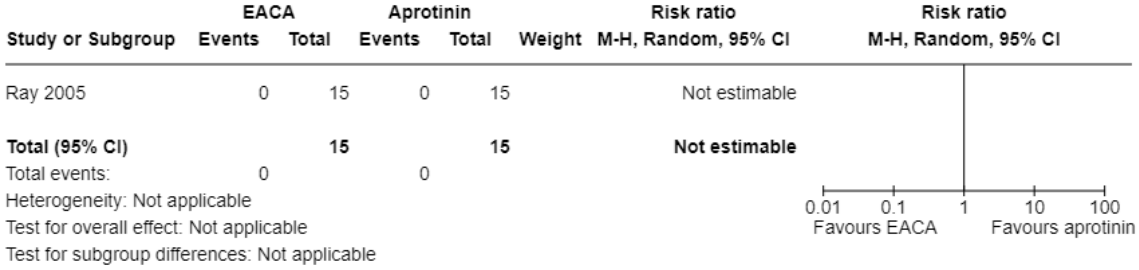
B.1.6.13 Aprotinin versus placebo



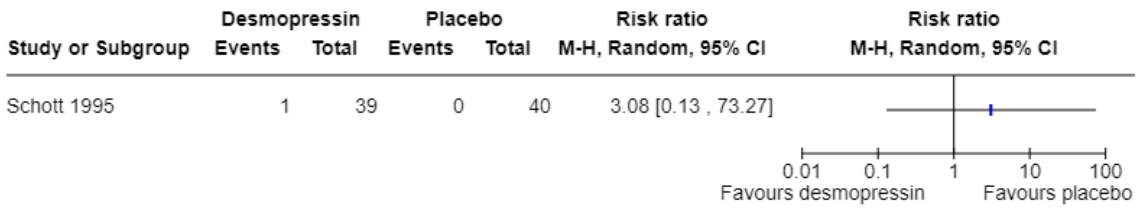
B.1.6.14 EACA versus placebo



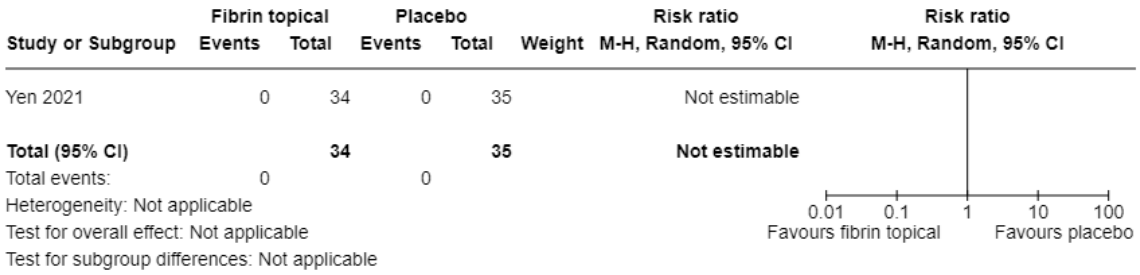
B.1.6.15 EACA versus Aprotinin



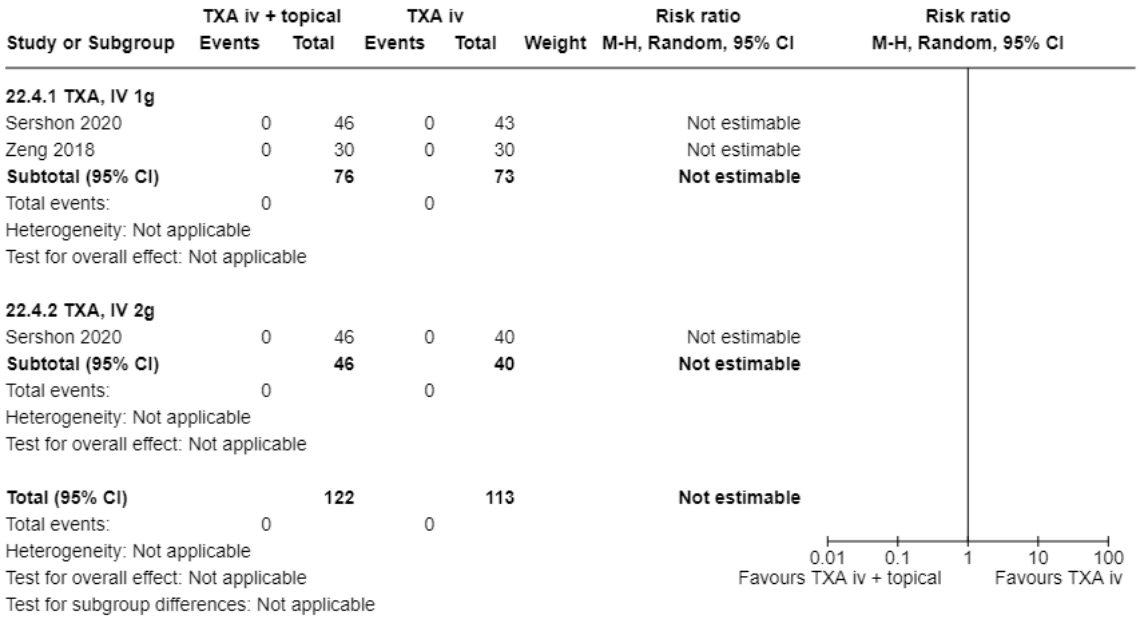
B.1.6.16 Desmopressin versus Placebo



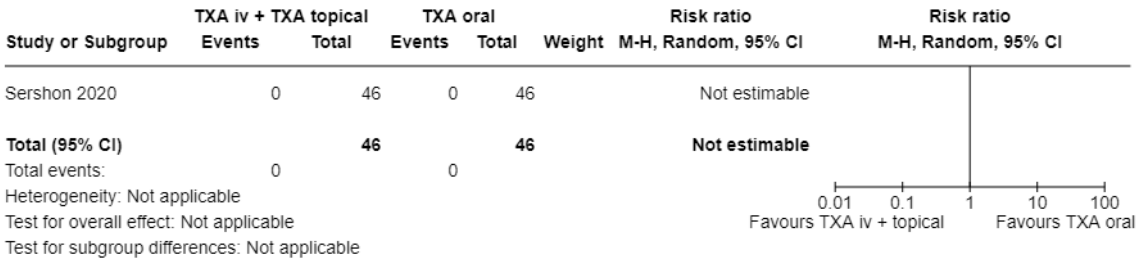
B.1.6.17 Fibrin topical versus Placebo



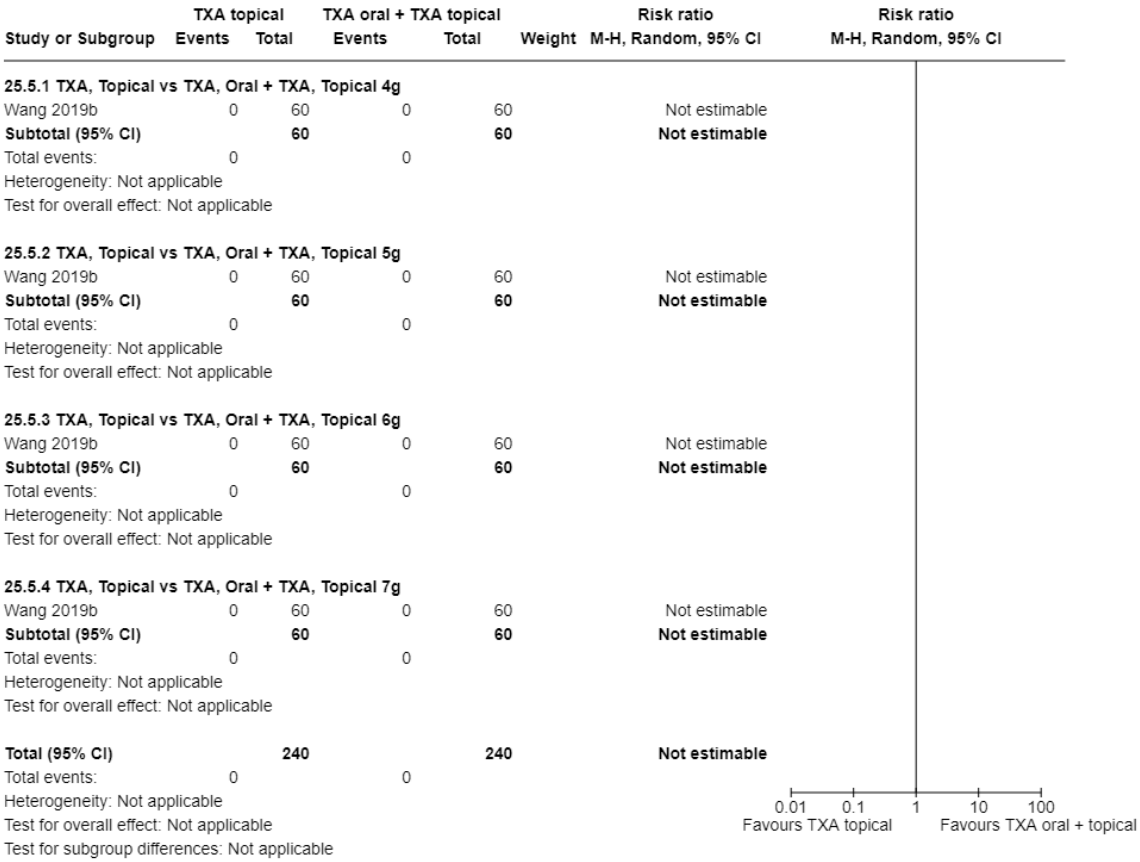
B.1.6.18 TXA IV and TXA topical versus TXA IV



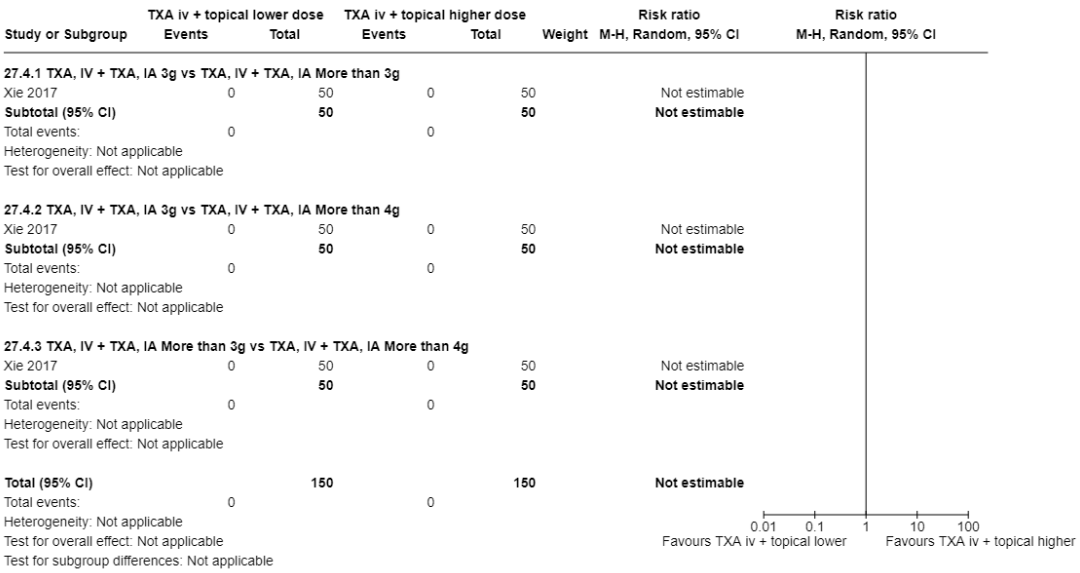
B.1.6.19 TXA IV and TXA topical versus TXA oral



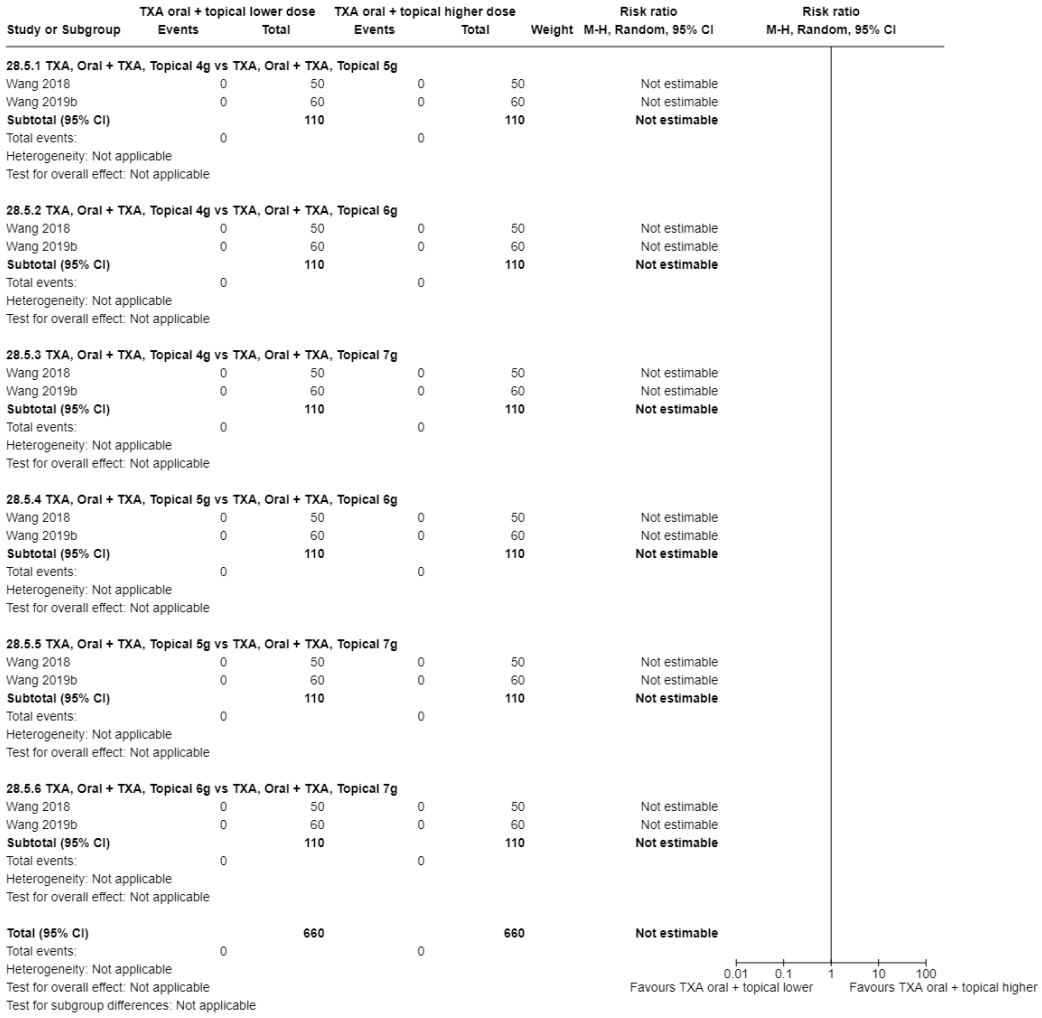
B.1.6.20 TXA topical versus TXA oral and TXA topical



B.1.6.21 TXA IV and topical lower dose versus TXA IV and topical higher dose



B.1.6.22 TXA oral and topical lower dose versus TXA oral and topical higher dose

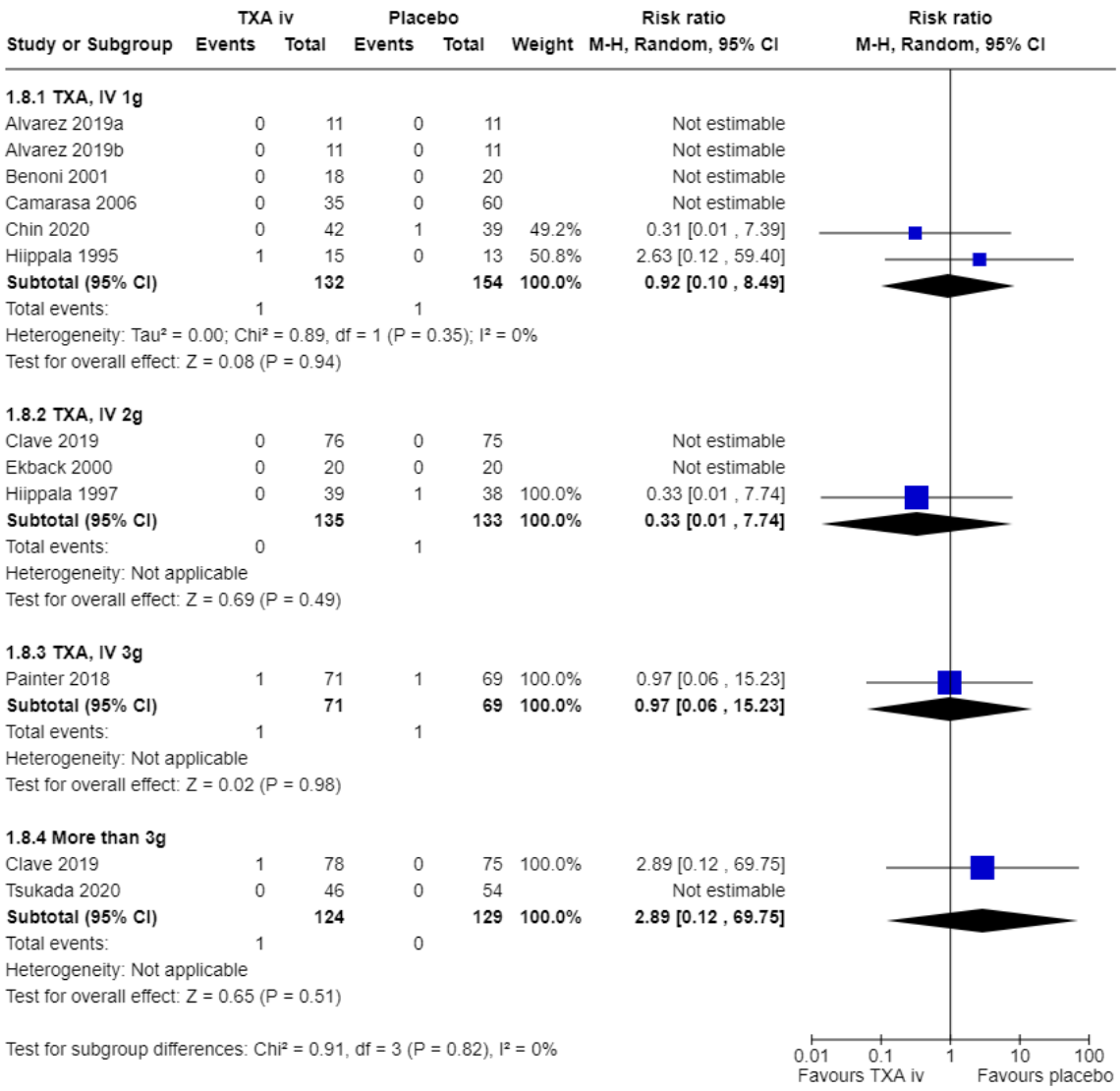


Study or Subgroup	TXA oral + topical lower dose Events	Total	TXA oral + topical higher dose Events	Total	Weight	Risk ratio M-H, Random, 95% CI
28.5.1 TXA, Oral + TXA, Topical 4g vs TXA, Oral + TXA, Topical 5g						
Wang 2018	0	50	0	50		Not estimable
Wang 2019b	0	60	0	60		Not estimable
Subtotal (95% CI)		**110**		**110**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
28.5.2 TXA, Oral + TXA, Topical 4g vs TXA, Oral + TXA, Topical 6g						
Wang 2018	0	50	0	50		Not estimable
Wang 2019b	0	60	0	60		Not estimable
Subtotal (95% CI)		**110**		**110**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
28.5.3 TXA, Oral + TXA, Topical 4g vs TXA, Oral + TXA, Topical 7g						
Wang 2018	0	50	0	50		Not estimable
Wang 2019b	0	60	0	60		Not estimable
Subtotal (95% CI)		**110**		**110**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
28.5.4 TXA, Oral + TXA, Topical 5g vs TXA, Oral + TXA, Topical 6g						
Wang 2018	0	50	0	50		Not estimable
Wang 2019b	0	60	0	60		Not estimable
Subtotal (95% CI)		**110**		**110**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
28.5.5 TXA, Oral + TXA, Topical 5g vs TXA, Oral + TXA, Topical 7g						
Wang 2018	0	50	0	50		Not estimable
Wang 2019b	0	60	0	60		Not estimable
Subtotal (95% CI)		**110**		**110**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
28.5.6 TXA, Oral + TXA, Topical 6g vs TXA, Oral + TXA, Topical 7g						
Wang 2018	0	50	0	50		Not estimable
Wang 2019b	0	60	0	60		Not estimable
Subtotal (95% CI)		**110**		**110**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**660**		**660**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						

B.1.7 Pairwise comparisons for Myocardial Infarction

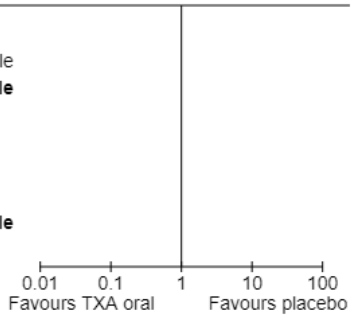
Data for all studies that reported the outcome are presented in pair-wise meta-analyses:

B.1.7.1 TXA IV versus placebo



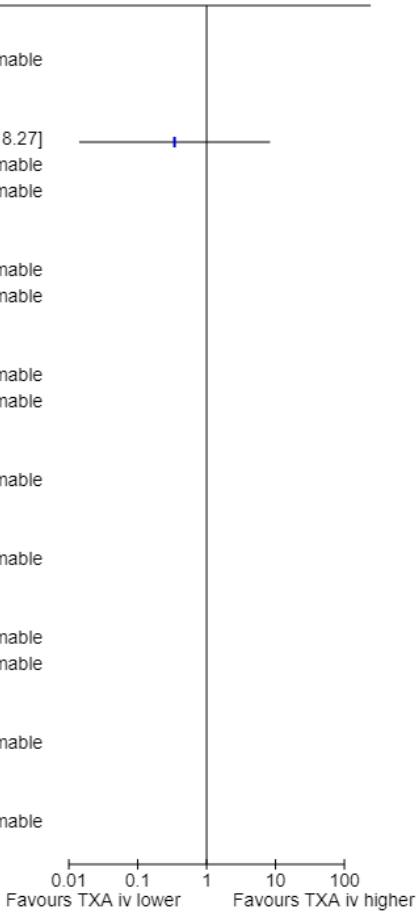
B.1.7.2 TXA oral versus placebo

Study or Subgroup	TXA oral Events	Total	Placebo Events	Total	Weight	Risk ratio M-H, Random, 95% CI
2.6.1 TXA, Oral More than 3g						
Cao 2018	0	51	0	51		Not estimable
Subtotal (95% CI)		**51**		**51**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**51**		**51**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						

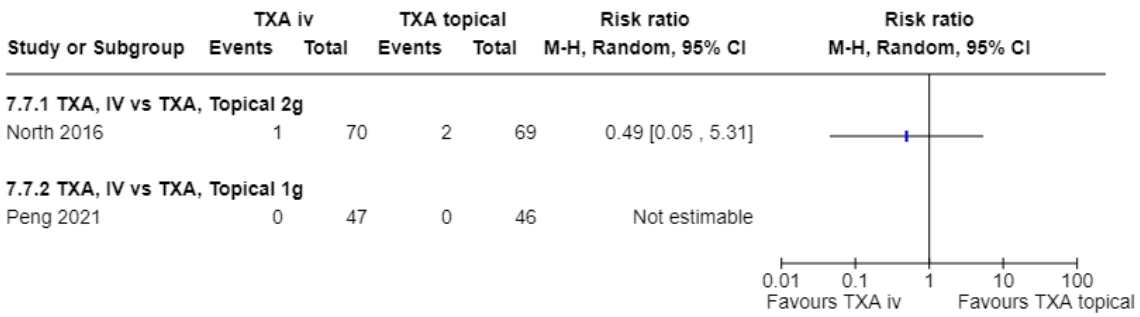


B.1.7.3 TXA IV lower dose versus TXA IV higher dose

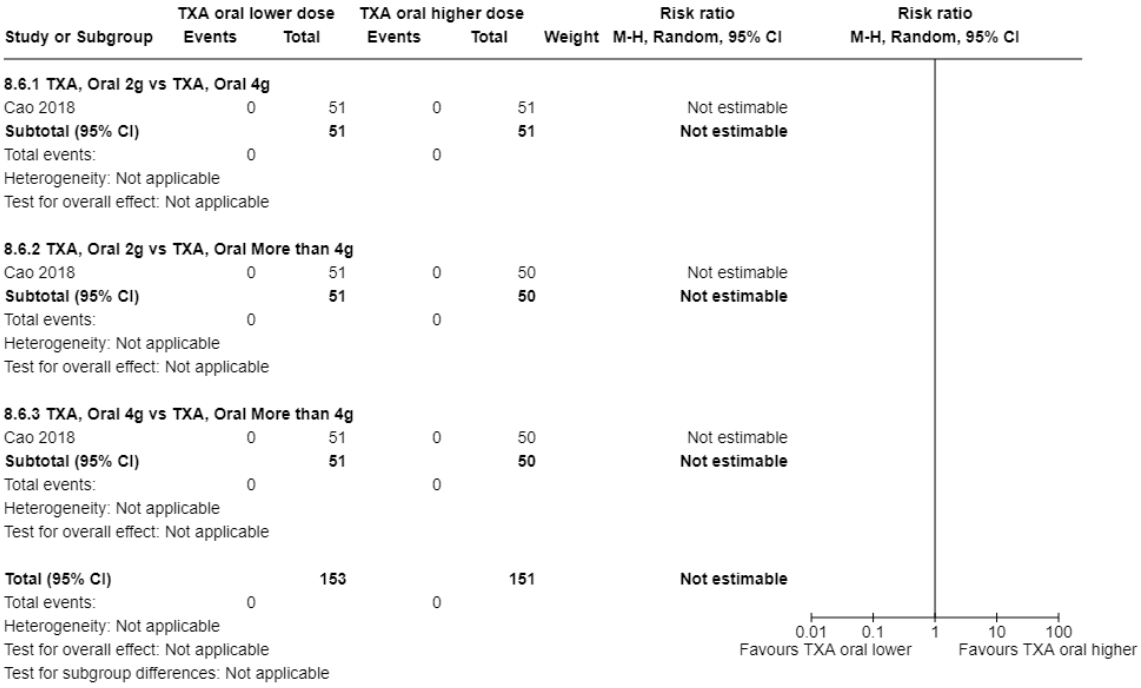
Study or Subgroup	TXA iv lower dose Events	Total	TXA iv higher dose Events	Total	Risk ratio M-H, Random, 95% CI
5.8.1 TXA, IV 1g vs TXA, IV 3g					
Kang 2021	0	48	0	49	Not estimable
5.8.2 TXA, IV 2g vs TXA, IV More than 3g					
Clave 2019	0	76	1	78	0.34 [0.01 , 8.27]
Lei 2017a	0	53	0	57	Not estimable
Xie 2016a	0	50	0	51	Not estimable
5.8.3 TXA, IV 2g vs TXA, IV 3g					
Lei 2017a	0	53	0	49	Not estimable
Xie 2016a	0	50	0	50	Not estimable
5.8.4 TXA, IV 3g vs TXA, IV More than 3g					
Lei 2017a	0	49	0	57	Not estimable
Xie 2016a	0	50	0	51	Not estimable
5.8.5 TXA, IV 3g vs TXA, IV 4g					
Lei 2018b	0	50	0	50	Not estimable
5.8.6 TXA, IV 3g vs TXA, IV 5g					
Lei 2018b	0	50	0	50	Not estimable
5.8.7 TXA, IV 4g vs TXA, IV 5g					
Lei 2018b	0	50	0	50	Not estimable
Lei 2020	0	50	0	50	Not estimable
5.8.8 TXA, IV 5g vs TXA, IV More than 5g					
Lei 2020	0	50	0	50	Not estimable
5.8.9 TXA, IV 4g vs TXA, IV More than 5g					
Lei 2020	0	50	0	50	Not estimable



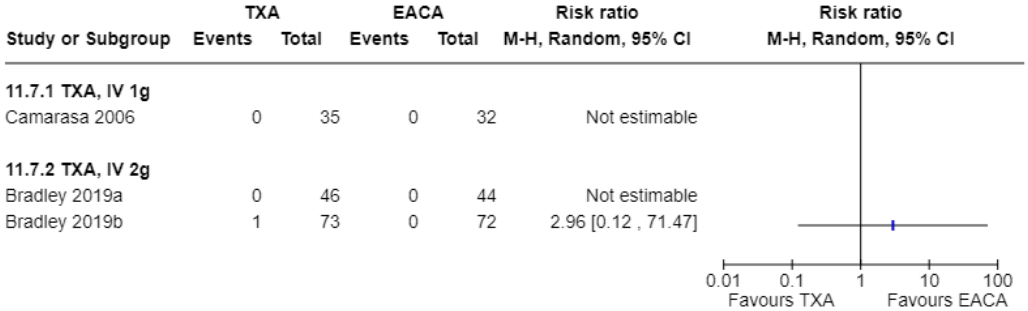
B.1.7.4 TXA IV versus TXA topical



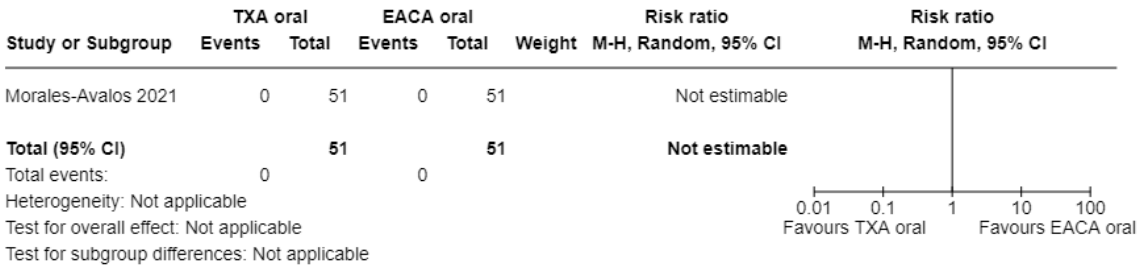
B.1.7.5 TXA oral lower dose versus TXA oral higher dose



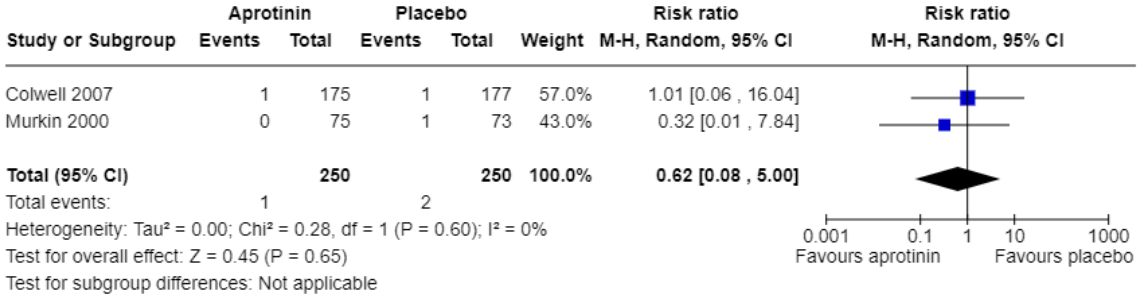
B.1.7.6 TXA IV versus EACA



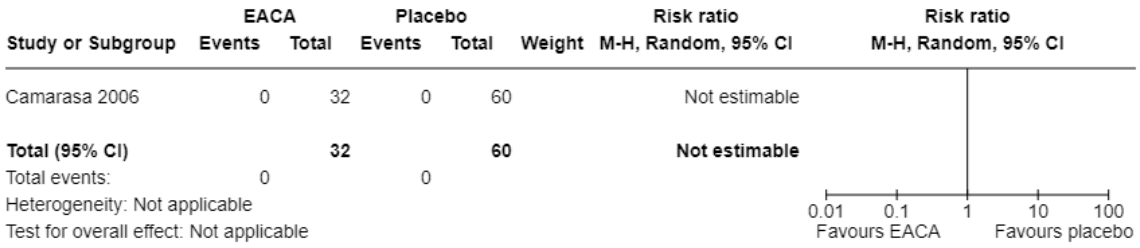
B.1.7.7 TXA oral versus EACA oral



B.1.7.8 Aprotinin versus placebo



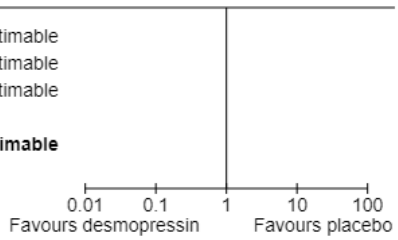
B.1.7.9 EACA versus placebo



B.1.7.10 Desmopressin versus Placebo

Study or Subgroup	Desmopressin Events	Desmopressin Total	Placebo Events	Placebo Total	Weight	Risk ratio M-H, Random, 95% CI
Karnezis 1994	0	17	0	19		Not estimable
Karnezis 1994a	0	26	0	30		Not estimable
Schott 1995	0	39	0	40		Not estimable
Total (95% CI)		**82**		**89**		**Not estimable**
Total events:	0		0			

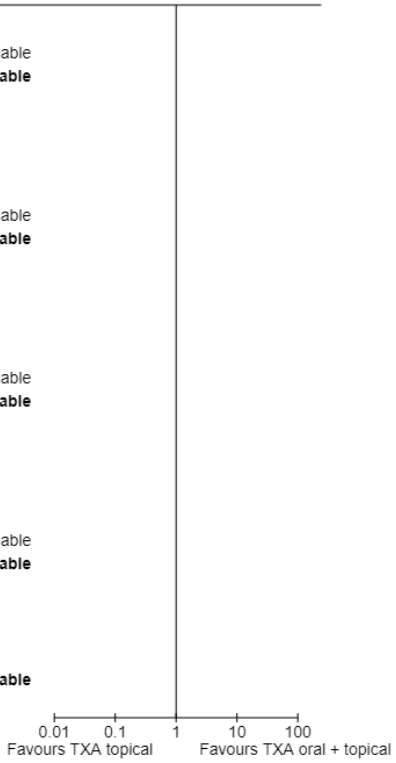
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



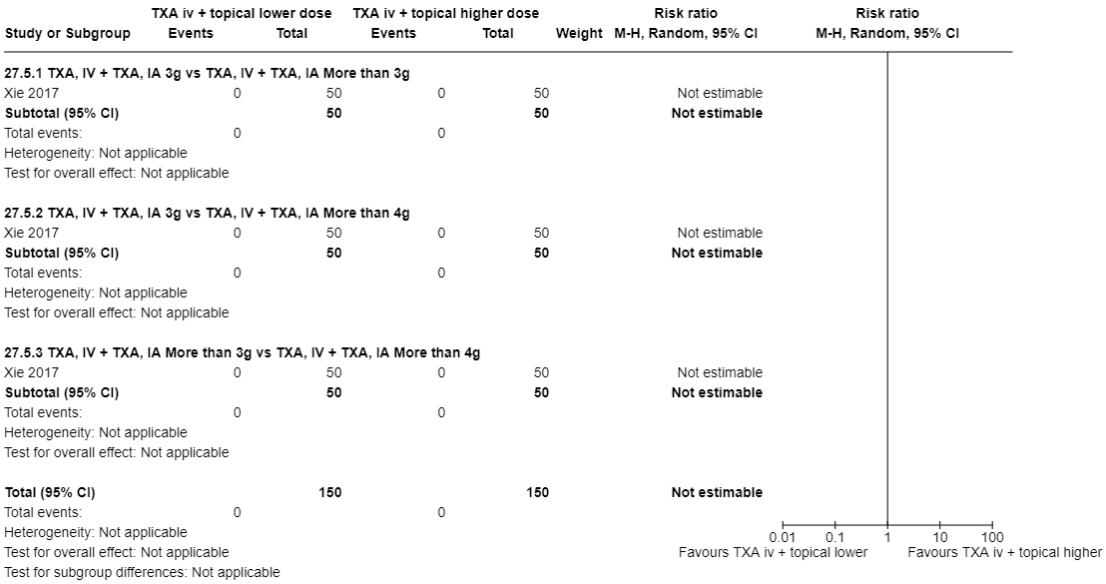
B.1.7.11 TXA topical versus TXA oral and TXA topical

Study or Subgroup	TXA topical Events	TXA topical Total	TXA oral + TXA topical Events	TXA oral + TXA topical Total	Weight	Risk ratio M-H, Random, 95% CI
25.6.1 TXA, Topical vs TXA, Oral + TXA, Topical 4g						
Wang 2019b	0	60	0	60		Not estimable
Subtotal (95% CI)		**60**		**60**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
25.6.2 TXA, Topical vs TXA, Oral + TXA, Topical 5g						
Wang 2019b	0	60	0	60		Not estimable
Subtotal (95% CI)		**60**		**60**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
25.6.3 TXA, Topical vs TXA, Oral + TXA, Topical 6g						
Wang 2019b	0	60	0	60		Not estimable
Subtotal (95% CI)		**60**		**60**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
25.6.4 TXA, Topical vs TXA, Oral + TXA, Topical 7g						
Wang 2019b	0	60	0	60		Not estimable
Subtotal (95% CI)		**60**		**60**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**240**		**240**		**Not estimable**
Total events:	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable

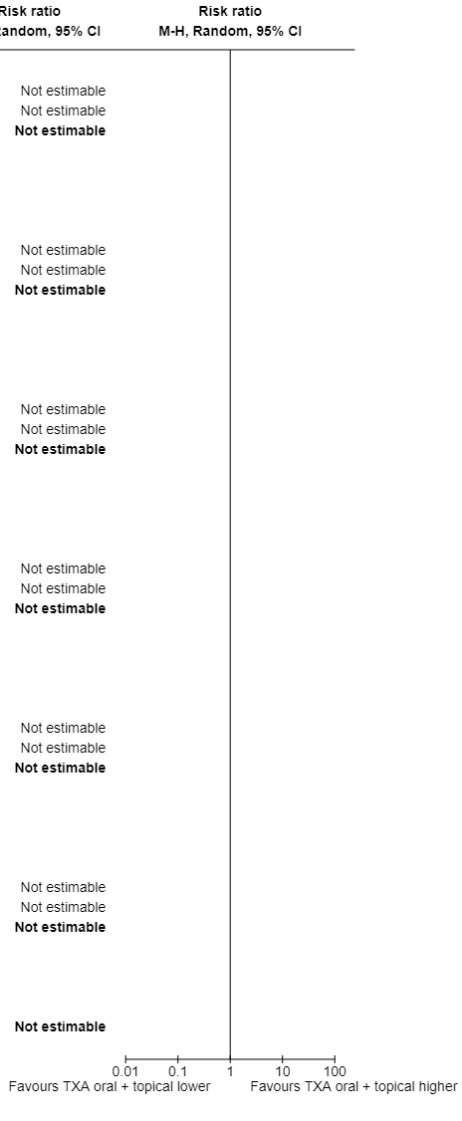


B.1.7.12 TXA IV and topical lower dose versus TXA IV and topical higher dose



B.1.7.13 TXA oral and topical lower dose versus TXA oral and topical higher dose

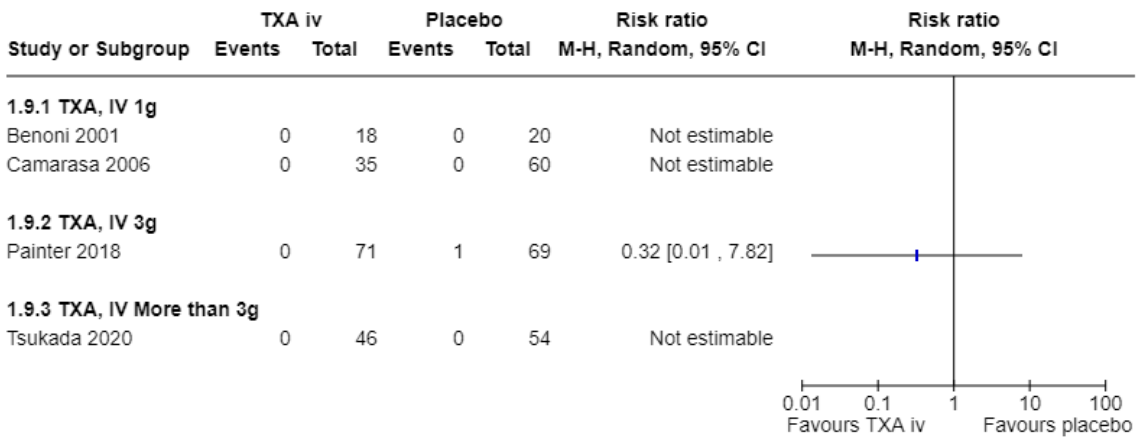
Study or Subgroup	TXA oral + topical lower dose Events	Total	TXA oral + topical higher dose Events	Total	Weight	Risk ratio M-H, Random, 95% CI
28.6.1 TXA, Oral + TXA, Topical 4g vs TXA, Oral + TXA, Topical 5g						
Wang 2018	0	50	0	50		Not estimable
Wang 2019b	0	60	0	60		Not estimable
Subtotal (95% CI)		**110**		**110**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
28.6.2 TXA, Oral + TXA, Topical 4g vs TXA, Oral + TXA, Topical 6g						
Wang 2018	0	50	0	50		Not estimable
Wang 2019b	0	60	0	60		Not estimable
Subtotal (95% CI)		**110**		**110**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
28.6.3 TXA, Oral + TXA, Topical 4g vs TXA, Oral + TXA, Topical 7g						
Wang 2018	0	50	0	50		Not estimable
Wang 2019b	0	60	0	60		Not estimable
Subtotal (95% CI)		**110**		**110**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
28.6.4 TXA, Oral + TXA, Topical 5g vs TXA, Oral + TXA, Topical 6g						
Wang 2018	0	50	0	50		Not estimable
Wang 2019b	0	60	0	60		Not estimable
Subtotal (95% CI)		**110**		**110**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
28.6.5 TXA, Oral + TXA, Topical 5g vs TXA, Oral + TXA, Topical 7g						
Wang 2018	0	50	0	50		Not estimable
Wang 2019b	0	60	0	60		Not estimable
Subtotal (95% CI)		**110**		**110**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
28.6.6 TXA, Oral + TXA, Topical 6g vs TXA, Oral + TXA, Topical 7g						
Wang 2018	0	50	0	50		Not estimable
Wang 2019b	0	60	0	60		Not estimable
Subtotal (95% CI)		**110**		**110**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**660**		**660**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



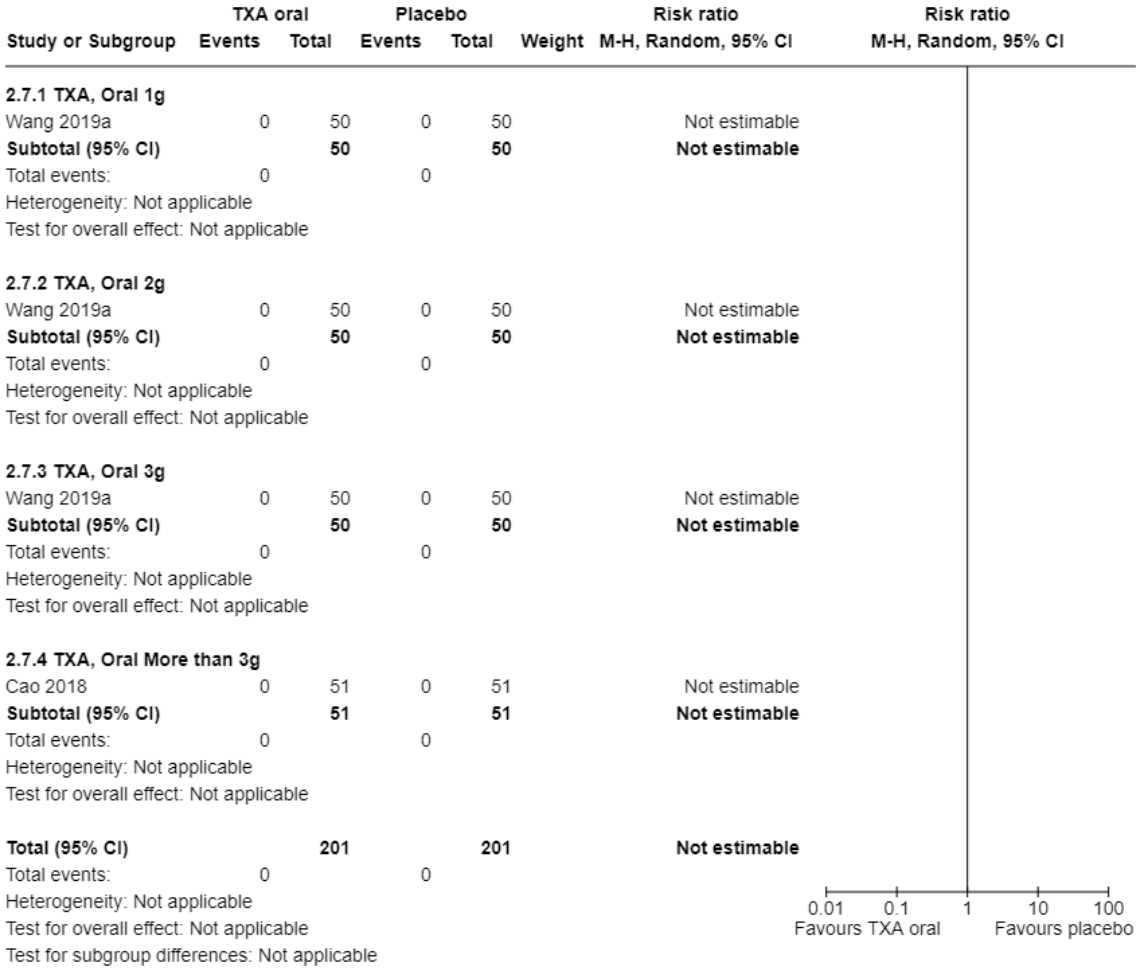
B.1.8 Pairwise comparisons for Cerebrovascular event

Data for all studies that reported the outcome are presented in pair-wise meta-analyses:

B.1.8.1 TXA IV versus Placebo

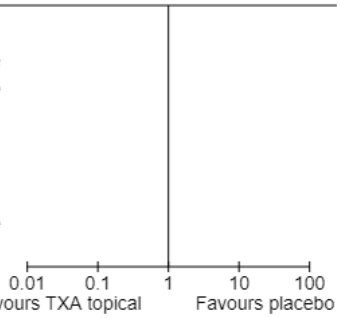


TXA oral versus placebo



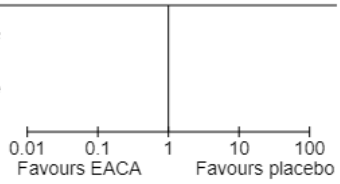
B.1.8.2 TXA topical versus placebo

Study or Subgroup	TXA topical Events	Total	Placebo Events	Total	Weight	Risk ratio M-H, Random, 95% CI
3.7.1 TXA, Topical 3g						
Yen 2021	0	34	0	35		Not estimable
Subtotal (95% CI)		**34**		**35**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**34**		**35**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



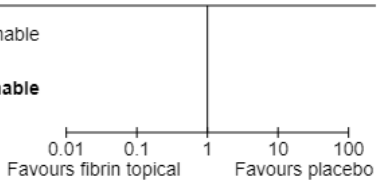
B.1.8.3 EACA versus placebo

Study or Subgroup	EACA Events	Total	Placebo Events	Total	Weight	Risk ratio M-H, Random, 95% CI
Camarasa 2006	0	32	0	60		Not estimable
Total (95% CI)		**32**		**60**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



B.1.8.4 Fibrin topical versus placebo

Study or Subgroup	Fibrin topical Events	Total	Placebo Events	Total	Weight	Risk ratio M-H, Random, 95% CI
Yen 2021	0	34	0	35		Not estimable
Total (95% CI)		**34**		**35**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						

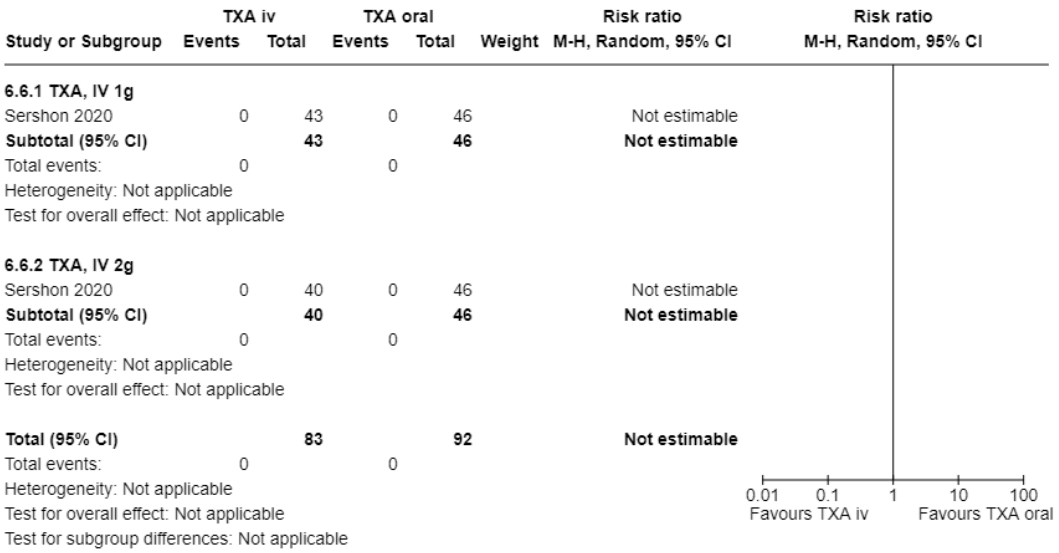


B.1.8.5 TXA IV lower dose versus TXA IV higher dose

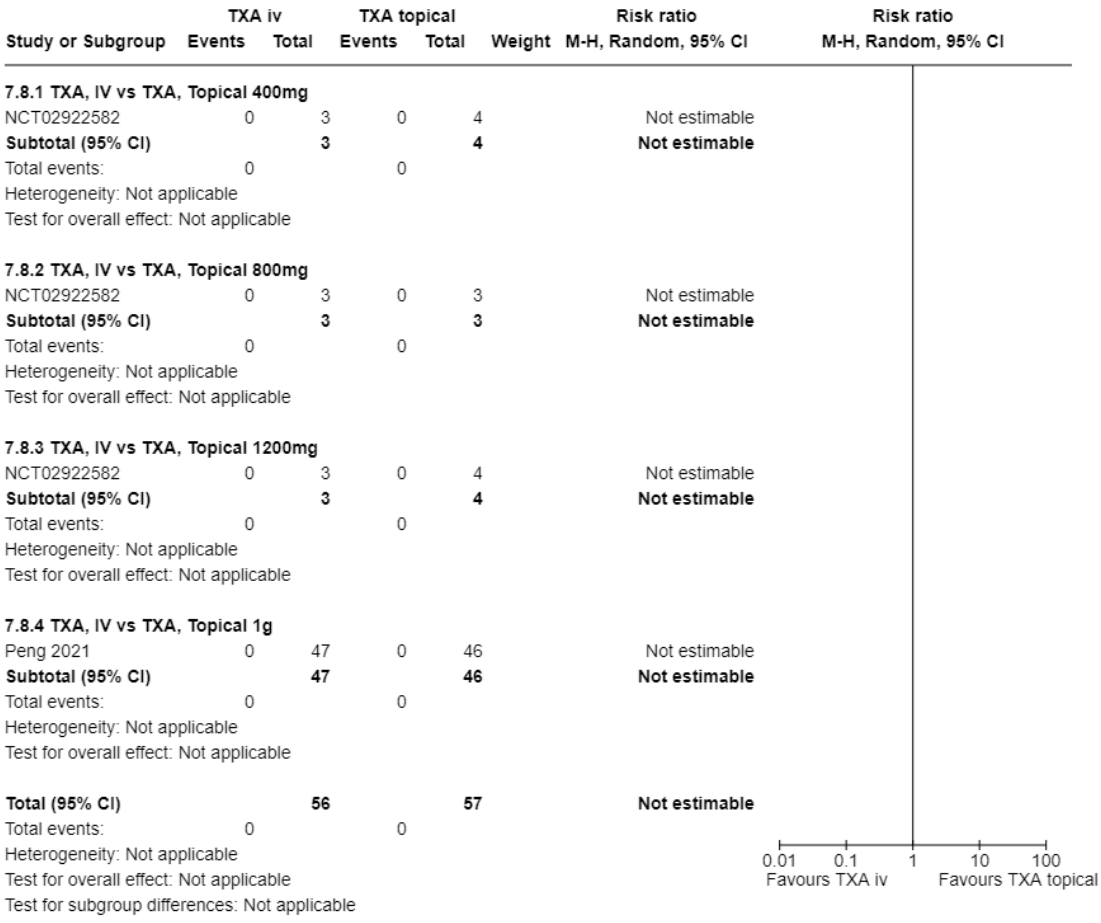
Study or Subgroup	TXA iv lower dose Events	Total	TXA iv higher dose Events	Total	Weight	Risk ratio M-H, Random, 95% CI
5.9.1 TXA, IV 1g vs TXA, IV 2g						
Sershon 2020	0	43	0	40		Not estimable
Subtotal (95% CI)		**43**		**40**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
5.9.2 TXA, IV 2g vs TXA, IV 3g						
Lei 2017a	0	53	0	49		Not estimable
Xie 2016a	0	50	0	50		Not estimable
Subtotal (95% CI)		**103**		**99**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
5.9.3 TXA, IV 2g vs TXA, IV More than 3g						
Lei 2017a	0	53	0	57		Not estimable
Xie 2016a	0	50	0	51		Not estimable
Subtotal (95% CI)		**103**		**108**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
5.9.4 TXA, IV 3g vs TXA, IV More than 3g						
Lei 2017a	0	49	0	57		Not estimable
Xie 2016a	0	50	0	51		Not estimable
Subtotal (95% CI)		**99**		**108**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
5.9.5 TXA, IV 3g vs TXA, IV 4g						
Lei 2018b	0	50	0	50		Not estimable
Subtotal (95% CI)		**50**		**50**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
5.9.6 TXA, IV 3g vs TXA, IV 5g						
Lei 2018b	0	50	0	50		Not estimable
Subtotal (95% CI)		**50**		**50**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
5.9.7 TXA, IV 4g vs TXA, IV 5g						
Lei 2018b	0	50	0	50		Not estimable
Lei 2020	0	50	0	50		Not estimable
Subtotal (95% CI)		**100**		**100**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
5.9.8 TXA, IV 5g vs TXA, IV More than 5g						
Lei 2020	0	50	0	50		Not estimable
Subtotal (95% CI)		**50**		**50**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
5.9.9 TXA, IV 4g vs TXA, IV More than 5g						
Lei 2020	0	50	0	50		Not estimable
Subtotal (95% CI)		**50**		**50**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**648**		**655**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



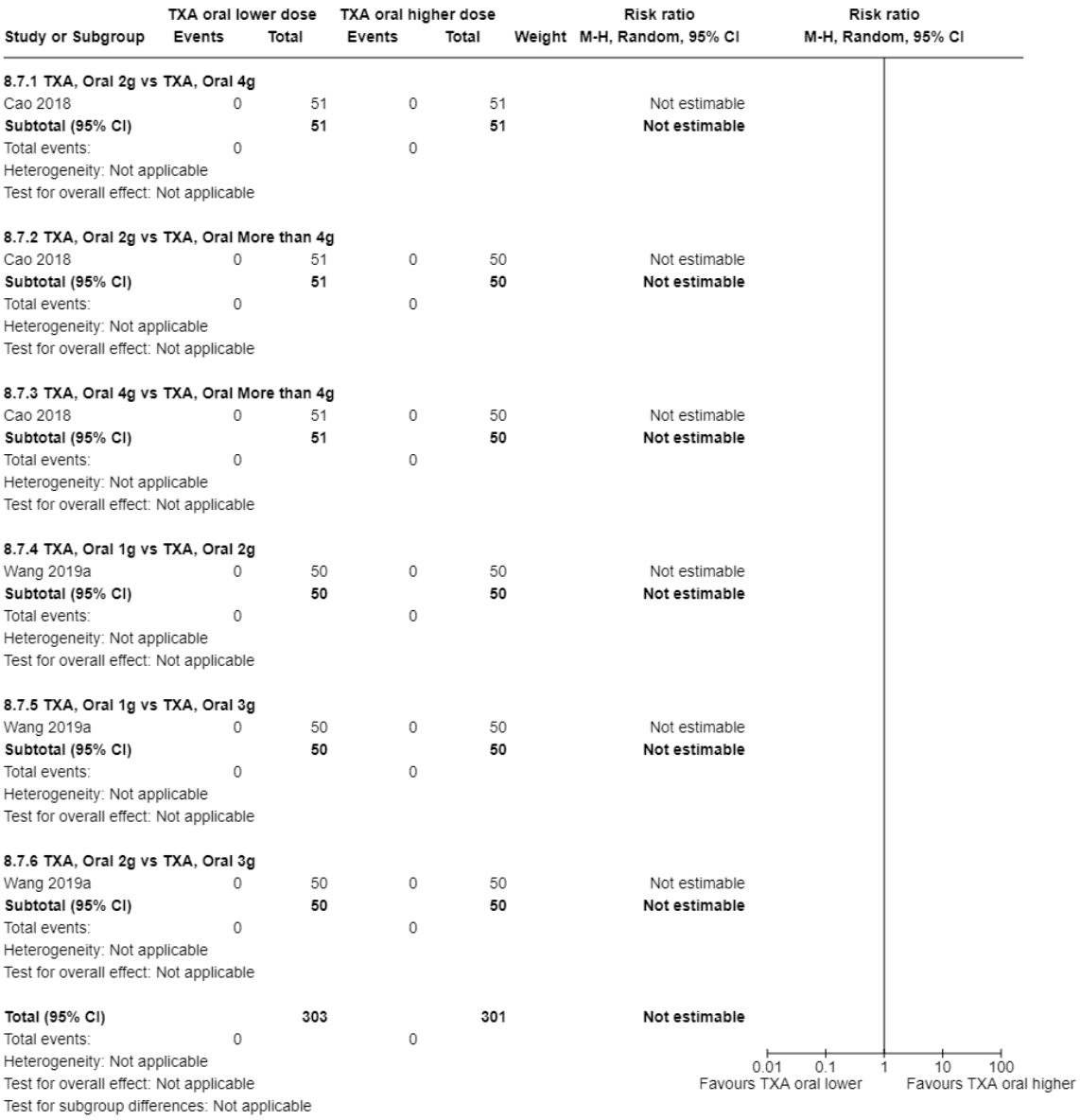
B.1.8.6 TXA IV versus TXA oral



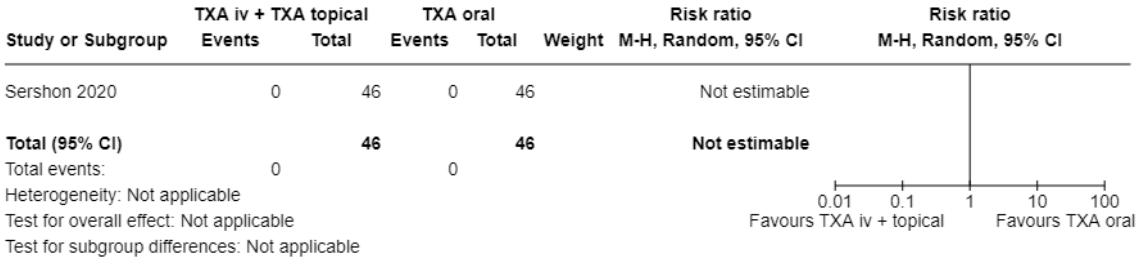
B.1.8.7 TXA IV versus TXA topical



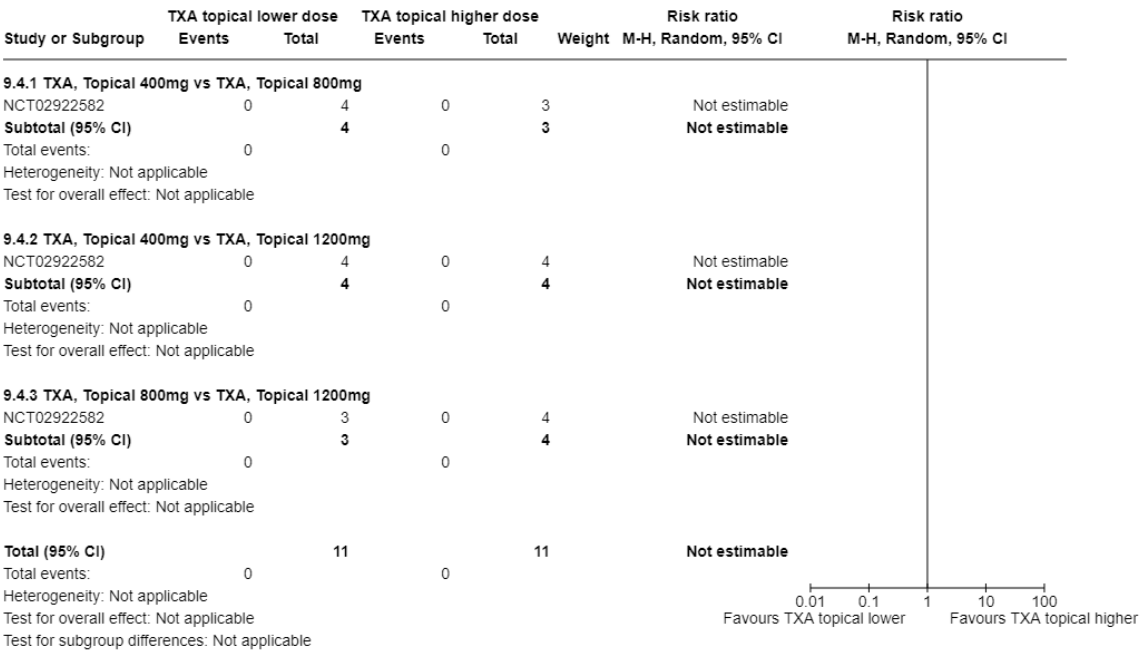
B.1.8.8 TXA oral lower dose versus TXA oral higher dose



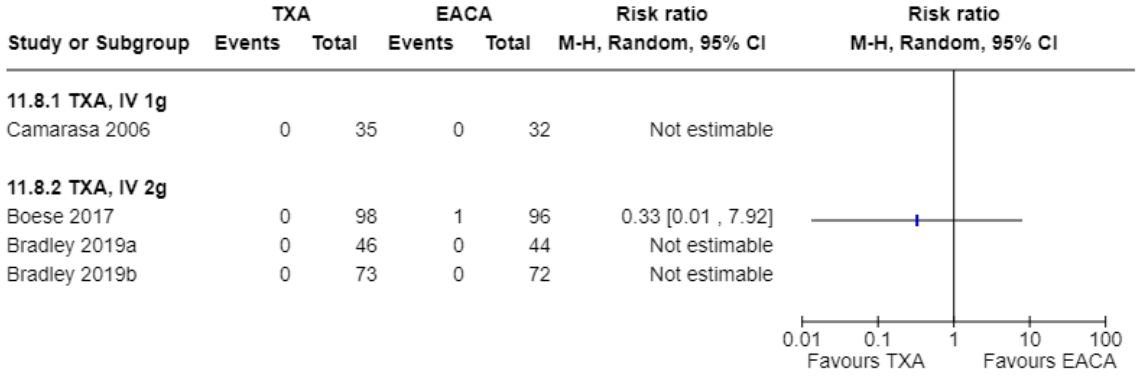
B.1.8.9 TXA IV and TXA topical versus TXA oral



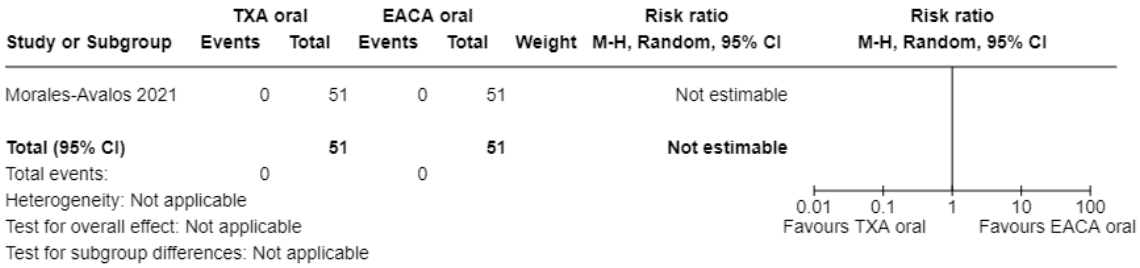
B.1.8.10 TXA topical lower dose versus TXA topical higher dose



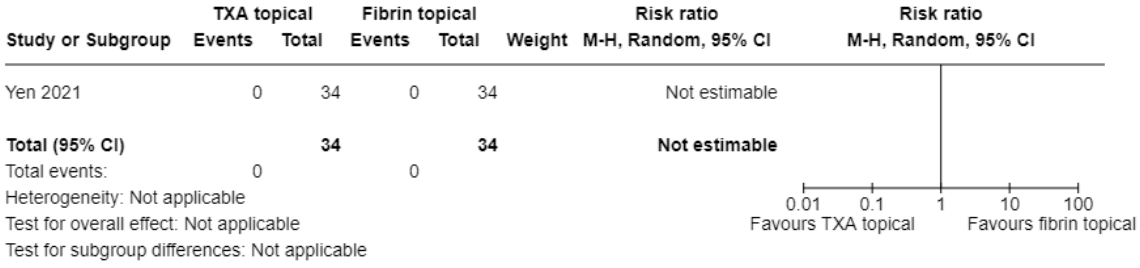
B.1.8.11 TXA IV versus EACA



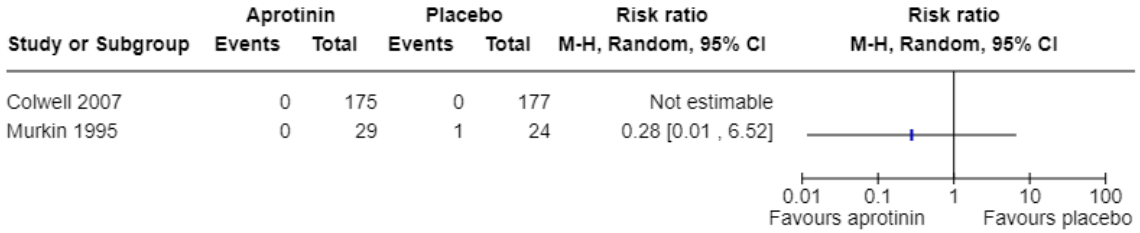
B.1.8.12 TXA oral versus EACA oral



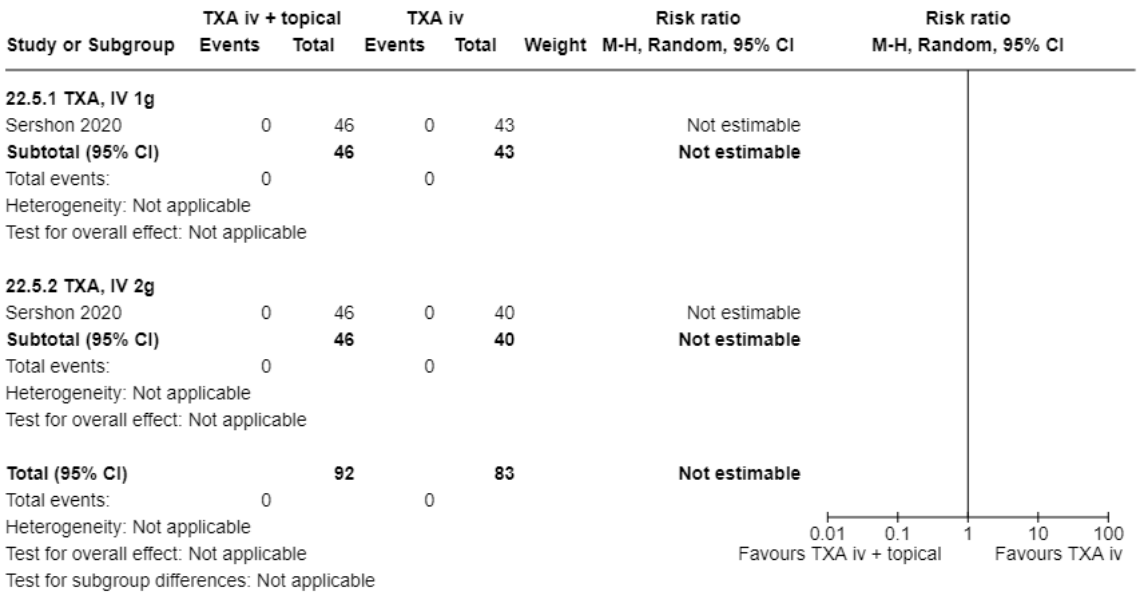
B.1.8.13 TXA topical versus fibrin topical



B.1.8.14 Aprotinin versus placebo

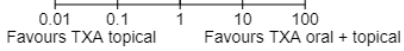


B.1.8.15 TXA IV and TXA topical versus TXA IV



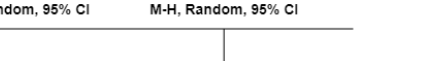
B.1.8.16 TXA topical versus TXA oral and TXA topical

Study or Subgroup	TXA topical Events	Total	TXA oral + TXA topical Events	Total	Weight	Risk ratio M-H, Random, 95% CI
25.7.1 TXA, Topical vs TXA, Oral + TXA, Topical 4g						
Wang 2019b	0	60	0	60		Not estimable
Subtotal (95% CI)		**60**		**60**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
25.7.2 TXA, Topical vs TXA, Oral + TXA, Topical 5g						
Wang 2019b	0	60	0	60		Not estimable
Subtotal (95% CI)		**60**		**60**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
25.7.3 TXA, Topical vs TXA, Oral + TXA, Topical 6g						
Wang 2019b	0	60	0	60		Not estimable
Subtotal (95% CI)		**60**		**60**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
25.7.4 TXA, Topical vs TXA, Oral + TXA, Topical 7g						
Wang 2019b	0	60	0	60		Not estimable
Subtotal (95% CI)		**60**		**60**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**240**		**240**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



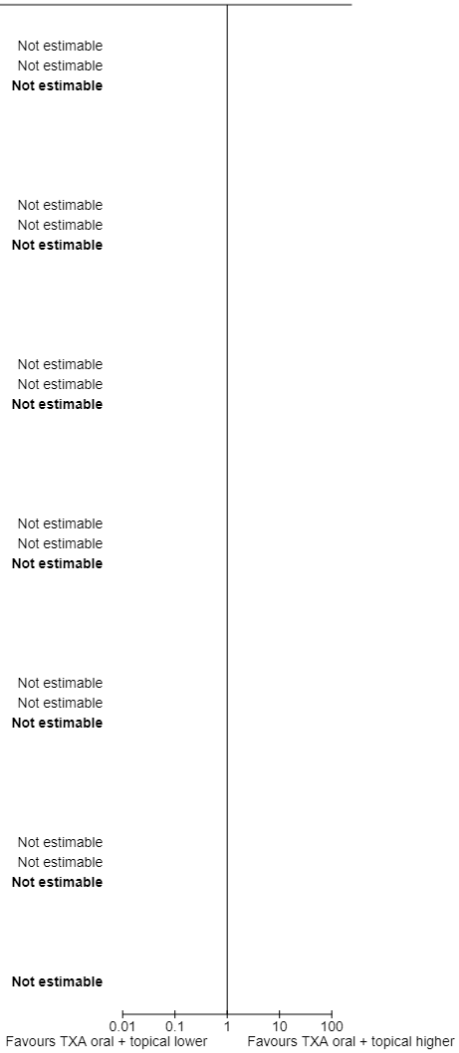
B.1.8.17 TXA IV and topical lower dose versus TXA IV and topical higher dose

Study or Subgroup	TXA iv + topical lower dose Events	Total	TXA iv + topical higher dose Events	Total	Weight	Risk ratio M-H, Random, 95% CI
27.6.1 TXA, IV + TXA, IA 3g vs TXA, IV + TXA, IA More than 3g						
Xie 2017	0	50	0	50		Not estimable
Subtotal (95% CI)		**50**		**50**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
27.6.2 TXA, IV + TXA, IA 3g vs TXA, IV + TXA, IA More than 4g						
Xie 2017	0	50	0	50		Not estimable
Subtotal (95% CI)		**50**		**50**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
27.6.3 TXA, IV + TXA, IA More than 3g vs TXA, IV + TXA, IA More than 4g						
Xie 2017	0	50	0	50		Not estimable
Subtotal (95% CI)		**50**		**50**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**150**		**150**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



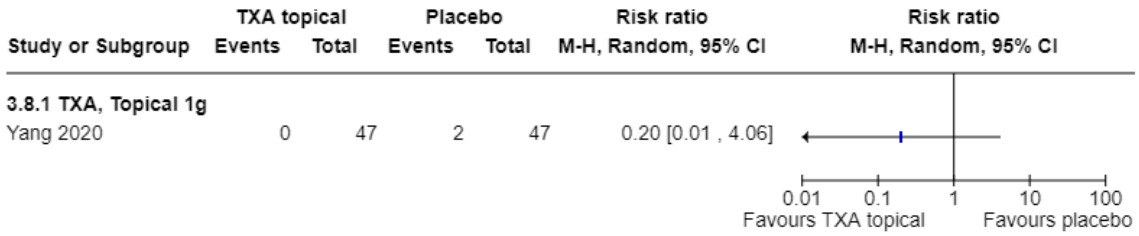
B.1.8.18 TXA oral and topical lower dose versus TXA oral and topical higher dose

Study or Subgroup	TXA oral + topical lower dose Events	Total	TXA oral + topical higher dose Events	Total	Weight	Risk ratio M-H, Random, 95% CI
28.7.1 TXA, Oral + TXA, Topical 4g vs TXA, Oral + TXA, Topical 5g						
Wang 2018	0	50	0	50		Not estimable
Wang 2019b	0	60	0	60		Not estimable
Subtotal (95% CI)		**110**		**110**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
28.7.2 TXA, Oral + TXA, Topical 4g vs TXA, Oral + TXA, Topical 6g						
Wang 2018	0	50	0	50		Not estimable
Wang 2019b	0	60	0	60		Not estimable
Subtotal (95% CI)		**110**		**110**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
28.7.3 TXA, Oral + TXA, Topical 4g vs TXA, Oral + TXA, Topical 7g						
Wang 2018	0	50	0	50		Not estimable
Wang 2019b	0	60	0	60		Not estimable
Subtotal (95% CI)		**110**		**110**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
28.7.4 TXA, Oral + TXA, Topical 5g vs TXA, Oral + TXA, Topical 6g						
Wang 2018	0	50	0	50		Not estimable
Wang 2019b	0	60	0	60		Not estimable
Subtotal (95% CI)		**110**		**110**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
28.7.5 TXA, Oral + TXA, Topical 5g vs TXA, Oral + TXA, Topical 7g						
Wang 2018	0	50	0	50		Not estimable
Wang 2019b	0	60	0	60		Not estimable
Subtotal (95% CI)		**110**		**110**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
28.7.6 TXA, Oral + TXA, Topical 6g vs TXA, Oral + TXA, Topical 7g						
Wang 2018	0	50	0	50		Not estimable
Wang 2019b	0	60	0	60		Not estimable
Subtotal (95% CI)		**110**		**110**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**660**		**660**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Test for subgroup differences: Not applicable						



B.1.9 Transfusion reactions within 24 hours

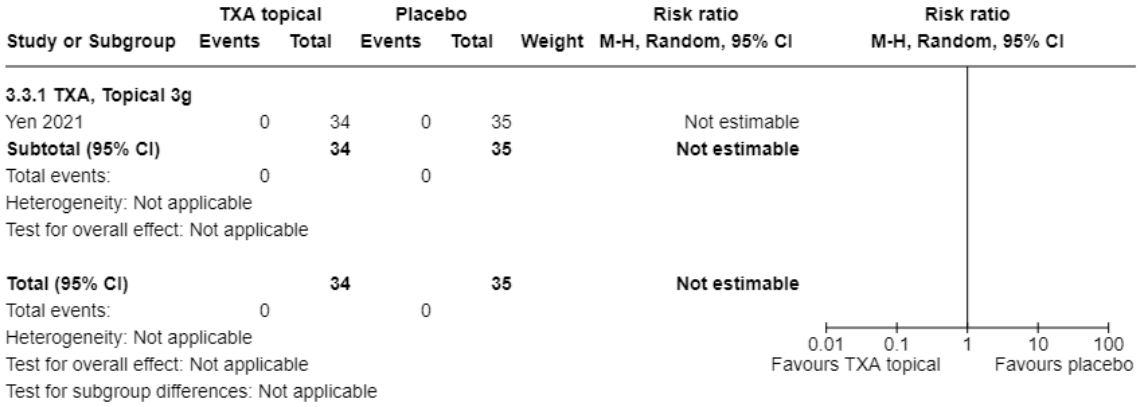
B.1.9.1 TXA topical versus Placebo



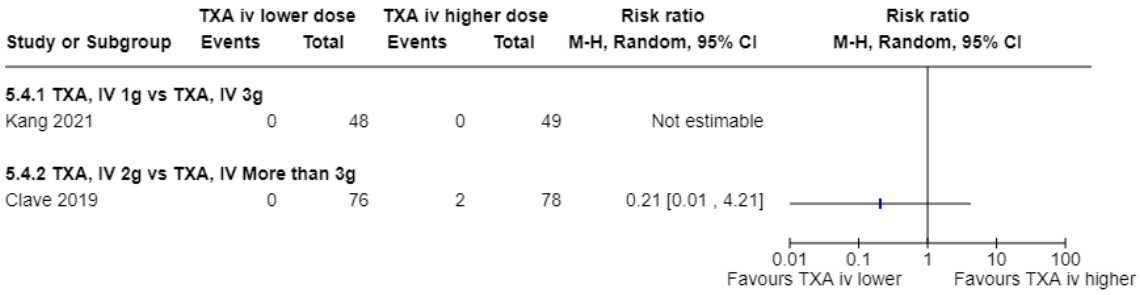
B.1.10 Re-operation due to bleeding within 7 days

B.1.10.1 TXA IV versus placebo

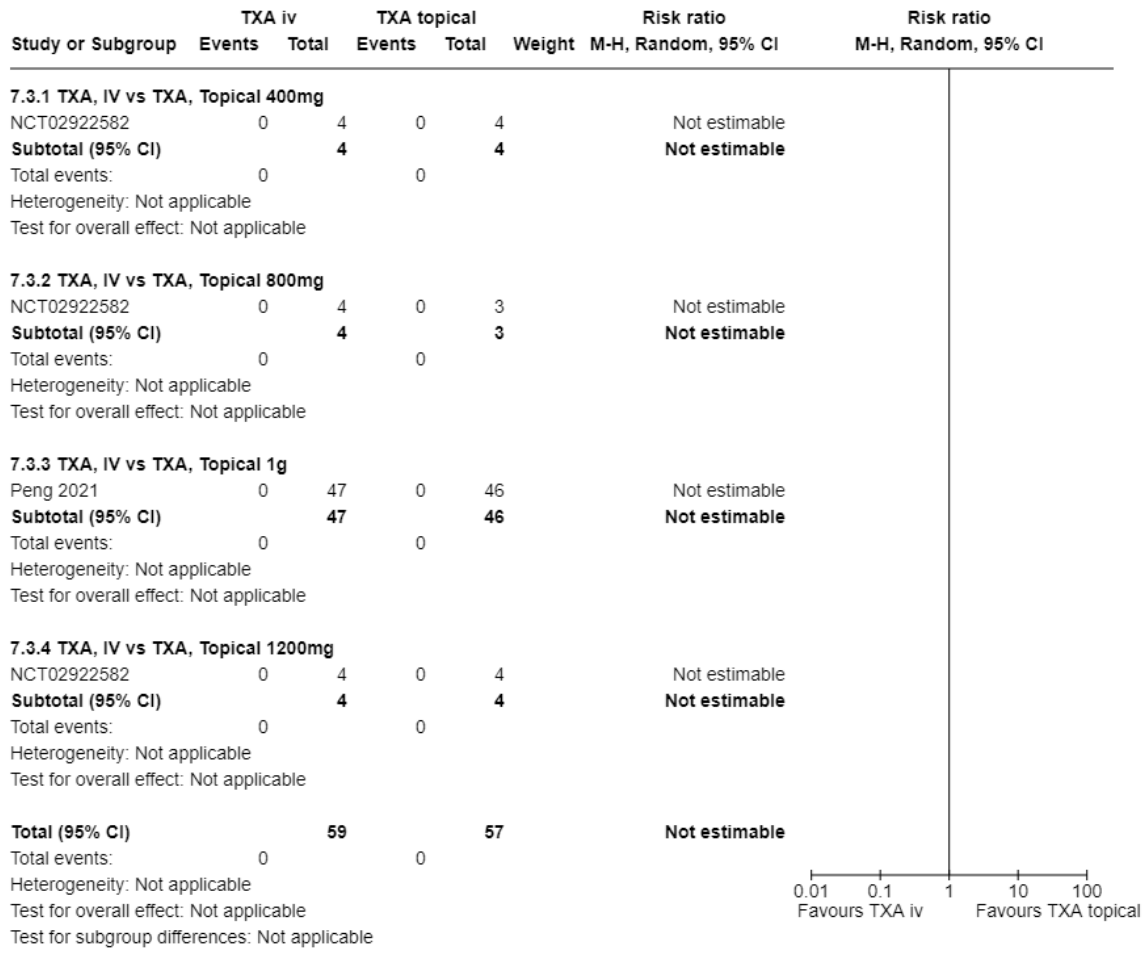
B.1.10.2 TXA topical versus placebo



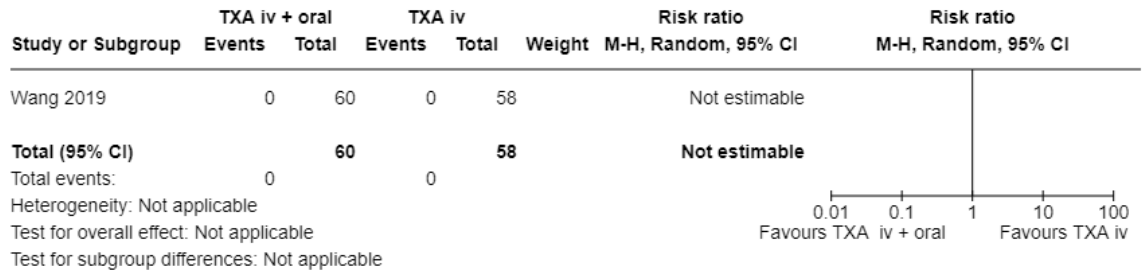
B.1.10.3 TXA IV lower dose versus TXA IV higher dose



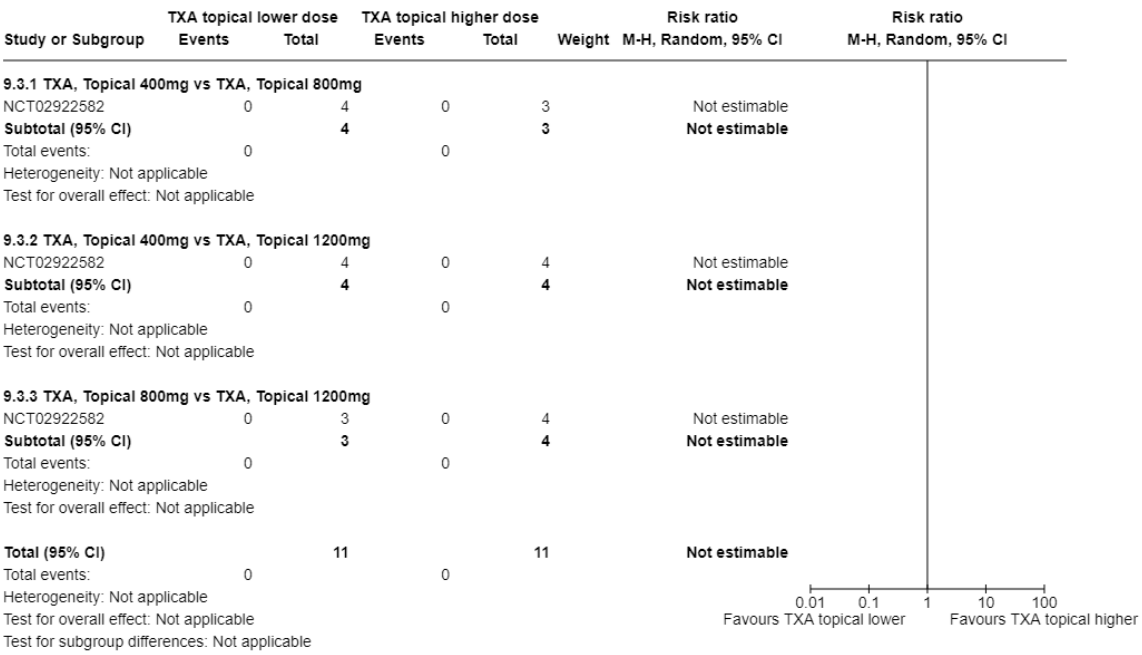
B.1.10.4 TXA IV versus TXA topical



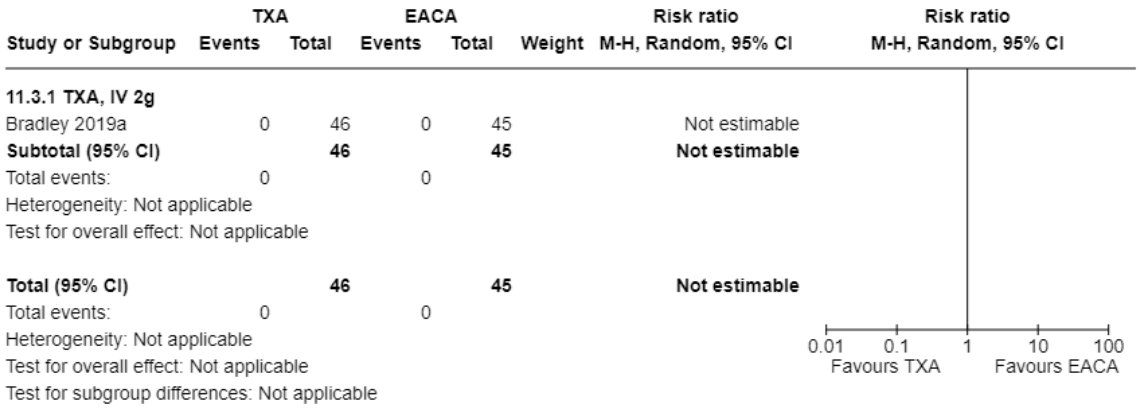
B.1.10.5 TXA IV and TXA oral versus TXA IV



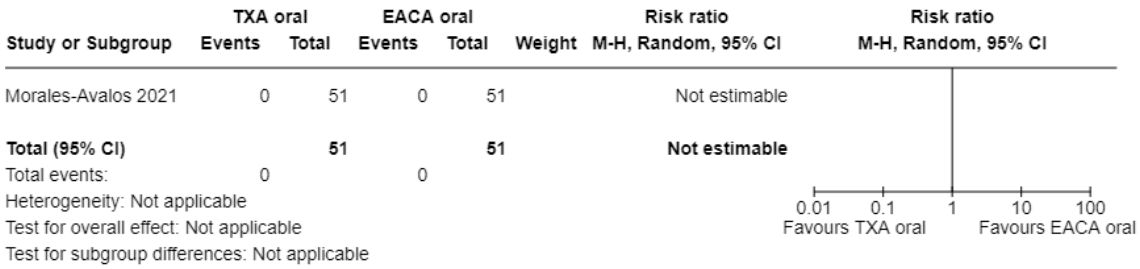
B.1.10.6 TXA topical lower dose versus TXA topical higher dose



B.1.10.7 TXA IV versus EACA



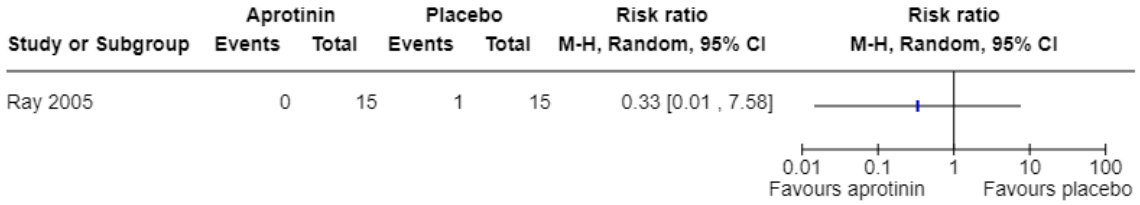
B.1.10.8 TXA oral versus EACA oral



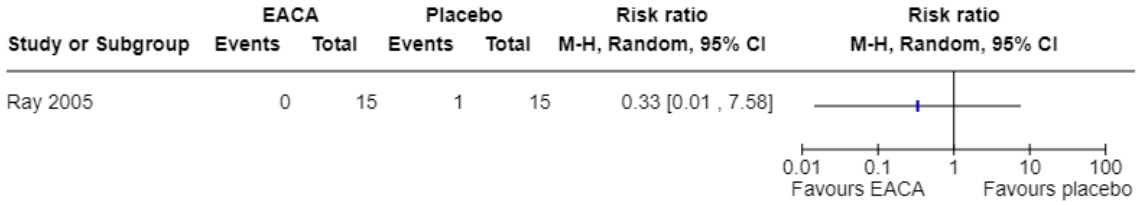
B.1.10.9 TXA topical versus fibrin topical



B.1.10.10 Aprotinin versus placebo



B.1.10.11 EACA versus placebo



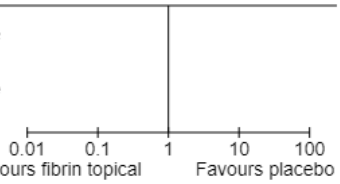
B.1.10.12 EACA versus Aprotinin



B.1.10.13 Fibrin topical versus placebo

Study or Subgroup	Fibrin topical Events	Total	Placebo Events	Total	Weight	Risk ratio M-H, Random, 95% CI
Yen 2021	0	34	0	35		Not estimable
Total (95% CI)		**34**		**35**		**Not estimable**
Total events:	0		0			

Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable

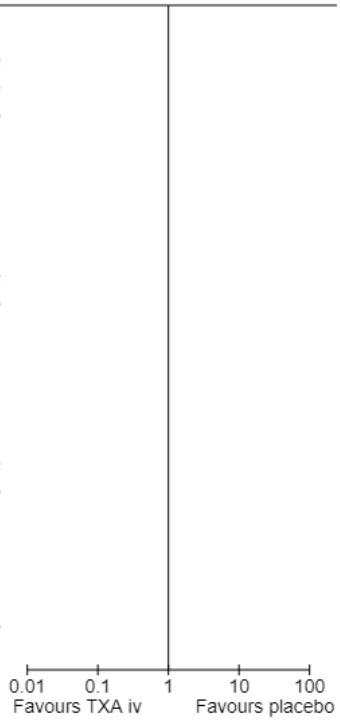


B.1.11 Suspected serious drug reactions: within 30 days

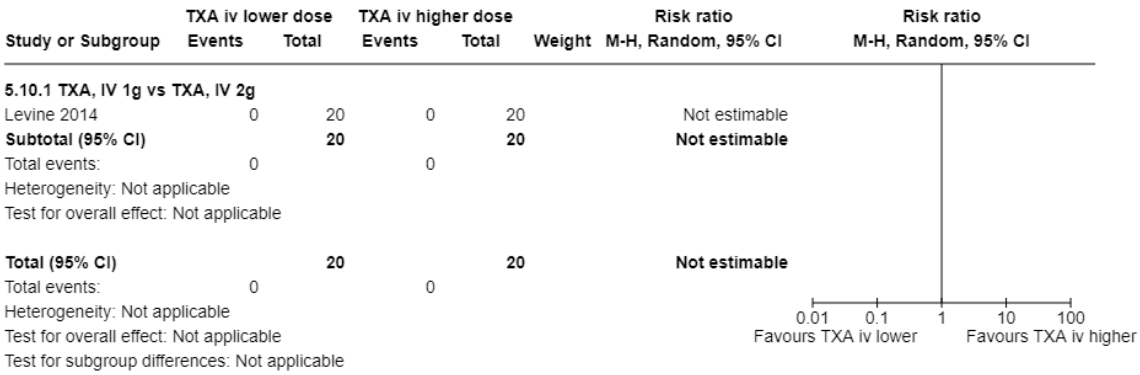
B.1.11.1 TXA IV versus placebo

Study or Subgroup	TXA iv Events	Total	Placebo Events	Total	Weight	Risk ratio M-H, Random, 95% CI
1.10.1 TXA, IV 1g						
Alvarez 2008	0	46	0	49		Not estimable
Benoni 2001	0	18	0	20		Not estimable
Subtotal (95% CI)		**64**		**69**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.10.2 TXA, IV 2g						
Niskanen 2005	0	19	0	20		Not estimable
Subtotal (95% CI)		**19**		**20**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
1.10.3 TXA, IV More than 3g						
Gill 2009	0	5	0	5		Not estimable
Subtotal (95% CI)		**5**		**5**		**Not estimable**
Total events:	0		0			
Heterogeneity: Not applicable						
Test for overall effect: Not applicable						
Total (95% CI)		**88**		**94**		**Not estimable**
Total events:	0		0			

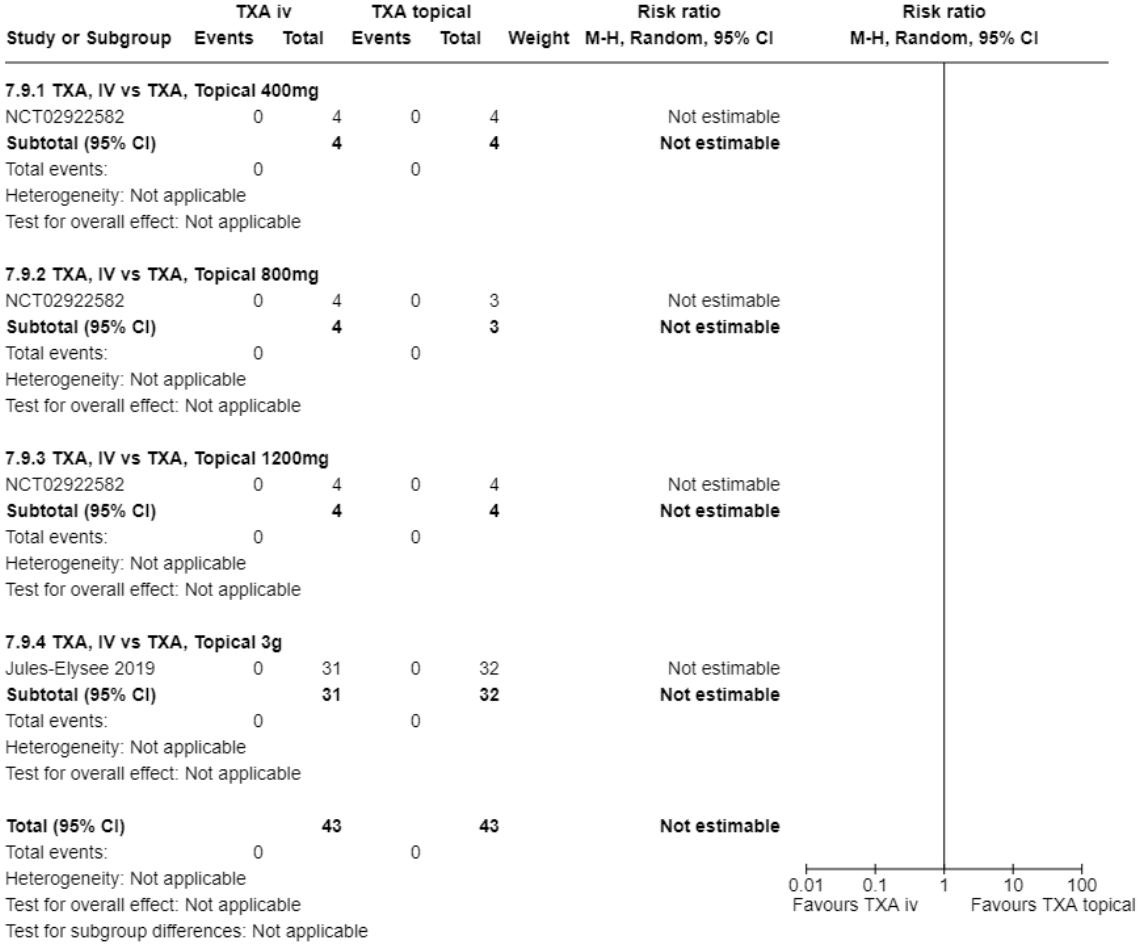
Heterogeneity: Not applicable
Test for overall effect: Not applicable
Test for subgroup differences: Not applicable



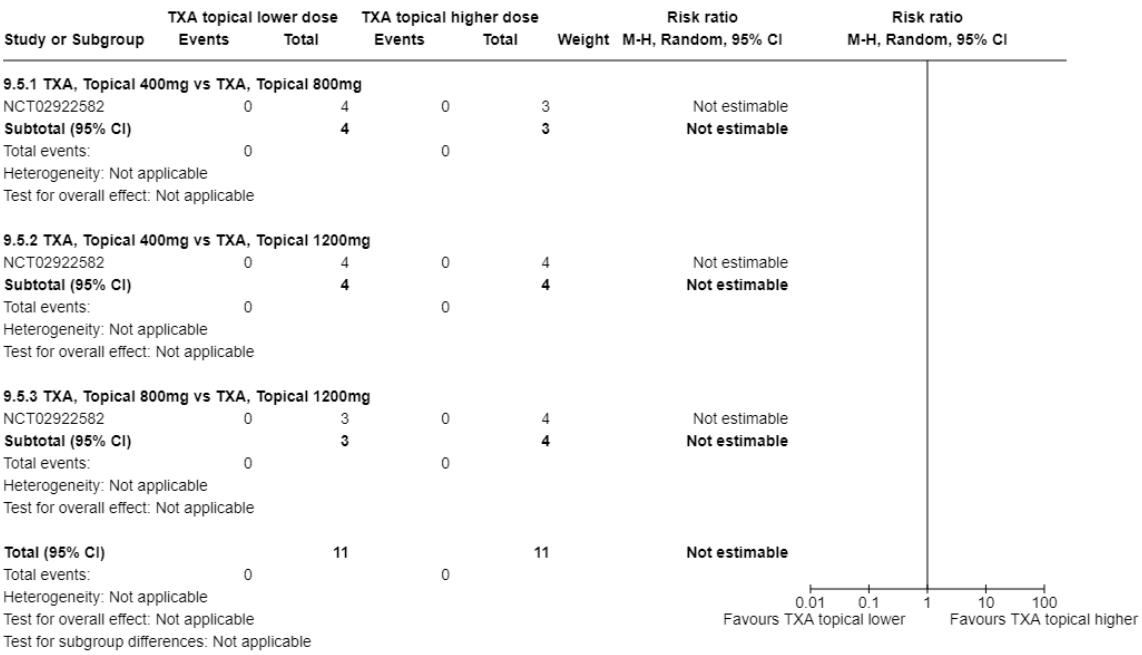
B.1.11.2 TXA IV lower dose versus TXA IV higher dose



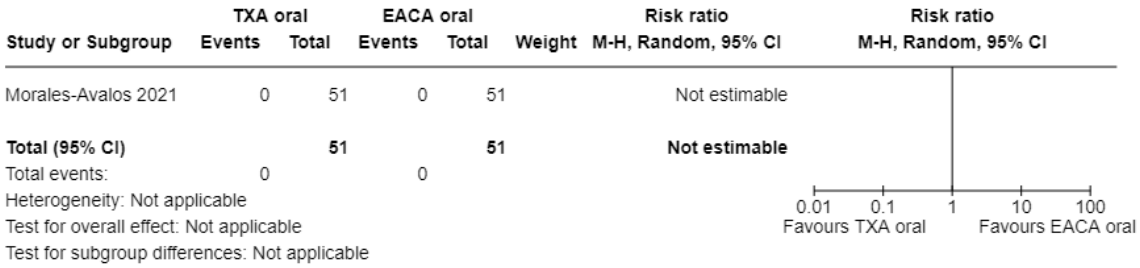
B.1.11.3 TXA IV versus TXA topical



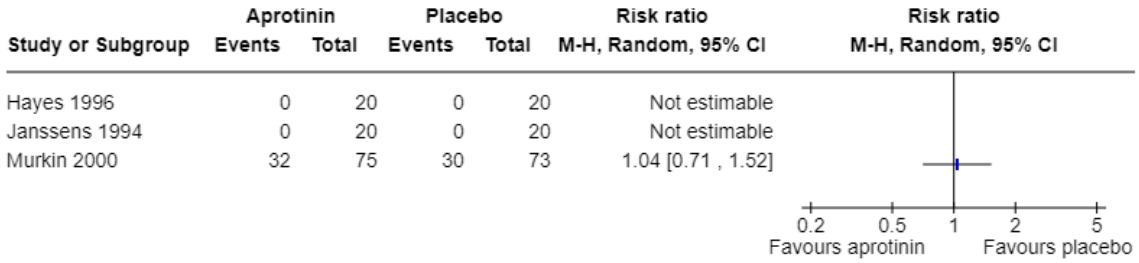
B.1.11.4 TXA topical lower dose versus TXA topical higher dose



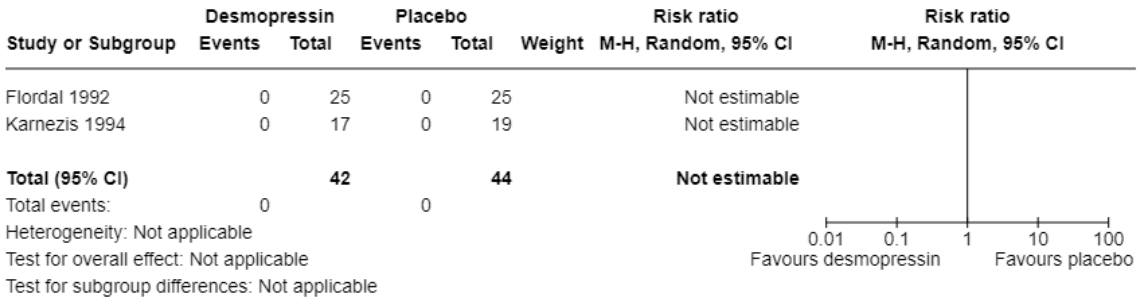
B.1.11.5 TXA oral versus EACA oral



B.1.11.6 Aprotinin versus placebo



B.1.11.7 Desmopressin versus placebo



B.1.12 Descriptive cost information

Study	Cost information
Alvarez 2008	In contrast, results of this study also question the use of presurgical donation of autologous blood in patients undergoing total knee arthroplasty in our institution because of 11 patients in which this procedure was used, only 3 received blood transfusion. Therefore, the use of presurgical donated units is far from the 70 percent recommended for an adequate cost effectiveness ratio.
Benoni 1996	At our hospital, one Sagman unit of blood costs 512 SEK (51 GBP). The price of one ampoule of Cyklokapron, containing one gram of tranexamic acid, is 42 SEK (4 GBP). The total cost of blood transfusions plus tranexamic acid was 9756 SEK (976 GBP) in the whole prophylactic group against 21 110 SEK (2111 GBP) in the whole placebo group.
Benoni 2001	The price of one ampoule of tranexamic acid (1 gram) in Sweden is 5 Euro. In our department, 1 unit of leukocyte-depleted erythrocyte concentrate costs 77 Euro. The total cost of tranexamic acid and blood transfusions in the TA group was 475 Euro versus 1100 Euro in the placebo group
Boese 2017	Antifibrinolytics were added to the blood management program for TKA in June 2012. At that time, TXA was not on the formulary, and its acquisition cost was much higher than that of EACA ($43/g for TXA compared with $0.20/g for EACA). Despite its higher cost, our surgeons preferred administrating TXA over EACA because of the paucity of data on the use of EACA in TKA. However, EACA was administered when TXA was unavailable, with no apparent differences in efficacy or drug-

	related adverse events.
Bradley 2019a	At the investigating hospital, TXA costs $465 per patient while EACA costs $60 per patient for the dosages used in this study. Due to the low rate of transfusion and no statistical difference in LOS, there appears to be a difference of about $400 (pharmacy cost) between these two agents. Unfortunately, there have been problems with the availability of EACA: currently, it is not available due to a national shortage
Chin 2020	When one considers the financial cost of such treatment, the total drug cost of tranexamic acid (NZ$58) is less than the production cost of a unit of allogenic blood (NZ$158) [12]. However, using the number needed to treat of 67, this study effectively spent $3886 on TXA to save 1 unit of blood. 'is cost was not retrieved in a significantly shorter duration of stay as shown by the time to discharge.
Claeys 2007	The reduction in the risk associated with the transfusion of allogenic blood, as well as the cost-effectiveness are obvious (3 ampoule TXA €5, 1 unit of packed cells €67 ; total cost TA group :€100 vs placebo group :€871).
Colwell 2007	We did not examine the costs of using aprotinin. Realizing costs and charges vary, the approximate direct cost of aprotinin we used was $450. This does not, however, consider the staff time in preparation in the pharmacy and administration in the OR.
Ekback 2000	As both IAT and PAD are costly and time-consuming procedures, it seems reasonable to refrain from using one or both of them if TA is to be used, although this was not examined in the present study.
Georgiadis 2013	We observed a trend towards decreased blood transfusion in the TNA group vs. the placebo group (8% and 0% respectively), but our results were not significant and therefore no “number needed to treat” analysis could be undertaken. Models that reflect the real-world costs of blood utilization in the United States estimate that a single unit of allogenic leuko reduced red blood cells costs $950[1]. At our institution one 2 g dose of tranexamic acid can be compounded for $60 USD, and it is readily available internationally for $6 USD per dose. A cost–benefit analysis would be beneficial in determining the realized benefit of TXA administration in preventing allogenic transfusion, as pecuniary considerations become increasingly important and regulated in orthopaedic surgery.

Gill 2009	The cost of allogenic blood transfusions was reduced by approximately $800 per patient (P<0.03) in the tranexamic acid group. Moreover, only one patient in the tranexamic acid group received a transfusion, whereas four patients received transfusions in the placebo group. This translated into a significantly lower cost in blood products administered in the tranexamic acid group with even considering the cost of tranexamic acid
Gomez Barrena 2014	Retrospective clinical and economical evaluations have indicated an estimated $1500 savings per primary total knee replacement performed with use of topical TXA, with significant decreases in length of stay, blood bank costs, and total direct costs to the hospital for the total knee replacement. We confirmed that the length of stay was short and blood bank costs were reduced to a minimum when TXA was used in the present study. Indirect cost savings would also result from the avoidance of transfusions that result in complications requiring additional treatment and an increased length of stay.
Good 2003	In our hospital the dose of tranexamic acid given would cost less than £7, compared with £46 for a unit of banked blood. Thus, the immediate saving in the patients given tranexamic acid would have been about £1100. To our knowledge, giving tranexamic acid is the only blood saving method that is cheaper, per saved unit, than banked blood in this type of surgery. This estimate does not include potential adverse effects from banked blood such as immediate transfusion reactions, transmission of infectious agents and disturbances of the immune system
Harley 2002	The cost of the preparation and administration of EACA as described in this study is Can$80 per patient, so this agent represents one of the most cost-effective modalities currently under investigation.
Husted 2003	1 blood transfusion costs 93 Euro; 4 ampoules (2 grams) of tranexamic acid cost 18 Euro. The total costs of maintaining or restoring levels of haemoglobin thus amounts to 1092 Euro in the tranexamic group and 2325 Euro in the placebo group.
Janssens 1994	Although Aprotinin is expensive (in Belgium, about $235 for 3.5 x 10 (6) kIU) the economic benefit of reducing the requirement for blood transfusion may justify the cost.

Jeserschek 2003	At the current price of aprotinin, approximately £75 (120 euros) per patient was spent on each operation. The price of 1.8 fewer units of blood (approximately £120 (190 euros)), led to a mean saving of £45 (70 euros) per patient.
Johansson 2005	In this study, 4/5 patients weighed more than 67 kg and would have needed 2 ampoules of TA, since 1 ampoule contains 1,000 mg. If all patients had received TA 15 mg/kg, the average cost would have been (180 ampoules × EUR 5)/ 100 patients = EUR 9 per patient. At our hospitals, the cost for 1 unit of blood is EUR 78. The cost saving for transfusions when tranexamic acid is used would be: EUR 78/unit × reduction in average transfusion (1.08 – 0.36 units) = EUR 56. Thus, if the results from this study were generalized, the cost saving would be EUR 56 – EUR 9 = EUR 47 per patient.
Kakar 2009 Bilateral TKR; Kakar 2009 Unilateral TKR	Patients in the tranexamic acid group were given 4 units of blood in total, compared with 26 units in the control group. In our hospital the dose of tranexamic acid given would cost Rs. 166, compared with Rs. 6000 for a unit of leuco-depleted banked blood. Thus, the immediate saving in the patients given tranexamic acid would have been about Rs. 5000. •Cost of 1-unit leuco-depleted PRBC = Rs. 6000 •Total cost of blood in Control patients (26 units) = Rs 1,56,000 •Total cost of blood in TAX patients (4 units) = Rs 24, 000 •Cost of 1 ampoule of TXA = Rs 166 •Cost of TXA (25 patients) = Rs 8,300 •Cost of blood saved by giving TXA= Rs 1,23,700 •Cost saved per patient = Rs 4958 •Potential savings per year (500 patients) = Rs 25,00,000
Kayupov 2017	In the present study, the oral TXA dosage cost $14 compared with $47-$108 depending on the availability of the generic IV formulation. Given the aging population, the utilization of primary total knee replacements will only grow from the current rate of approximately 700,000 per year in the United States. As a result, the transition to oral TXA could yield total cost savings of between $23 million and $67 million dollars per year for our health care system
Molloy 2007	At the time of our study, the cost of the pharmaceutical intervention involved in the topical fibrin group was £380 per patient whereas in the tranexamic acid group it was less than £4
Murkin 1995	Currently, the cost of aprotinin in Canada averages $450 ($590 Cdn) for this dosage of 3.8 m KIU. The

	average reduction in transfusion requirements of 0.9 U PRBC shown here, may not be sufficient to justify this expenditure. If the trend to reduction in DVT, as demonstrated in both recent studies in this high-risk population, can be confirmed, however, the resultant decrease in morbidity and associated length of stay could render this therapy cost effective.
Murkin 2000	Notably, the direct cost of one unit of allogeneic blood (approximately $150 [United States dollars] per unit) is comparable with that of the starting dose of aprotinin, with a current hospital acquisition cost for use in a hip replacement of approximately $162 for a low dose of 100 millilitres of aprotinin to $486 for a high dose of 300 millilitres. Moreover, on the basis of the total incremental hospital costs of hip arthroplasty, allogeneic blood transfusion may be associated with $1000 to $1500 per unit in additional costs compared with the cost of no transfusion or of transfusion of one to five units of autologous blood. Thus, use of aprotinin may be of particular clinical and economic benefit in patients at high risk of receiving allogeneic blood, such as those who have not pre-donated blood or perhaps those with a low baseline haemoglobin level
Niskanen 2005	One unit of red cells costs EUR 90, and 6 ampoules of tranexamic acid used for one patient cost EUR 13. Thus, the total cost per patient amounts to EUR 58 in the tranexamic acid group and EUR 81 in the placebo group. If we use only 2 ampoules of tranexamic acid preoperatively and drain only in the placebo group, the costs would amount to EUR 50 and EUR 100. According to the Finnish arthroplasty registry, about 2500 hip operations per year in Finland might be suitable for this kind of policy (Nevalainen et al. 2003). It means a saving of about EUR 32,500–125,000. If we take uncemented and revision cases into account, the saving will increase many folds.
North 2016	cost analysis using IV TXA demonstrated a savings of $314 USD per patient
Ray 2005	The cost of these doses of aprotinin and EACA is Aus. $401 and $71 respectively, i.e. aprotinin is more than five times the cost, bears a risk of anaphylactic reaction and has similar effect in reducing bleeding.
Veien 2002	The blood-sparing effect of TXA has a high cost-benefit ratio. The cost of short-term TXA therapy is significantly less than the cost of autologous and

	allogenic blood transfusions.
Wang 2018	An appropriate oral dose can save between $33 and $94 compared with an equivalent intravenous or intra-articular dose, depending on the formulations of TXA. We came to the same conclusion about the costs. Although several authors have confirmed the enhanced efficacy of higher or additional intravenous administration of TXA in arthroplasty, to our knowledge there have been no prior RCTs determining the optimum regimen for oral TXA, which is associated with great cost savings, ease of administration, and equivalent clinical blood-conserving efficacy.
Wu 2018	The total TXA cost in the oral TXA group was significantly less compared to that in the IV TXA group (¥600 and ¥ 3150, P < 0.01)
Zeng 2018	The mean hospital charge in the extension, and controlled group was 7070$, and 7140$, respectively, without significant intergroup differences.
Zhao 2018	The cost associated with oral TXA (546 RMB total patients) was significantly lower than that of intravenous TXA (4573.2 RMB total patients; p = 0.001; Table 2). The oral TXA dosage cost 6.83 RMB per dose. The cost of 1g of IV TXA was 76.30 RMB, the cost of oral form of TXA is cheaper than the intravenous form, and beside its relatively low cost, the advantage of oral TXA is simple application avoiding IV access, which is requirement for expensive nursing care for IV application. The transfusion cost per two U red blood cells was estimated to be 930 RMB at our hospital. Costs of TXA and transfusions were significantly lower in the oral group than the intravenous group (p < 0.05). Similarly, the cost of transfusion was significantly lower in the oral group (929.65 RMB total transfusion) than in the intravenous group (1859.3 RMB total transfusion) and control group (8366.8 RMB, total transfusion; p = 0.004; Table 2).
*TXA, TA, TNA – Tranexamic acid, EACA –Epsilon-aminocaproic acid, LOS – length of stay, IV – intravenous, OR – operating room, IAT – intraoperative autotransfusion, PAD – preoperative autologous blood donation, DVT – deep vein thrombosis, TKA – Total knee arthroplasty, RCT – Randomised controlled trial	

B.1.13 Descriptive health related quality of life information

Study	Intervention	HRQoL information
Chin 2020	TXA, IV, 1g	There was no significant difference between TXA and placebo groups in the improvement of functional scales, comparing the preoperative to the one-year postoperative scores. The Oxford Hip Score showed a mean improvement of 25.9 points in those patients who received TXA, compared with 26.7 points in those who received placebo (p = 0.679). The WOMAC scores were improved by 49.9 points in the TXA group, compared with 50.7 points in the placebo group (p = 0.864). The mean improvement in the HAAS was 7.5points in the TXA group, compared with 8.2 points in the placebo group (p = 0.278)
	Placebo	
Morales-Avalos 2021	TXA, Oral	VAS score, Harris hip score. VAS preop 7.88 +/- 1.54, HHS (points) 48.10 +/- 8.48. VAS post op 30 days 1.38 +/- 0.95. HHS post op 30 days 84.99 +/- 12.92
	EACA, Oral	VAS score, Harris hip score. VAS preop 8.01 +/- 1.22 HHS 49.56 +/- 9.01. VAS post op 30 days 1.59 +/- 1.02. HHS post op 30 days 83.13 +/-14.69
Painter 2018	Placebo	EQ-5D indexed, median (interquartile range [IQR]) Preoperative: 0.38 (0.22 – 0.60), Week 3: 0.64 (0.54 – 0.74), Week 6: 0.67 (0.59 – 0.84), Month 3: 0.73 (0.64 – 0.84), Month 6: 0.77 (0.59 – 0.91) Quality of recovery score, median (IQR) Day 3: 102 (84 – 123), Week 3: 120 (107 – 138), Week 6: 124 (102 – 140) WOMAC® Index, median (IQR) Preoperative: 64 (51 – 72), Week 3: 30 (21 – 48), Week 6: 28 (16 -38), Month 3: 21 (10 – 37), Month 6: 18 (10 – 33) Oxford score (hip or knee), median (IQR) Preoperative: 44 (38–50), Week 3: 35 (26–41), Week 6: 28 (21–35), Month 3: 24 (17–30), Month 6: 21 (15–29)
	TXA	EQ-5D indexed, median (interquartile range [IQR]) Preoperative: 0.42 (0.19 to 0.58), Week 3: 0.65 (0.52 to 0.74), Week 6: 0.73 (0.59 to 0.84), Month 3: 0.74 (0.64 to 0.84), Month 6: 0.77 (0.66 to 1.00) Quality of recovery score, median

		(IQR) Day 3: 106 (88 to 122), Week 3: 119 (104 to 127), Week 6: 129 (116 to 139) WOMAC® Index, median (IQR) Preoperative: 61 (54 to 71), Week 3: 35 (25 to 45), Week 6: 28 (16 to 37), Month 3: 19 (12 to 31), Month 6: 17 (8 to 32) Oxford score (hip or knee), median (IQR) Preoperative: 43 (39 to 50), Week 3: 32 (28 to 37), Week 6: 26 (21 to 32), Month 3: 23 (19 to 28), Month 6: 23 (17 to 28)
Xie 2017 (knees)	TXA, IV pre-op + placebo, IV, post-op, repeated dose	VAS score pre-op day 1: 3.1 VAS score post-op day 1: 2.7, VAS score post-op day 2: 2.4, VAS score post op day 3: 2.2
	TXA, IV pre-op + TXA, IV, post-op + placebo, IV, post-op	VAS score pre-op day 1: 2.9 VAS score post-op day 1: 2.5, VAS score post-op day 2: 2.2, VAS score post op day 3: 2.2
	TXA, IV pre-op + TXA, IV, post-op, repeated dose	VAS score pre-op day 1: 3.3 VAS score post-op day 1: 1.8, VAS score post-op day 2: 2.0, VAS score post op day 3: 1.9
Yen 2017	Placebo	Average VAS mean score (1-day post-op): 3.89 +/- 0.83
	TXA, IV	Average VAS mean score (1-day post-op): 3.84 +/- 0.74
	TXA, IA	Average VAS mean score (1-day post-op): 3.93 +/- 0.84
*HRQoL – Health related quality of life, IQR – interquartile range, TXA – Tranexamic acid, IV – intravenous, IA – intra-articular, VAS – visual analogue scale		