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*Cochrane Database of Systematic Reviews* 2023, Issue 6. Art. No.: CD013737.

DOI: [10.1002/14651858.CD013737.pub2](https://doi.org/10.1002/14651858.CD013737.pub2).

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## [Overview of Reviews]

# Interventions for reducing red blood cell transfusion in adults undergoing hip fracture surgery: an overview of systematic reviews

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**Editorial group:** Cochrane Bone, Joint and Muscle Trauma Group.

**Publication status and date:** New, published in Issue 6, 2023.

**Citation:** Lewis SR, Pritchard MW, Estcourt LJ, Stanworth SJ, Griffin XL. Interventions for reducing red blood cell transfusion in adults undergoing hip fracture surgery: an overview of systematic reviews. *Cochrane Database of Systematic Reviews* 2023, Issue 6. Art. No.: CD013737. DOI: [10.1002/14651858.CD013737.pub2](https://doi.org/10.1002/14651858.CD013737.pub2).

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## ABSTRACT

### Background

Following hip fracture, people sustain an acute blood loss caused by the injury and subsequent surgery. Because the majority of hip fractures occur in older adults, blood loss may be compounded by pre-existing anaemia. Allogenic blood transfusions (ABT) may be given before, during, and after surgery to correct chronic anaemia or acute blood loss. However, there is uncertainty about the benefit-risk ratio for ABT. This is a potentially scarce resource, with availability of blood products sometimes uncertain. Other strategies from Patient Blood Management may prevent or minimise blood loss and avoid administration of ABT.

### Objectives

To summarise the evidence from Cochrane Reviews and other systematic reviews of randomised or quasi-randomised trials evaluating the effects of pharmacological and non-pharmacological interventions, administered perioperatively, on reducing blood loss, anaemia, and the need for ABT in adults undergoing hip fracture surgery.

### Methods

In January 2022, we searched the Cochrane Library, MEDLINE, Embase, and five other databases for systematic reviews of randomised controlled trials (RCTs) of interventions given to prevent or minimise blood loss, treat the effects of anaemia, and reduce the need for ABT, in adults undergoing hip fracture surgery. We searched for pharmacological interventions (fibrinogen, factor VIIa and factor XIII, desmopressin, antifibrinolytics, fibrin and non-fibrin sealants and glue, agents to reverse the effects of anticoagulants, erythropoiesis agents, iron, vitamin B12, and folate replacement therapy) and non-pharmacological interventions (surgical approaches to reduce or manage blood loss, intraoperative cell salvage and autologous blood transfusion, temperature management, and oxygen therapy).

We used Cochrane methodology, and assessed the methodological quality of included reviews using AMSTAR 2. We assessed the degree of overlap of RCTs between reviews. Because overlap was very high, we used a hierarchical approach to select reviews from which to report data; we compared the findings of selected reviews with findings from the other reviews. Outcomes were: number of people requiring ABT, volume of transfused blood (measured as units of packed red blood cells (PRC)), postoperative delirium, adverse events, activities of daily living (ADL), health-related quality of life (HRQoL), and mortality.

### Main results

We found 26 systematic reviews including 36 RCTs (3923 participants), which only evaluated tranexamic acid and iron. We found no reviews of other pharmacological interventions or any non-pharmacological interventions.

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## Tranexamic acid (17 reviews, 29 eligible RCTs)

We selected reviews with the most recent search date, and which included data for the most outcomes. The methodological quality of these reviews was low. However, the findings were largely consistent across reviews.

One review included 24 RCTs, with participants who had internal fixation or arthroplasty for different types of hip fracture. Tranexamic acid was given intravenously or topically during the perioperative period. In this review, based on a control group risk of 451 people per 1000, 194 fewer people per 1000 probably require ABT after receiving tranexamic acid (risk ratio (RR) 0.56, 95% confidence interval (CI) 0.46 to 0.68; 21 studies, 2148 participants; moderate-certainty evidence). We downgraded the certainty for possible publication bias.

Review authors found that there was probably little or no difference in the risks of adverse events, reported as deep vein thrombosis (RR 1.16, 95% CI 0.74 to 1.81; 22 studies), pulmonary embolism (RR 1.01, 95% CI 0.36 to 2.86; 9 studies), myocardial infarction (RR 1.00, 95% CI 0.23 to 4.33; 8 studies), cerebrovascular accident (RR 1.45, 95% CI 0.56 to 3.70; 8 studies), or death (RR 1.01, 95% CI 0.70 to 1.46; 10 studies). We judged evidence from these outcomes to be moderate certainty, downgraded for imprecision.

Another review, with a similarly broad inclusion criteria, included 10 studies, and found that tranexamic acid probably reduces the volume of transfused PRC (0.53 fewer units, 95% CI 0.27 to 0.80; 7 studies, 813 participants; moderate-certainty evidence). We downgraded the certainty because of unexplained high levels of statistical heterogeneity.

No reviews reported outcomes of postoperative delirium, ADL, or HRQoL.

## Iron (9 reviews, 7 eligible RCTs)

Whilst all reviews included studies in hip fracture populations, most also included other surgical populations. The most current, direct evidence was reported in two RCTs, with 403 participants with hip fracture; iron was given intravenously, starting preoperatively. This review did not include evidence for iron with erythropoietin. The methodological quality of this review was low.

In this review, there was low-certainty evidence from two studies (403 participants) that there may be little or no difference according to whether intravenous iron was given in: the number of people who required ABT (RR 0.90, 95% CI 0.73 to 1.11), the volume of transfused blood (MD -0.07 units of PRC, 95% CI -0.31 to 0.17), infection (RR 0.99, 95% CI 0.55 to 1.80), or mortality within 30 days (RR 1.06, 95% CI 0.53 to 2.13). There may be little or no difference in delirium (25 events in the iron group compared to 26 events in control group; 1 study, 303 participants; low-certainty evidence). We are very unsure whether there was any difference in HRQoL, since it was reported without an effect estimate. The findings were largely consistent across reviews. We downgraded the evidence for imprecision, because studies included few participants, and the wide CIs indicated possible benefit and harm.

No reviews reported outcomes of cognitive dysfunction, ADL, or HRQoL.

## Authors' conclusions

Tranexamic acid probably reduces the need for ABT in adults undergoing hip fracture surgery, and there is probably little or no difference in adverse events. For iron, there may be little or no difference in overall clinical effects, but this finding is limited by evidence from only a few small studies. Reviews of these treatments did not adequately include patient-reported outcome measures (PROMS), and evidence for their effectiveness remains incomplete. We were unable to effectively explore the impact of timing and route of administration between reviews.

A lack of systematic reviews for other types of pharmacological or any non-pharmacological interventions to reduce the need for ABT indicates a need for further evidence syntheses to explore this. Methodologically sound evidence syntheses should include PROMS within four months of surgery.

## PLAIN LANGUAGE SUMMARY

### What treatments reduce the need for a blood transfusion in adults who have broken their hip?

#### Key messages

- Using a medicine called tranexamic acid before, during, or after surgery for a broken hip probably reduces the need for a blood transfusion.
- Treatment with iron may make little to no difference to whether people need a blood transfusion after they have broken their hip.

#### What is the condition?

A broken hip (a break at the top of the leg bone) is common in older adults whose bones may have weakened because of a condition called osteoporosis. People can lose large amounts of blood with this injury, and they will also lose blood while the bone is fixed in an operation. Many of these older people also have anaemia, with fewer red blood cells to help carry oxygen around the body. Often people will need to be given a blood transfusion (donated from another person) as part of their treatment. There are some risks with this, such as infections, a longer stay in hospital, or becoming confused after surgery.

## What did we want to find out?

We wanted to find out whether there were any treatments that could reduce the need for a blood transfusion. We were interested in any medicine, or any other method that reduces additional blood loss. We also wanted to know if these treatments improved people's quality of life after surgery, or caused any unwanted effects.

## What did we do?

We searched for systematic reviews that looked at treatments to reduce blood loss in people with a broken hip. These reviews collect all the available evidence for a treatment from published studies and analyse their results. In this overview, we summarised the results of reviews and rated our confidence in the evidence that they reported. We based our judgements about our confidence on factors such as study methods and sizes.

## What did we find?

We found 17 reviews about tranexamic acid and nine reviews about iron, which included 36 studies with 3923 participants. These reviews included many of the same studies; we summarised evidence from three reviews that provided the most relevant information.

For tranexamic acid, one review included 24 studies with 2148 people with a broken hip, and another included 10 studies with 1123 people. In these studies, people were given tranexamic acid before, during, or after surgery (or at all three times); it was given either directly into a person's vein, or applied onto open wounds.

For iron, one review included two studies with 403 people. The treatment was given directly into a vein either before surgery, or before and after surgery.

We found no reviews for any other types of treatment.

## Main results

Compared to no treatment (or a 'dummy' treatment that does not contain a medicine), tranexamic acid:

- probably reduces the need for a blood transfusion. For every 1000 people who have a hip fracture, 257 people might need a blood transfusion after receiving tranexamic acid, compared to 451 people who did not receive it;
- probably reduces the amount of transfused blood that a person is given;
- probably makes little to no difference to the number of people who have side effects from treatment (such as blood clots that develop in a deep vein), or the number of people who die within a month of breaking their hip.

Compared to no treatment (or a 'dummy' treatment), iron may make little to no difference to:

- the number of people who need to have a blood transfusion;
- the amount of transfused blood, confusion after surgery, infections, or deaths within one month.

We were not sure if receiving iron would affect people's health-related quality of life four months after surgery.

No reviews reported whether these treatments affected people's ability to carry out daily activities four months after surgery. No reviews about tranexamic acid reported information about confusion or health-related quality of life.

## What are the limitations of the evidence?

We are only moderately confident in the evidence that tranexamic acid reduces the need for blood transfusion. The studies that provided results in our selected review may not represent all of the evidence, and this may have exaggerated the benefits of this treatment. For other outcomes, some studies were too small, reported wide differences in their results, and we could not be certain if all the studies were well-designed to give a reliable result.

We have little confidence in our findings for iron treatment, because the studies were too small to produce reliable results.

There were some flaws in the way all of the reviews came to their final conclusions, meaning that they may not have been conducted to the highest possible standard. However, the results in each review were all similar, and this meant that we were more confident that their results were accurately collected from study reports.

## How up to date is this evidence?

This overview is up to date to January 2022.

## BACKGROUND

### Description of the condition

A hip fracture, or proximal femoral fracture, is a break in the upper region of the femur (thigh bone) between the subcapital region (the area just under the femoral head) and 5 cm below the lesser trochanter (a bony projection of the upper femur). The incidence of hip fractures rises with age. The overwhelming majority occur in adults aged over 65 years, with greater numbers in women (Court-Brown 2017; Kanis 2001). For example, in the UK, the mean age of a person with a hip fracture is 83 years; approximately two-thirds occur in women (NHFD 2017). However, incidence rates for hip fracture and characteristics of the people affected, vary around the world; these variations mainly reflect differences in population demographics (Dhanwal 2011). Most hip fractures in older adults are fragility fractures associated with osteoporosis. The World Health Organization defines fragility fractures as those sustained from injuries equivalent to a fall from a standing height or less (Kanis 2012). Such fractures are caused by mechanical forces that would not ordinarily result in fracture. Hip fractures in younger adults are usually associated with poor bone health (Karantana 2011; Rogmark 2018). High-energy traumas, such as road traffic collisions, industrial injuries, and sports injuries cause a very small proportion of hip fractures in younger adults (Court-Brown 2017).

Hip fracture is typically treated with an operation. Whilst hip fracture surgery is considered urgent worldwide, different healthcare systems are able to respond in different ways. For example, in the UK, 98% of people with a fractured hip undergo surgery, with 71% having surgery by the day following their presentation (NHFD 2017). In India, 95% of people with a fractured hip undergo surgery, but 21% experience delays exceeding two weeks (Rath 2017). The type of surgery is guided by the type of fracture. Intracapsular fractures are usually fixed with screws, or the hip is replaced with an arthroplasty, whereas extracapsular fractures are usually treated with an intramedullary nail or a sliding hip screw. The results of a Cochrane network meta-analyses examining the relative effectiveness of different implants for these two subgroups of hip fracture are reported in Lewis 2022b and Lewis 2022d. Hip fracture surgeries are substantial and invasive operations. Most people with these fractures are frail, have multiple comorbidities associated with age, including chronic anaemia, and there is a high risk of death in the perioperative and early postoperative period (Kannegaard 2010; Kenzora 1984; Lloyd 2019; Penninx 2006; Roche 2005). For example, in England, Wales, and Northern Ireland in 2016, the 30-day mortality rate was 6.7%, which rose to 30% at one year (NHFD 2017). However, fewer than half of those deaths were attributable to the fracture itself, which reflects the frailty of this population, and the associated high prevalence of comorbidities and complications. The impact of morbidity associated with hip fractures is similar to that of stroke, and entails a substantial loss of healthy life-years in older adults (Griffin 2015).

As a consequence of both the fracture and the urgent surgery required, people with a hip fracture sustain an acute blood loss, compounding any pre-existing anaemia (Foss 2006). Postoperative anaemia is associated with increased disability and delirium, reduced muscle strength, and reduced physical performance (Foss 2008; Penninx 2006; van der Zanden 2016). Beyond the perioperative period, anaemia is associated with an increased risk of falls, hospitalisation, and mortality (Penninx 2005; Penninx

2006). In this elderly, frail, and anaemic population, perioperative allogeneic blood transfusion (ABT) — meaning blood from an unrelated donor — is often required to correct anaemia and to improve the oxygen-carrying capacity of the blood. Blood from a donor is a costly and potentially scarce resource (Murphy 2013; WHO 2021). At the time of writing this overview, NHS Blood and Transport issued a four-week 'amber alert' to hospitals in the UK to put in place management plans to protect blood stocks because of uncertainty in the supply and availability of donated blood.

There is uncertainty about the benefit-risk ratio for ABT (Brunskill 2015). As documented by UK haemovigilance systems, risks of ABT include transfusion-transmitted infections, transfusion reactions, circulatory overload, and errors in the transfusion process (Serious Hazards of Transfusion). ABTs may increase rates of local (e.g. wound) and systemic (e.g. pneumonia) infections in those who are postoperative, which may be attributable to the immunomodulatory effect of allogeneic blood on the recipient (Rohde 2014), though this has not been reported in later reviews (Carson 2021). Allogeneic blood use within 30 days of surgery has been shown to cause deep wound infections in people following hip fracture surgery (Holleyman 2016). In people with a fractured hip, a severe complication, such as a deep infection, can be fatal. Notably, a World Health Organization priority is to reduce perioperative infections (Alleganzi 2016). In people with a hip fracture, postoperative transfusion is also associated with a higher risk of delirium (Wang 2018b), and is independently associated with increased length of hospital stay in orthopaedic surgery (Monsef 2014).

Delirium is a common complication after a hip fracture, or its surgical treatment (Inouye 2014). Delirium is an acute confusional state that is under recognised, but can have a serious impact on outcomes for a person, including increased mortality (Inouye 2014; Marcantonio 2017). Anaemia and a restrictive blood transfusion have been associated with an increased risk of delirium, however, these factors are not included in validated risk-factor models for delirium (Blandford 2016; Inouye 2014; van der Zanden 2016).

### Description of the interventions

Patient Blood Management (PBM) refers to an international, evidence-based approach that aims to optimise the care of people who might need a blood transfusion. The strategies in PBM include optimal use of transfusion therapy that aims to avoid inappropriate use of blood or blood components (National Blood Transfusion Committee 2014).

Practitioners have advocated alternative interventions that aim to prevent or minimise blood loss, the tendency to administer inappropriate transfusions, or both (Stanworth 2011). This overview considers these alternatives delivered during the perioperative period. Examples of pharmacological interventions include antifibrinolytics, desmopressin, fibrinogen, and fibrin and non-fibrin sealants, which all support blood clotting or the strengthening of blood clots, and therefore, may reduce bleeding (Desborough 2016). Non-pharmacological interventions are wide-ranging, and include methods to minimise blood loss (such as surgical approaches that are less invasive), alternative surgical positioning of the person undergoing surgery, intraoperative temperature control, and methods to improve the oxygen-carrying potential of the blood, such as oxygen therapy.



## How the intervention might work

The varied strategies for PBM that may reduce or avoid red blood cell transfusion work by minimising blood loss, and reversing anaemia. Each intervention has multiple and different mechanisms of action.

### Pharmacological interventions

We will include pharmacological agents that minimise blood loss by modifying the stages of blood coagulation.

- Fibrinogen. This is a glycoprotein complex that is cleaved to produce the fibrin monomers that are essential to clot formation. This agent is given to replace fibrinogen that may be lost during acute bleeding (with insufficient time to reproduce further fibrinogen in the liver). It is converted by thrombin to fibrin and then to a fibrin-based blood clot (Najafi 2014).
- Factor XIII and factor VIIa. Factor XIII enables the cross-linking of fibrin monomers to the fibrin matrix, which makes the clot more stable (Gödjje 2006). Factor VIIa is also a protein in the coagulation matrix that works in conjunction with tissue factor found on the outside of blood vessels, and may improve haemostasis at the site of injury (Simpson 2012).
- Desmopressin. This synthetic vasopressin stimulates the release of factor VIII and von Willebrand factor, promotes platelet adhesiveness to the vascular endothelium, and also works to improve clot stability (Leino 2010).
- Antifibrinolytics. These include tranexamic acid, aprotinin, and epsilon-aminocaproic acid. These agents inhibit the natural enzymatic breakdown of fibrin clots (fibrinolysis), making the clots longer lasting and more stable (Yuan 2019).
- Fibrin sealants/glue. These are used as a topical application, containing fibrinogen and thrombin; they act to bind the damaged tissue through clot formation when applied directly to the site of the tissue damage (Randelli 2013).
- Non-fibrin sealants. These use components other than fibrin, with the same intention to seal a wound without sutures through clot formation (Scognamiglio 2016).

We will also include other pharmacological agents given to reverse the effect of anticoagulants. To manage comorbidities, people may take anticoagulants, which are given to thin the blood by reducing coagulation and increasing the time to clot formation. Specific reversal agents are given depending on the anticoagulant agent (e.g. protamine sulfate for heparin and enoxaparin; 4F-PCC for warfarin and fondaparinux; activated charcoal for apixaban; idarucizumab for dabigatran (Christos 2016)).

In addition, we will include agents given to restore normal blood composition.

- Erythropoiesis-stimulating agents, such as erythropoietin, may be used to stimulate the bone marrow to make red blood cells (Alsaleh 2013).
- Iron, vitamin B12, and folate replacement therapy. Essential for the development of red blood cells, these haematons may be given perioperatively to address the management of anaemia directly, by stimulating the production of red blood cells through erythropoiesis (Cuenca 2007; Rowlands 2013).

### Non-pharmacological interventions

- Approaches used during and after surgery to reduce or manage intraoperative or postoperative blood loss, including secondary haemorrhage. These approaches are wide-ranging. Examples include: electrocautery or diathermy during surgery to cauterise (seal) damaged tissue to reduce excessive bleeding; positioning of the person undergoing surgery, which may influence blood loss by changes in local tissue blood pressure and hydrostatic blood pressure at the wound site (Pace 2008); internal fixation implants, which may reduce blood loss by improving the stabilisation of the bone (Parker 2001); surgical procedures, such as osteotomy of the femur, which may stabilise the fracture before surgery or reduce the risk of further collapse of the fracture site; or cement augmentation, which may improve the stabilisation of the internal fixations at the fracture site (Parker 2009); dressings, such as compression bandages, which may reduce blood loss after surgery by increasing external pressure and allowing for clot formation (Tan 2016); perioperative fluid therapy and optimisation methods for volume expansion, using alternative products to blood, such as colloids or saline solutions (Lewis 2016; Lewis 2018).
- Intraoperative cell salvage and autologous blood transfusion. This intervention involves the collection of blood lost during or after surgery (or collected from the person before planned surgery), which is then re-infused into the person in order to replace the lost volume of blood (Esper 2011).
- Temperature management during surgery. As hypothermia may slow down the enzymatic reactions and impair blood coagulation, active warming or methods to maintain normothermia may reduce blood loss (Yi 2018).
- Oxygen therapy. Increasing the partial pressure of oxygen in the lungs will increase oxygen saturation of the blood, and may reduce the need for ABT.

Whilst interventions may help to restore or maintain blood composition, or both, these interventions may increase other risks to the person. For example, hypotension may be more frequent with desmopressins (Desborough 2017); the effect of antifibrinolytics on the risk of thromboembolytic events is uncertain (Ker 2012); and it is uncertain whether some colloids increase the risk of allergic skin reactions (Lewis 2018).

### Why it is important to do this overview

A variety of pharmacological and non-pharmacological interventions are available in addition to ABT, and these could be used in a PBM approach for people who present for hip fracture surgery. However, blood transfusion and alternative interventions, delivered independently or as part of bundles of care, have varying degrees of benefit, risk, and cost-effectiveness. Cochrane and non-Cochrane systematic reviews, international guidelines for red blood cell transfusion therapy, and a recent international initiative on PBM have all evaluated the evidence for these interventions (Carson 2021; Carson 2016b; Mueller 2019; NICE 2015). Given the diversity of interventions, an overview provides the best opportunity to evaluate these treatment options. This overview aims to identify existing evidence from systematic reviews, and to describe the effectiveness of any intervention that has been applied to people with hip fracture, as an alternative to ABT. This overview is written at a time when supply and availability of blood is uncertain in the UK; therefore, it is an important and timely evaluation.

## OBJECTIVES

To summarise the evidence from Cochrane Reviews and other systematic reviews of randomised or quasi-randomised trials evaluating the effects of pharmacological and non-pharmacological interventions, administered perioperatively, on reducing blood loss, anaemia, and the need for allogeneic blood transfusion in adults undergoing hip fracture surgery.

## METHODS

### Criteria for considering reviews for inclusion

#### Types of reviews

We included systematic reviews of randomised controlled trials (RCTs) and quasi-RCTs; we included Cochrane Reviews and non-Cochrane systematic reviews. We included a systematic review if it reported a comprehensive search strategy, clear study inclusion criteria, and a narrative or quantitative synthesis of included studies.

Some systematic reviews included studies with non-randomised study designs. We only included systematic reviews if it was possible to extract data separately for RCTs and quasi-RCTs. This was reported in systematic reviews as sensitivity analyses, or data for individual RCTs were available from forest plots.

#### Types of participants

We included systematic reviews that selected studies with the following participant group.

- Adults with a fragility hip fracture, from a low-energy trauma, undergoing surgery.
- Fractures may be intracapsular (displaced and undisplaced) or extracapsular (trochanteric or subtrochanteric), and may be stable or unstable.

We excluded systematic reviews that selected only studies of participants undergoing elective hip arthroplasty, who had not sustained a fragility fracture; unless clearly stated, we assumed that reviews of arthroplasty surgery were for elective indications and not the result of hip fracture.

We would have preferred to include only reviews that included RCTs of participants with hip fracture, as this would provide the most direct evidence for our overview. However, as anticipated, some systematic reviews included studies with mixed populations, some of which were not directly eligible for inclusion in the overview, such as hip arthroplasty without fracture, or hip and knee arthroplasty studies (which may include some participants with hip fracture). We took a pragmatic approach to such reviews. Therefore, we included systematic reviews of mixed populations in the overview in the absence of direct evidence for each intervention. If we reported findings from these reviews, we planned to ensure that this evidence was clearly highlighted for likely indirectness.

#### Types of interventions

We included systematic reviews of studies that evaluated the effects of pharmacological or non-pharmacological interventions for preventing or minimising blood loss, for treating the effects of anaemia by improving the oxygen-carrying potential of the blood, and for reducing the need for allogeneic blood transfusion. We

included interventions that were given during the perioperative period.

Comparisons were between categories of intervention (e.g. pharmacological versus non-pharmacological), or within-category (e.g. two different types of surgery), or an active treatment against a control (standard of care or placebo). If systematic reviews had included multiple interventions, we planned to only include data from the interventions that were relevant to this review.

In our overview, we categorised pharmacological interventions and non-pharmacological interventions as two separate comparison groups.

#### Pharmacological interventions

We included the following types of interventions.

- Fibrinogen
- Factor VIIa and factor XIII
- Desmopressin
- Antifibrinolytics (tranexamic acid; aprotinin; epsilon-aminocaproic acid)
- Fibrin and non-fibrin sealants and glue (excluding surface dressings)
- Agents to reverse the effect of anticoagulants (e.g. protamine sulfate; 4F-PCC; activated charcoal)
- Erythropoiesis-stimulating agents
- Iron, vitamin B12, folate replacement therapy

#### Non-pharmacological interventions

We included the following types of interventions.

- Approaches used during and after surgery to reduce or manage intraoperative or postoperative blood loss, including secondary haemorrhage: e.g. surgical procedures, implants, use of diathermy or electrocautery, dressings, perioperative fluid management, positioning of the person during surgery
- Intraoperative cell salvage and autologous blood transfusion
- Temperature management: e.g. normothermia versus hypothermia, different types of intraoperative warming devices
- Oxygen therapy

We anticipated that some interventions could be used concomitantly as part of an individualised package (e.g. goal-directed management). We included a systematic review if the intervention was evaluated separately, rather than as part of a package. We collected information on these concomitant treatments along with other descriptive information about the reviews.

#### Type of outcome measures

We planned to collect measures that were plausibly linked to the interventions of interest in this overview, and those that people who had suffered a hip fracture had prioritised in the published hip fracture core outcome set ([Haywood 2014](#)).

#### Primary outcomes

- Number of people requiring allogeneic blood transfusion (ABT)



- Volume of transfused allogeneic blood (packed red blood cells; in units or millilitres)

### Secondary outcomes

- Postoperative delirium. We accepted validated measurement tools, such as the Confusion Assessment Method or Diagnostic and Statistical Manual of Mental Disorders, measured in the early postoperative period (up to 72 hours).
- Postoperative cognitive dysfunction. We accepted validated measurement tools, such as the Mini-Mental State Examination or the Digit Symbol Substitution Test, measured in the postoperative period (up to 30 days).
- Adverse events experienced by participants within 30 days of surgery, such as postoperative infection, acute respiratory distress syndrome, and thromboembolism
- Activities of daily living (ADL) at four months postoperatively. We used validated measurement tools, such as the Barthel Index or Functional Independence Measure.
- Health-related quality of life (HRQoL) at four months postoperatively. We used validated measurement tools, such as the SF-36 or EQ-5D.
- All-cause mortality at one month postoperatively.
- All-cause mortality at four months postoperatively.

In addition, we proposed to collect data for ADL, HRQoL, and mortality measured at a longer follow-up, after four months and up to one year postoperatively. We anticipated that some outcomes would be reported at different time points or using different measurement tools to those specified above. We included all data for these specified outcomes and reported where time points differed. If non-validated measurement tools had been used, we planned to report the findings, but would have considered downgrading the certainty of the evidence.

### Search methods for identification of reviews

We searched the following databases for relevant systematic reviews.

- Cochrane Database of Systematic Reviews (CDSR; 2022, Issue 1) in the Cochrane Library (searched 14 January 2022)
- MEDLINE OvidSP (1946 to 5 January 2022)
- PubMed (for e-publications ahead of print only; searched 6 January 2022)
- Embase OvidSP (1974 to 5 January 2022)
- Epistemonikos (searched 18 January 2022)
- PROSPERO (searched 6 January 2022)
- Transfusion Evidence Library ([transfusionevidencelibrary.com](http://transfusionevidencelibrary.com); 1950 to 7 January 2022)
- Web of Science Core Collection (Science Citation Index Expanded (SCI-EXPANDED); 1945 to 7 January 2022; Conference Proceedings Citation Index - Science (CPCI-S; 1990 to 7 January 2022); Book Citation Index - Science (BKCI-S 2005 to 2007; searched 7 January 2022)

We developed a subject-specific search strategy, with terms for the participant group combined with a study design filter for systematic reviews (see [Appendix 1](#)). For searches in MEDLINE and Embase, strategies were combined with adaptations of the Scottish Intercollegiate Guidelines Network (SIGN) Systematic Review filters

([www.sign.ac.uk/search-filters](http://www.sign.ac.uk/search-filters)); we adapted these filters for other databases. We did not restrict our search by language or publication date. We also conducted backward-citation searches (by looking through reference lists of eligible reviews).

### Data collection and analysis

We based the methods for data collection and analysis on those described by [Pollock 2022](#).

### Selection of reviews

We used reference management software to collate the results of searches and to remove duplicates ([Endnote](#)). We used [Covidence](#) software to screen results of the search of titles and abstracts, and to identify potentially relevant studies. We used standard Cochrane methods, using two overview authors (SL and MP) to independently screen titles and abstracts, and source full-texts ([Higgins 2022](#)). We selected systematic reviews for inclusion in the overview that met the review design, participant, and intervention criteria above. We resolved disagreements through discussion, or if necessary, through input from a third author. We recorded the number of papers retrieved at each stage and reported this information using a PRISMA flow chart. In the overview, we reported brief details of closely related but excluded reviews.

### Data extraction and management

We collected and reported the following descriptive information and quantitative data reported by the systematic review authors.

- Review criteria (primary aim or objectives of the review; types of study designs; types of participants; types of interventions and comparisons; types of outcomes)
- Review search details (date of last search; date range of searches; number and names of databases searched; restrictions or limitations on searches, such as language of publication)
- Characteristics of primary studies in reviews (primary study objectives; number of studies; types of study designs, details of participants, and details of interventions and comparisons; methods of risk of bias assessments and risk of bias judgements on included studies; judgements on the certainty of the evidence)
- Outcomes measured and reported in the review (methods and units of measurement; time points of measurement; effect estimates for dichotomous and continuous outcome data)
- Other information (review protocol; methodology to select studies and extract data; tools used to assess risk of bias, or certainty of the evidence, or both; methodology or decisions related to meta-analysis; sources of funding and conflicts of interest)

Two overview authors (SL and MP) independently extracted data and compared results, using a data extraction form in [Covidence](#). We resolved disagreements through discussion, or if necessary, through input from a third author. In the event of missing information in reviews regarding primary study characteristics or outcome data, we referred to the primary study reports. In the event that important information was missing, we attempted to contact review authors. We noted any outstanding gaps in coverage of data.

Using [Review Manager 2020](#), we presented tables to summarise characteristics of included systematic reviews, and tables to

summarise characteristics of primary studies in the included reviews.

We acknowledge the risk of overlapping systematic reviews when conducting overviews. Therefore, we mapped which primary studies were included in which systematic review(s). Because primary studies may be reported using different references in each systematic review, we considered study characteristics to help determine whether primary studies were the same. We used a table specifically to present overlap, and described the number and size of overlapping studies, and the amount of weight they contributed to the analyses. We were guided by the work of [Pieper 2014](#) to calculate a numerical measure of any overlap.

### Assessment of methodological quality of included reviews

We assessed risk of bias in systematic reviews using the AMSTAR 2 critical appraisal tool for systematic reviews and its related guidance tools ([Shea 2017](#)). Two overview authors (SL and MP) independently considered the 16 questions of the appraisal tool for each included systematic review ([Appendix 2](#)). We resolved disagreements through discussion, or if necessary, through input from a third author. We presented a table that provided a judgement for each item in the assessment tool, to explain how we rated our confidence in the results in each systematic review.

AMSTAR 2 is not designed to generate an overall score. A high score may disguise critical weaknesses in specific domains, such as an inadequate literature search or a failure to assess risk of bias in individual studies ([Shea 2017](#)). Therefore, we took account of the potential impact of an inadequate rating for each item, as these inadequacies may weaken the confidence that we can have in a systematic review's findings. Using our assessments from AMSTAR 2, we rated our overall confidence in the results of each systematic review as follows:

- High (no, or one non-critical weakness) — the systematic review provides an accurate and comprehensive summary of the results of the available studies that address the question of interest;
- Moderate (no critical flaws, and more than one non-critical weakness) — the systematic review has more than one weakness but no critical flaws. It may provide an accurate summary of the results of the available studies that address the question of interest;
- Low (one critical flaw, with or without non-critical weaknesses) — the review has a critical flaw and may not provide an accurate and comprehensive summary of the available studies that address the question of interest;
- Very low (more than one critical flaw, with or without non-critical weaknesses) — the review has more than one critical flaw and should not be relied on to provide an accurate and comprehensive summary of the available studies that address the question of interest.

### Data synthesis

We planned to present outcome data separately for pharmacological interventions and non-pharmacological interventions. Based on the findings, we then grouped systematic reviews by appropriate groups of interventions (e.g. agents with the same mode of action, such as antifibrinolytics).

We presented narrative summaries according to the type of intervention and following the order of our outcomes. We extracted outcome data as they were presented in each systematic review, to include effect estimates (and 95% confidence intervals). It was not our intention to make inferences about effects using indirect comparisons from more than one systematic review; therefore, where relevant, we reported summaries separately for each systematic review. We enhanced the presentation of our findings using tables and figures, as necessary, and we adhered to the methods of narrative synthesis, developed from the work of [Campbell 2020](#).

In the narrative summaries, we planned to take account of our prespecified subgroups (as below). We took account of studies with a mixed population (such as those that included participants who had knee arthroplasty, as well as participants who had hip arthroplasty; or those that included participants who had intramedullary nailing for humeral shaft fractures, as well as participants who had intramedullary nailing for intertrochanteric fractures), or those that included RCTs and non-randomised studies. If reviews included studies with a mixed population or both types of study design, we aimed primarily to report data only for the types of participants consistent with the overview criteria; if data were not reported separately, we highlighted when the evidence was indirect.

In the event we found multiple overlapping reviews with a large measure of overlap, we planned to adopt a hierarchy to prioritise from which systematic review we reported data: to prioritise Cochrane systematic reviews, followed by the most recent systematic review, the systematic review with the highest methodological quality, the most relevant systematic review, and the most comprehensive systematic review. However, whilst still considering all of these criteria, we adopted a pragmatic approach in order to ensure that we selected the most relevant review. We acknowledge that any approach, whilst avoiding double-counting, included the potential for missing data. We explored the effects of our approach in sensitivity analyses.

We planned to consider re-analysis of outcome data only in these prespecified circumstances:

- If re-analysis allowed for the inclusion of a specific subgroup; or
- To ensure that effect estimates were reported in a consistent manner that was easily understood by the end-user of the overview.

If re-analysis of outcome data had been necessary, we would have adhered to standard meta-analytic principles, according to [Higgins 2022](#).

### Subgroup analysis and investigation of heterogeneity

We collected information from review reports for the following prespecified subgroups.

- Time of administration of the intervention (preoperatively, intraoperatively, postoperatively)
- Age of participants (to include 'elderly', according to specified age cut-offs, 'frail elderly')
- Baseline comorbidities (using validated scales or scoring systems that measure comorbidities to indicate physical status,

such as the American Society of Anesthesiologists (ASA) physical status classification system, or the Charlson Comorbidity Index

- People at higher risk of bleeding

We also collected information on an additional subgroup.

- Route of administration (intravenous or topical)

Firstly, we noted whether any of the systematic reviews included interventions or participants from only one subgroup (for example, only frail elderly participants); for this, we assessed both the review inclusion criteria and the characteristics of studies included in each review. Secondly, we noted whether the reviews conducted subgroup analyses for any of our prespecified subgroups. We described differences in review characteristics between systematic reviews (e.g. such as study design eligibility) in [Description of included reviews](#). In the event of differences in subgroup categories between systematic reviews, we used a narrative approach to describe the outcome data according to these subgroups (in [Effects of interventions](#)); we reported these findings for all outcomes relevant to this overview. We reported effect estimates, alongside a narrative description, in the event that review authors noted differences between subgroups.

### Sensitivity analysis

We used sensitivity analyses to explore the effects of decisions made during the overview process. In particular, we examined and reported the effects of presenting data according to a hierarchical approach. We compared the effect estimates of systematic reviews which we prioritised using the hierarchical approach, with the effect estimates of the other systematic review(s). Where we observed important differences in effect estimates such that our interpretation of the findings differed (for example, when the direction of an effect estimate differed between reviews), we observed possible reasons for this, such as the dates of searches in the systematic reviews and the number of included studies, to establish whether the prioritisation of reviews in the hierarchy led to missing data.

### Summary of findings table and GRADE

Two overview authors independently assessed the certainty of the body of evidence associated with the following outcomes ([Guyatt 2008](#)).

- Number of people requiring allogeneic blood transfusion (ABT)
- Volume of transfused allogeneic blood
- Postoperative delirium
- Adverse events experienced by participants within 30 days of surgery
- Activities of daily living (ADL) at four months postoperatively
- Health-related quality of life (HRQoL) at four months postoperatively
- All-cause mortality at one month postoperatively

If data were only available at later time points, we planned to assess the certainty of the evidence for ADL, HRQoL, and all-cause mortality at available time points, up to one year postoperatively. For adverse events, we reported absolute effects for the type of adverse event that included the most participants. We used the comments section of the summary of findings table to report the effect estimates of other adverse events.

The GRADE approach appraises the certainty of a body of evidence based on the extent to which we can be confident that an estimate of effect or association reflects the item being assessed. Evaluation of the certainty of a body of evidence considers risk of bias, directness of the evidence, heterogeneity of the data, precision of the effect estimates, and risk of publication bias.

Because we identified overlapping reviews, we only reported data from prioritised reviews in the summary of findings table. We used more than one review to report data for as many of our selected outcomes as possible. Our prioritised reviews did not report summary of findings tables or conduct their own GRADE assessments, therefore, we made GRADE judgements based on the information reported in these reviews. We were also guided by the checklist in [Meader 2014](#) when assessing GRADE in published reviews. We used risk of bias tables reported in the review, as well as the results of any reported sensitivity analyses, when considering limitations owing to risk of bias. For directness of the evidence, we considered whether to downgrade the certainty of the evidence for indirectness if reviews included studies with a mixed surgical population (such as participants having other types of orthopaedic surgery).

The GRADE system rates the certainty of the evidence according to the following categories.

- High - further research is very unlikely to change confidence in the estimate of effect
- Moderate - further research is likely to have an important impact on the confidence in the estimate of effect, and may change the estimate
- Low - further research is very likely to have an important impact on confidence in the estimate of effect, and is likely to change the estimate
- Very low - any estimate of effect is very uncertain

We constructed summary of findings tables using the GRADE GDT software ([GRADEpro GDT](#)). Because reviews were unavailable for non-pharmacological interventions, we constructed tables only for the following comparison.

- Pharmacological interventions for reducing red blood cell transfusion in adults undergoing hip fracture surgery

Rather than separately presenting the data within the same summary of findings table for each group of interventions (e.g. agents with the same mode of action such as antifibrinolytics), we constructed separate summary of findings table for each group of pharmacological interventions.

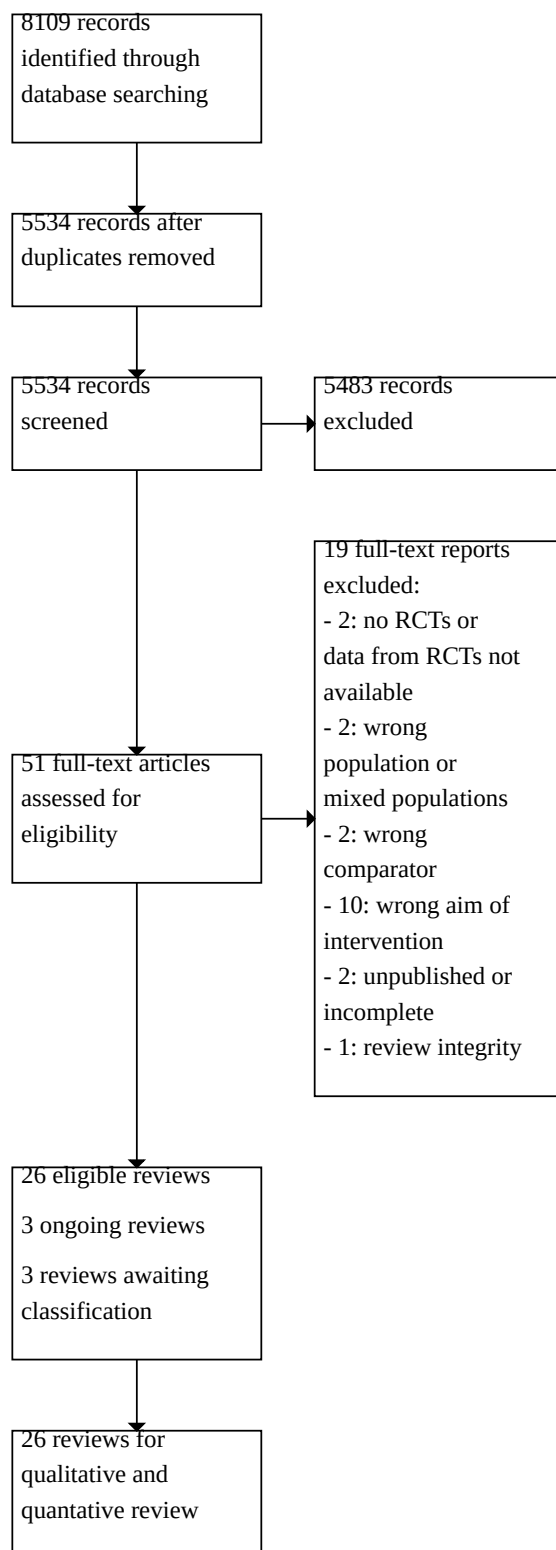
## RESULTS

For this overview of reviews, we searched for Cochrane and non-Cochrane systematic reviews of randomised controlled trials (RCTs) of interventions for reducing red blood cell transfusion in adults undergoing hip fracture surgery. In total, we identified 8109 records from the following databases: Cochrane Database of Systematic Reviews (172), MEDLINE (1372), PubMed (94), Embase (2263), Epistemonikos (1652), PROSPERO (1114), Transfusion Evidence Library (20), and the Web of Science (1422). After removing 2575 duplicates, we screened 5534 titles and abstracts. We excluded 5483 records at this stage, and screened 51 full texts against our inclusion and exclusion criteria (see [Criteria for considering reviews](#)

for inclusion). We excluded 19 records that did not meet the inclusion criteria following closer inspection; we summarise these

19 reviews, with reasons for their exclusion, in [Appendix 3](#). The selection process is shown in [Figure 1](#).

**Figure 1.**





**Figure 1. (Continued)**



During the search process, we contacted 10 review authors identified in PROSPERO to ask if their reviews were completed. We received replies from six review authors (Agius 2022; Charity 2015; Chawla 2018; Gibbs 2020; Miangul 2021; Sinclair 2020); of these, two were able to supply either published or unpublished review information that we could use in the overview (Agius 2022; Sinclair 2020). We received no reply from four review authors.

### Description of included reviews

Overall, we found 26 systematic reviews. Three ongoing reviews are described in Appendix 4, and three reviews awaiting classification are described in Appendix 5. We found no reviews for non-pharmacological interventions, and only two types of pharmacological interventions (tranexamic acid and iron). Here, we summarise the characteristics of reviews for these different intervention types.

#### Tranexamic acid

We included 17 reviews of tranexamic acid (Agius 2022; Baskaran 2018; Farrow 2016; Haj-Younes 2020; Jiang 2019; Liu 2022; Luo 2020; Masouros 2022; Qi 2019; Wang 2017a; Xiao 2019; Xing 2020; Yu 2020; Zhang 2017; Zhang 2018; Zhou 2019a; Zhu 2018). The earliest search was conducted in June 2016 (Farrow 2016); the latest in February 2021 (Agius 2022; Liu 2022; Masouros 2022). Characteristics of these reviews are summarised in Table 1; more detailed information is in Appendix 6.

Most reviews included only RCTs; those that included a mix of study types reported data separately for RCTs. All reviews included people undergoing surgery for hip fracture. Taking into account the overlap between reviews, 2642 participants with hip fracture were randomised to the included RCTs in these reviews. Whilst some reviews specified the inclusion of participants over a certain age (> 60 years of age in Luo 2020 and Xing 2020; > 70 years of age in Masouros 2022), this was not usually specified; no studies included only 'frail elderly'. In addition, no studies specified the inclusion of a subset of participants according to baseline comorbidities or risk of bleeding, and no reviews reported this level of detail in their characteristics tables of included studies.

Whilst most reviews did not limit the types of surgical treatment, five of the reviews included only studies of trochanteric fractures with internal fixation (Luo 2020; Wang 2017a; Xing 2020; Zhou 2019a; Zhu 2018).

In seven reviews, tranexamic acid was only administered intravenously (Agius 2022; Baskaran 2018; Haj-Younes 2020; Masouros 2022; Qi 2019; Xiao 2019; Zhang 2017). The remaining reviews included a mix of intravenous and topical administration, or a combination of both types of administration. No reviews included a specific dose or formulation. From summary information of study characteristics, all reviews included studies in which administration of tranexamic acid was before, during, or after surgery, or a combination of these time points.

All reviews reported outcome data for the number of people who had an allogeneic blood transfusion (ABT) and adverse events. In addition, two reviews reported the volume of transfused blood (Luo 2020; Masouros 2022). Types of adverse events varied between studies, but overall, included thromboembolic events, deep vein thrombosis (DVT), pulmonary embolism, cerebrovascular accident, acute coronary syndrome, myocardial infarction, renal failure, wound complications, haematoma, and infection. Three reviews also reported mortality (Xing 2020; Yu 2020; Zhang 2018). No reviews of tranexamic acid reported postoperative delirium, postoperative cognitive dysfunction, activities of daily living, or health-related quality of life.

Three reviews reported funding from a source that we deemed to be independent, such as a government research body (Qi 2019; Xing 2020; Zhou 2019a); four reviews did not specify the source of research funding (Jiang 2019; Masouros 2022; Zhang 2017; Zhang 2018). The remaining studies reported that they received no funding. Most review authors declared that they had no conflicts of interest; only one study did not specify this information (Masouros 2022). For specific declared conflicts of interest in Perel 2013, see information in Appendix 6.

Overall, this set of reviews included 29 RCTs. We found that the measure of study overlap was very high, and we used methods described by Pieper 2014 to formally calculate the level of overlap (overlap = 65.5%; covered area (CA) = 31.2%; corrected covered area (CCA) = 26.9%); see Table 2. Therefore, we used a hierarchical approach to decide from which review to report effect estimates. As the only Cochrane Review in this set of reviews was published in 2013, we instead prioritised by the publication that had the most recent search. Therefore, we prioritised the data from Liu 2022. However, as Liu 2022, did not report outcome data for all outcomes, we considered other reviews, again prioritising by date of search. Therefore, we also prioritised data from Masouros 2022 in order to report data for volume of transfused blood, which was not reported in Liu 2022. Liu 2022 included 24 RCTs with broad inclusion criteria. Participants in Liu 2022 had internal fixation or arthroplasty for different types of hip fracture. Tranexamic acid was given either intravenously or by topical administration; it was given preoperatively, and sometimes also intraoperatively and postoperatively. No studies included intramuscular administration. In 20 of the studies included in Liu 2022, participants received DVT prophylaxis, and participants in most studies were screened for DVT, using ultrasound. Masouros 2022 included 10 RCTs, again with broad inclusion criteria, which did not specify type of surgery or fracture type. Study characteristics for these two reviews are summarised in Table 3 and Appendix 6.

#### Iron and erythropoietin (EPO)

We included nine reviews of iron or iron with EPO (Chen 2021; Gomez-Ramirez 2019; Lin 2013; Schack 2019; Shah 2018; Shin 2019; Sinclair 2020; Smith 2020; Yang 2011). At the time of the search and data extraction for this review, Sinclair 2020 was still unpublished, and all information and outcome data from the review were supplied through personal communication with



the review authors. Communication from Sinclair and colleagues included an unpublished manuscript prepared for a journal; we used this manuscript to extract data and make our AMSTAR 2 judgements. Searches in the included reviews were conducted between May 2011 (Yang 2011) and January 2021 (Sinclair 2020). Characteristics of these reviews are summarised in Table 4 and more detailed information is in Appendix 7.

Only two reviews included only RCTs, however, all reviews reported data for RCTs that could be extracted separately from data for non-randomised trials; not all the data for RCTs were pooled. Only two reviews included only studies of participants who had hip fracture (Chen 2021; Sinclair 2020); again, it was possible to extract separately pooled or unpooled data for hip fractures from the remaining reviews of mixed populations. The type of treatment for hip fractures was not specified in these two reviews, and we assumed they included participants undergoing any type of treatment. Taking into account the overlap between the reviews, 1281 participants with hip fracture were randomised to the included RCTs. Age limits at recruitment were limited in Chen 2021 (> 64 years of age), but all other reviews included studies regardless of participant age; no studies included only 'frail elderly'. As for reviews of tranexamic acid, we found that no studies specified the inclusion of a subset of participants according to baseline comorbidities or risk of bleeding, and no reviews reported this level of detail in their characteristics tables of included studies.

All reviews reported the number of people who needed a blood transfusion, and all but two reviews reported the volume of transfused blood (Gomez-Ramirez 2019; Schack 2019). All reviews reported mortality and most also reported adverse events. The types of adverse events were wide-ranging, and differed between studies. Examples of adverse events included gastrointestinal symptoms, general discomfort, skin rash, infection, and thromboembolic events. Three studies reported health-related quality of life (Shah 2018; Sinclair 2020; Smith 2020). In addition, Sinclair 2020 reported activities of daily living and Shah 2018 reported incidences of delirium. No studies reported postoperative cognitive dysfunction.

Six reviews received either no funding or no external funding for their research (Gomez-Ramirez 2019; Lin 2013; Shah 2018; Shin 2019; Sinclair 2020; Smith 2020); one review received funding from a government research body, which we deemed to be independent (Chen 2021). Funding sources were not specified in Schack 2019 or Yang 2011. Three reviews declared that they had no conflicts of interest (Chen 2021; Shin 2019; Smith 2020), and three reviews did not specify (Lin 2013; Schack 2019; Yang 2011). For

specific declared conflicts of interest in Gomez-Ramirez 2019, Shah 2018 and Sinclair 2020, see information in Appendix 7.

Overall, this set of reviews included seven RCTs. Again, we found that the measure of study overlap was very high (overlap = 85.7%; CA = 42.9%; CCA = 35.7%); see Table 5. We found no Cochrane Reviews in this set of reviews. Sinclair 2020 had the most recent search date as well as the highest overall scores from AMSTAR 2 (see Methodological quality of included reviews). However, because data from this review were unpublished, and therefore, not subject to external peer review, we did not prioritise this review for the reporting of outcome data. Subsequently, our hierarchical approach for this comparison considered which was the most relevant systematic review. Only two reviews in this comparison reported effect estimates for our primary outcome, with pooled data taken only from RCTs in a hip fracture surgical population (Shah 2018; Yang 2011). As Shah 2018 had the most recent search, we prioritised data from Shah 2018, assuming this to be the most relevant review for this comparison. Shah 2018 included only RCTs, but with a broader non-elective surgical population that included hip fracture surgery, of which there were two RCTs. Both studies compared iron given intravenously to a control; one of the studies also included a comparison group of iron with EPO. In both studies, treatment was given preoperatively; in one study, further doses were also given postoperatively. Study characteristics from Shah 2018 are summarised in Table 6; because review authors provided only minimal study characteristics, we obtained additional detail from the primary study reports.

## Methodological quality of included reviews

### AMSTAR 2 for tranexamic acid

Using the methods described in Assessment of methodological quality of included reviews, we rated our overall confidence in these reviews from very low to moderate (Table 7). We rated our overall confidence as moderate in two reviews (Farrow 2016; Jiang 2019), low in five reviews (Liu 2022; Masouros 2022; Yu 2020; Zhang 2017; Zhu 2018), and very low in the remaining 10 reviews. We present a narrative summary of our judgements on the methodological quality of reviews for this treatment in Appendix 8.

### Risk of bias assessment for prioritised reviews for tranexamic acid

Because we reported the outcome data for Liu 2022 and Masouros 2022, we also collected the risk of bias assessments conducted by these review authors (see Figure 2 and Figure 3).

**Figure 2. Liu 2022 risk of bias summary**

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Ahmed 2020	+	+	+	+	+	+	?
Baruah 2016	?	?	?	?	+	+	+
Chen 2019	+	+	+	+	+	+	?
Drakos 2016	+	+	?	?	+	+	+
Emara 2014	?	?	+	+	+	+	+
Jordan 2019	+	+	-	-	+	-	+
Lei 2017	+	+	-	-	+	+	+
Li 2015	+	?	?	?	+	+	+
Luo 2018	+	+	+	+	?	+	+
Luo 2019	+	+	+	+	?	+	+
Mohib 2015	+	?	+	+	+	+	+
Sadeghi 2007	+	+	+	+	+	+	+
Schiavone 2018	?	+	+	+	+	+	?
Shi 2018	?	?	?	?	+	+	?
Tengberg 2016	+	+	+	+	+	+	+
Tian 2018	?	?	?	?	+	+	+
Vijay 2013	+	+	+	+	+	+	?
Virani 2016	?	?	-	-	+	+	?
Wang 2021	+	?	?	?	+	+	+
Watts 2017	+	+	+	+	+	+	+

**Figure 2. (Continued)**

Watts 2017	+	+	+	+	+	+	+
Zhang 2020	+	+	+	+	+	+	+
Zhang 2020b	+	?	?	?	+	+	+
Zhou 2019b	+	+	+	+	+	+	+
Zufferey 2010	+	+	+	+	+	+	+

**Figure 3. Masouros 2022 risk of bias summary** When making judgements for the summary of findings table, we did not include risk of bias assessments for [Luo 2019](#), [Zhang 2022](#), and [Zufferey 2009](#); these studies did not provide data for the outcomes reported in our summary of findings table

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Chen 2019	+	+	+	+	+	+	?
Lei 2017	+	+	-	?	+	+	?
Luo 2019	+	+	+	+	+	+	?
Nikolaou 2021	+	+	+	+	?	+	?
Tengberg 2016	?	+	+	+	?	+	?
Tian 2018	+	?	?	+	+	+	?
Watts 2017	+	?	?	?	+	+	?
Zhang 2020	+	+	+	+	+	+	?
Zhou 2019	+	?	?	?	+	+	?
Zufferey 2009	+	?	+	+	+	+	?

In [Liu 2022](#), we noted that review authors had assessed six studies to be at low risk of bias in all domains ([Sadeghi 2007](#); [Tengberg 2016](#); [Watts 2017](#); [Zhang 2022](#); [Zhou 2019b](#); [Zufferey 2009](#)). Whilst all other studies included some judgements of unclear risks of bias, review authors judged three studies to be at high risk of bias for performance and detection bias ([Jordan 2019](#); [Lei 2017](#); [Virani 2016](#)), and judged [Jordan 2019](#) to also be at high risk of selective reporting bias.

In [Masouros 2022](#), we noted that all studies included some judgements of unclear risk of bias, with all having an unclear risk of bias in the domain of Other bias. Review authors judged one study to be at high risk of bias for performance bias ([Lei 2017](#)).

#### AMSTAR 2 for iron and iron with EPO

Using the methods described in [Assessment of methodological quality of included reviews](#), we rated our overall confidence in

these reviews from high to very low ([Table 8](#)). We assessed high confidence in one study ([Lin 2013](#)), moderate confidence in five reviews ([Chen 2021](#); [Schack 2019](#); [Shin 2019](#); [Sinclair 2020](#); [Smith 2020](#)), low confidence in two reviews ([Shah 2018](#); [Yang 2011](#)), and very low confidence in the remaining review ([Gomez-Ramirez 2019](#)). We present a narrative summary of our judgements of the methodological quality of reviews for this treatment in [Appendix 9](#).

#### Risk of bias for prioritised review for iron

Because we reported the outcome data for [Shah 2018](#), we also collected the risk of bias assessments conducted by Shah and colleagues for individual studies (see [Figure 4](#)). We noted that review authors had assessed both studies to be at low risk of bias for all domains, except for allocation concealment, for which risk of bias for [Bernabeu-Wittel 2016](#) was unclear.

**Figure 4. Shah 2018 risk of bias summary**

	Random sequence generation (selection bias)	Allocation concealment (selection bias)	Blinding of participants and personnel (performance bias)	Blinding of outcome assessment (detection bias)	Incomplete outcome data (attrition bias)	Selective reporting (reporting bias)	Other bias
Bernabeu-Wittel 2016	+	?	+	+	+	+	+
Serrano-Trenas 2011	+	+	+	+	+	+	+

## Effect of interventions

### Tranexamic acid

Here, we report the outcome data as presented in [Liu 2022](#) and [Masouros 2022](#). We prioritised the data from [Liu 2022](#) when data were available for our overview outcomes, otherwise, we reported data from [Masouros 2022](#). No reviews reported postoperative delirium, postoperative cognitive dysfunction, activities of daily living, or health-related quality of life. See the summary of findings in [Table 9](#).

### Primary outcomes

#### Number of people requiring allogeneic blood transfusion

Based on evidence in [Liu 2022](#), fewer people required ABT after receiving tranexamic acid (risk ratio (RR) 0.56, 95% confidence interval (CI) 0.46 to 0.68;  $I^2 = 60.1\%$ ; 21 studies, 2148 participants). [Liu 2022](#) presented a forest plot for each study in this effect estimate, but these data did not include participant numbers. Therefore, we extracted the number of participants separately from each primary study to include alongside this effect estimate. Of the 21 studies that reported data for this outcome, 17 studies (1785 participants) overlapped with studies in other reviews; hence, the weight of overlap in this effect estimate is 83%. Using information presented in [Liu 2022](#), we judged this to be moderate-certainty evidence. We downgraded the evidence by one level for publication bias, because [Liu 2022](#) identified a risk of publication bias (Egger's test  $P = 0.001$ ).

#### Volume of transfused allogeneic blood

Based on evidence in [Masouros 2022](#), fewer units of packed red blood cells (PRC) were transfused in participants receiving tranexamic acid (mean difference (MD) -0.53 units per person, 95% CI -0.27 to -0.80;  $I^2 = 78\%$ ; 7 studies, 813 participants). Of the seven studies that reported data for this outcome, three studies (252 participants) overlapped with studies in another review; giving a weight of overlap in this effect estimate of 31%. Using information presented in [Masouros 2022](#), we judged this to be moderate-certainty evidence. We downgraded the evidence by one level for inconsistency, because the effect estimate included substantial levels of statistical heterogeneity, which were not explained.

### Secondary outcomes

#### Adverse events

Based on evidence in [Liu 2022](#), there is probably little or no difference in the incidence of adverse events. Study authors reported:

- little or no difference in the incidence of DVT (RR 1.16, 95% CI 0.74 to 1.81;  $I^2 = 0\%$ ; 22 studies);
- little or no difference in the incidence of pulmonary embolism (RR 1.01, 95% CI 0.36 to 2.86;  $I^2 = 0\%$ ; 9 studies);
- little or no difference in the incidence of myocardial infarction (RR 1.00, 95% CI 0.23 to 4.33;  $I^2 = 0\%$ ; 8 studies);
- little or no difference in the incidence of cerebrovascular accident (RR 1.45, 95% CI 0.56 to 3.70;  $I^2 = 0\%$ ; 8 studies).

We were unable to report participant numbers for these effects as the names of individual studies were not included in the review report. Because we did not know which studies were included in these effect estimates, we could not determine the weight from

overlapping studies in these findings. We judged the evidence for adverse events to be moderate certainty. We downgraded the certainty of the evidence by one level because effect estimates were imprecise, i.e. the CIs included the possibility of both benefit and harm.

#### All-cause mortality at one month and at four months postoperatively

Based on evidence from 10 studies in [Liu 2022](#), there was little or no difference in mortality (RR 1.01, 95% CI 0.70 to 1.46;  $I^2 = 0\%$ ; 10 studies). The time point for mortality was not clearly reported, but we assumed from other information in the report that it included data measured both before and later than three months. Again, we were unable to report participant numbers because we could not determine from which studies the data were derived, so neither could we determine the weight of study overlap. We judged the evidence for mortality to be moderate certainty. We downgraded the evidence by one level because the effect estimate was imprecise, including the possibility of both benefit and harm.

### Sensitivity analysis

In a sensitivity analysis, we assessed the impact of selecting data from only [Liu 2022](#) and [Masouros 2022](#) by comparing the effect estimates from other reviews with the effect estimates from these two reviews (see [Appendix 10](#)). We found that all but one review reported effect estimates consistent with those in [Liu 2022](#), indicating that fewer people required ABT after receiving tranexamic acid. Only [Zhu 2018](#) reported an imprecise effect estimate, with evidence of both increased and reduced blood transfusions after tranexamic acid (RR 0.75, 95% CI 0.50 to 1.11); this effect estimate included considerable levels of statistical heterogeneity ( $I^2 = 98\%$ ), which were not explained by subgroup analyses. However, review authors conducted sensitivity analysis, and found that excluding [Baruah 2016](#) from their primary analysis led to a finding consistent with other reviews (RR 0.73, 95% CI 0.55 to 0.96). Only one other review reported volume of transfused blood, which was consistent with the effect estimate in [Masouros 2022](#).

Effect estimates for adverse events (which were DVT, pulmonary embolism, myocardial infarction, and cerebrovascular accident) were consistent with [Liu 2022](#), indicating little or no difference between treatments (see [Appendix 10](#)). Some reviews reported a composite outcome for adverse events, i.e. any thromboembolic events, and other reviews reported adverse events in addition to those reported in [Liu 2022](#); again, these are missing from the report of our primary findings, therefore, we reported the effect estimates for all adverse events in all reviews in [Appendix 11](#). Except for the incidence of haematoma, we found that all effect estimates indicated little or no difference between treatments in these adverse events. Both reviews that measured haematoma reported a decreased incidence after the use of tranexamic acid (RR 0.34, 95% CI 0.15 to 0.78;  $I^2 = 0\%$ ; 4 studies ([Jiang 2019](#)); and RR -0.05, 95% CI -0.09 to -0.00; 2 studies, 277 participants ([Xing 2020](#))).

Effect estimates from other reviews that reported mortality were similar to those in [Liu 2022](#).

### Subgroup analysis

We summarised whether each review included information on our subgroup categories in [Appendix 12](#). For completeness, we also listed all subgroup analyses conducted in each review in this



appendix (including subgroup analyses that were not specified in this overview); we did not report data for these subgroup analyses.

### Time of administration

Of the reviews in which time of administration was described, no reviews included the administration of tranexamic acid at only one time point (e.g. only preoperative or only postoperative administration). No reviews conducted subgroup analysis for this criterion, either.

### Age of participants

Only three reviews included an age cutoff in their inclusion criteria (Masouros 2022; Luo 2020; Xing 2020); of these, no reviews included only participants that might be described as 'frail elderly'.

However, three reviews reported subgroup data according to the age of participants (Farrow 2016; Zhang 2017; Zhang 2018). For older participants ( $\geq 76$  years of age), Farrow 2016 noted an imprecise effect estimate for blood transfusion requirement (RR 0.67, 95% CI 0.37 to 1.22;  $I^2 = 84\%$ ; 3 studies, 453 participants). The CI in this effect estimate included the possibility of both benefit and harm; we noted that these subgroup data included high levels of statistical heterogeneity. Such imprecision was not evident in their findings for participants  $\leq 75$  years of age, in which the effect estimate indicated a reduction in blood transfusion after tranexamic acid use (RR 0.48, 95% CI 0.33 to 0.72;  $I^2 = 10\%$ ; 4 studies, 297 participants); the result for younger participants was consistent with pooled data across all age groups in other reviews. Farrow 2016 found no evidence of a difference in the risk of thromboembolic events when subgrouping data according to these age categories. We noted that the data for these subgroups were not supported in the review by statistical results of formal tests for subgroup differences.

Both Zhang 2017 and Zhang 2018 reported subgroup data using an earlier age cutoff of 65 years, and noted no evidence of a difference in blood transfusion risk between the two age groups (results for both age groups were consistent with the pooled data in other reviews). Zhang 2018 also reported no evidence of a difference in thromboembolic events between the age groups. Again, none of these subgroup data were supported by statistical results of formal tests for subgroup differences.

### Baseline co-morbidities and people at higher risk of bleeding

No reviews specified inclusion criteria, or included only reviews from a distinct subgroup category, according to baseline comorbidities, or people who were at higher risk of bleeding.

Farrow 2016 reported subgroup data according to body mass index (BMI)  $\leq 40$  or  $> 40$ . Four of their six included studies provided this information, all of which included participants with a BMI  $\leq 40$ ; review authors did not explain whether BMI status was absent in the remaining two studies. In this smaller subgroup of participants, Farrow 2016 found an imprecise effect estimate for ABT requirement (RR 0.73, 95% CI 0.49 to 1.11;  $I^2 = 68\%$ ; 4 studies, 289 participants). The CI in this effect estimate included the possibility of both benefit and harm; we noted that these subgroup data included moderate levels of statistical heterogeneity. Subgroup data for other outcomes were consistent with pooled data in other reviews. None of the subgroup data in Farrow 2016 were supported by statistical results of formal tests

for subgroup differences. No other reviews reported subgroup data for baseline comorbidities or for people at higher risk of bleeding.

### Route of administration

Eight reviews only included studies in which tranexamic acid was given intravenously; no reviews included studies in which tranexamic acid was only given topically. We observed no important differences between effect estimates according to whether reviews pooled data with only IV tranexamic administration, or both IV and topical administration; this finding was the same for all outcomes.

Four reviews reported subgroup data according to route of administration (Jiang 2019; Liu 2022; Luo 2020; Zhu 2018). Jiang 2019 reported effect estimates indicating a decrease in the need for blood transfusion with both IV and topical administration, which is consistent with the findings of other reviews. However, in Liu 2022, pooled data for topical administration indicated a less precise result, with the possibility of no benefit in blood transfusion risk (RR 0.74, 95% CI 0.54 to 1.01;  $I^2 = 0\%$ ; 4 studies); the pooled data in 18 studies with IV administration were consistent with the findings of other reviews.

Luo 2020 only reported subgroup data according to administration route for thromboembolic events, with each subgroup showing similar findings to the other reviews, and no evidence of subgroup differences in formal tests ( $P = 0.86$ ).

Zhu 2018 conducted subgroup analysis with studies in which administration was given locally at the end of surgery, one dose intravenously before surgery, or intravenously before and after surgery. Whilst pooled estimates from two studies of local administration did not show a clear reduction in blood transfusion rates (RR 0.83, 95% CI 0.55 to 1.26; 2 studies, 337 participants), review authors noted no statistical evidence of subgroup differences between these three administration types ( $P = 0.89$ ). In addition, Zhu 2018 noted no differences in thromboembolic events according to administration route.

### Iron and iron with EPO

Here we report the outcome data as reported in Shah 2018, in which all participants received iron intravenously. Although the review included studies of iron given with or without EPO, the pooled outcome data in Shah 2018 only included studies in which participants were given iron alone; therefore, the data reported in this review do not include evidence for iron given with EPO. All the studies in this review overlapped with those in other reviews, therefore, overlapping studies contributed 100% of the weight in these analyses. No reviews reported data for postoperative cognitive dysfunction and activities of daily living. See the summary of findings in Table 10. We downgraded all the evidence by two levels to low certainty for imprecision, owing to wide CIs and evidence derived from few participants.

### Primary outcomes

#### Number of people requiring allogenic blood transfusion

Shah 2018 reported an imprecise effect estimate, indicating little or no difference in the number of people given a blood transfusion according to whether they received iron (RR 0.90, 95% CI 0.73 to 1.11;  $I^2 = 0\%$ ; 2 studies, 403 participants).

## Volume of transfused allogenic blood

The review also found little or no difference between groups in the volume of transfused PRC (MD -0.07 units, 95% CI -0.31 to 0.17;  $I^2 = 0\%$ ; 2 studies, 403 participants).

## Secondary outcomes

### Postoperative delirium

Shah 2018 noted that one study (303 participants) reported delirium. Review authors did not present an effect estimate for these data, but reported there were 25 events in the intervention group and 26 events in the control group.

### Adverse events

The review found little or no difference in the risk of infection (RR 0.99, 95% CI 0.55 to 1.80;  $I^2 = 9\%$ ; 2 studies, 403 participants). Data for other adverse events were not pooled, however, study authors reported no significant differences between groups for these outcomes. Types of reported adverse events included gastrointestinal events, hypotension, low-grade fever, cholestasis, peripheral phlebitis, drug-related side effects (skin rash, general discomfort), and medical complications (acute coronary disease, stroke, heart failure, venous thromboembolism, chronic obstructive pulmonary disease exacerbation, renal function deterioration, delirium, and skin pressure ulcer).

### Health-related quality of life (HRQoL)

Shah 2018 noted that one study (303 participants) reported this outcome, measured at 60 days after hospital discharge, using the SF-36. Review authors did not report an effect estimate, but noted that the study found no significant differences between groups.

### All-cause mortality at one month postoperatively

The review reported no evidence of a difference in short-term mortality, which we assumed meant mortality within one month of surgery (RR 1.06; 95% CI 0.53 to 2.13;  $I^2 = 0\%$ ; 2 studies, 403 participants).

### All-cause mortality at four months postoperatively

Similarly, the review reported little difference in mortality at 60 days, as reported in one study (12 in the iron group versus 10 deaths in the control group; no denominators;  $P > 0.05$ ).

## Sensitivity analysis

In a sensitivity analysis, we assessed the impact of selecting data from Shah 2018 only, by comparing the effect estimates from each review with the effect estimates from Shah 2018 (see Appendix 13). The data from Sinclair 2020 were most comparable to Shah 2018, as it included separate pooled estimates for RCTs in a hip fracture population. Sinclair 2020 included evidence from an additional two studies for the number of people requiring ABT, and for mortality within one month. Effect estimates from these two outcomes also showed no evidence of a difference, according to whether participants received iron. Sinclair 2020 also noted that one study measured the Barthel Index score in participants (a measure used to assess activities of daily living); the review did not report an effect estimate or data from this study, but noted that there was no difference in improvement in scores during a median 10-day hospital stay.

Most effect estimates from other reviews pooled data across population groups (i.e. including participants undergoing hip fracture surgery, as well as other types of surgery), or pooled data from both RCTs and non-randomised trials. For completeness, we also reported these indirect data in Appendix 13. All findings were comparable to those in Shah 2018 (i.e. little or no difference in effect for each outcome), except infection in Chen 2021, which reported a reduced infection risk with iron use. Although we could not clearly determine a reason for this difference, we noted that these data were derived from both RCTs and non-randomised trials.

## Subgroup analysis

### Time of administration

No reviews included administration of iron at only one time point. Two reviews conducted subgroup analysis for the time of administration (Chen 2021; Shin 2019). In Chen 2021, these analyses included pooled data from both RCTs and non-randomised trials, therefore, we did not include the findings here. In Shin 2019, the effect estimates when the intervention was given preoperatively, postoperatively, or perioperatively were similar to those reported in Shah 2018 and in other reviews.

### Age of participants, baseline co-morbidities and people at higher risk of bleeding.

Most reviews did not specify an age limit other than adults; no reviews only included participants that might be described as 'frail elderly'. No reviews specified inclusion criteria, or only included reviews from a distinct subgroup category, according to baseline co-morbidities, or people who were at higher risk of bleeding. In addition, no reviews conducted subgroup analysis for these criteria.

### Route of administration

Four reviews only included studies in which iron was given intravenously (Lin 2013; Shin 2019; Sinclair 2020; Smith 2020). As described in the sensitivity analysis (above), we observed no evidence of differences between effect estimates in each review, regardless of the route of administration.

Only one review conducted subgroup analysis according to route of administration, but because this analysis included pooled data from both RCTs and non-randomised trials, we did not include the findings here (Chen 2021).

## DISCUSSION

### Summary of main results

We found 26 systematic reviews assessing the effectiveness of interventions for reducing blood transfusion in adults undergoing hip fracture surgery. Most reviews reported data for tranexamic acid; the remaining reviews reported data for iron given with or without erythropoietin (EPO). We found no reviews for other types of pharmacological interventions, and no reviews for non-pharmacological interventions.

### Tranexamic acid

There was a large degree of overlap in the reviews of each intervention type, and we used a hierarchical approach to select reviews that provided the most relevant evidence for this overview. We compared the results of selected reviews with those reported

in the other reviews, and found that the results were largely comparable. Selected reviews did not report GRADE judgements of their evidence, therefore, we assessed the certainty of the evidence in these reviews using the information presented in the review reports.

For tranexamic acid, we prioritised data from [Liu 2022](#). This review included 24 randomised controlled trials (RCTs) with 2148 participants undergoing hip fracture surgery. Studies in the review included administration of tranexamic acid intravenously or topically (or both), given at different doses, and at different times during the perioperative period; no studies included intramuscular administration. The review included moderate-certainty evidence of reduced risk of blood transfusion after tranexamic acid. Based on a control group risk of 451 per 1000, it is probable that 194 fewer people are likely to need allogeneic blood transfusion (ABT) after receiving tranexamic acid. The review also reported data for adverse events (deep vein thrombosis, pulmonary embolism, myocardial infarction, and cerebrovascular accident) and mortality within one month of surgery. Data for some of these adverse events were limited by fewer studies than for the effectiveness data. We judged the evidence for these outcomes to be moderate certainty, with imprecise effect estimates that indicated that there is probably little or no difference in the risk of these adverse events, or in early mortality when tranexamic acid is administered.

The review by [Liu 2022](#) did not include data for all outcomes relevant to this overview. Therefore, we also prioritised data from [Masouros 2022](#), which reported data for the volume of transfused blood. This similarly recent review included 10 RCTs with 1123 participants, and also included broad criteria for the administration of tranexamic acid in people having hip fracture surgery. The review included moderate-certainty evidence that tranexamic acid probably reduces the volume of transfused units of packed red blood cells (PRC) given to those undergoing hip fracture surgery. We identified no reviews that reported outcome data for postoperative delirium, activities of daily living, or health-related quality of life.

## Iron

For the use of iron, we prioritised data from [Shah 2018](#). This small review, including two RCTs with 503 participants, provided the most up-to-date, direct, published evidence solely from RCTs in people who had hip fractures. The review reported low-certainty evidence that after administration of iron, there may be little or no difference in the number of people who need ABT, the volume of transfused PRC, infection rates, or mortality within one month. Whilst [Shah 2018](#) did not report an effect estimate for postoperative delirium, data from one study indicated that there may be little or no difference in incidence. [Shah 2018](#) also reported that there were no significant differences between groups in health-related quality of life, but this finding was reported without quantitative data, and we could not be certain of this finding. We identified no reviews of iron given to people with hip fracture that reported outcome data for postoperative delirium, or activities of daily living.

## Overall completeness and applicability of evidence

The evidence in this overview relates to only two possible types of interventions for reducing ABT in a people with hip fracture. Whilst other pharmacological and non-pharmacological interventions may be used, we found no systematic reviews.

It was apparent that data were available from more published studies, with a larger number of systematic reviews evaluating the use of tranexamic acid than for iron use.

For tranexamic acid, the evidence presented in this overview is applicable to the general hip fracture population. None of the reviews reported important secondary outcomes, including postoperative delirium, activities of daily living, or health-related quality of life. We could not confidently interpret the results of subgroup analyses, reported within a subset of the published reviews, to determine whether tranexamic acid may be more or less effective in some groups of people (according to age, baseline risk of bleeding, and different types of fracture and surgical approaches to its treatment). In addition, we could not be certain of any other effect modifiers that may affect the results of these subgroups, for example the use of concomitant medication (such as antithrombotics for cardiovascular disease) in older participants when subgrouping by age, or the appropriateness of subgroup thresholds for body mass index (BMI), when the impact of a low BMI (18 to 25 kg/m<sup>2</sup>) might be more useful for older, frail adults. Similarly, we could not determine whether one route of administration was more effective than another; some reviews included only intravenous administration, but no reviews exclusively evaluated topical administration. In the prioritised reviews for tranexamic acid, no studies evaluated intramuscular administration of tranexamic acid; although intramuscular administration is rarely used. In addition, no studies evaluated oral administration of tranexamic acid.

For iron, the evidence was more sparse, with more reviews including a broader surgical population, and often incorporating the results of non-randomised trials. None of the reviews reported outcome data for postoperative delirium or activities of daily living. The prioritised review in this overview only pooled data for iron, rather than data available from one of its included studies for participants given iron with erythropoietin. Again, we were not confident about the reliability of subgroup analyses within reviews to determine whether iron may be more effective in some patient groups, or when administered by a particular route.

For both types of intervention, we identified recently published reviews with some included studies conducted as recently as 2021. Due to the limitations in reporting in the reviews, we could not determine the range of countries in which studies were conducted.

Additional data will become available in the future from the unpublished and ongoing reviews identified within this overview. No ongoing reviews are assessing non-pharmacological interventions.

## Certainty of the evidence

For the certainty of the evidence in this overview, we report the results of two separate assessments.

Firstly, we used AMSTAR 2 to critically appraise the methodological quality of included reviews, and rate our overall confidence in the results of the reviews. For tranexamic acid, our confidence in the reviews ranged from moderate to very low. For iron, our confidence in the reviews ranged from high to very low. The wide range of judgements for each review represents the differences in reporting standards in these reviews. We did not contact individual review authors for additional details about their review methods, and it

is possible that some of our judgements may be a consequence of poor reporting, with reporting standards not imposed by journal requirements at the time of publication, rather than lack of methodological rigour.

When prioritising key reviews to manage the high degree of study overlap, we based our decisions on relevancy (e.g. recency of the search date, or completeness of the study populations) before review quality. Our prioritised reviews for both types of interventions all had an overall rating of low confidence.

Secondly, we used GRADE to judge the certainty of the evidence within our selected reviews. For tranexamic acid, we judged that all the evidence was moderate-certainty. We did not re-assess any of the risk of bias judgements in the published reports, and we did not downgrade for risk of bias in the evidence. We also did not downgrade for indirectness because the population and intervention types in the studies included in these reviews met our own inclusion criteria. In [Masouros 2022](#), for which we only reported data for the volume of transfused blood, we downgraded the evidence for inconsistency, owing to unexplained, considerable statistical heterogeneity in the effect estimate; we judged that this outcome provided moderate-certainty evidence. We downgraded the certainty of the evidence for outcomes where we noted imprecise effect estimates in which wide confidence intervals (CIs) included the possibility of both benefit and harm. We noted that [Liu 2022](#) found evidence of publication bias for one of the outcomes (number of people requiring ABT), and therefore, we downgraded the evidence.

For the evidence for iron use, we were less certain of the effect estimates, and judged all the evidence to be low certainty. We did not downgrade for risk of bias because the review authors judged risk of bias in the included studies to be largely low. We also did not downgrade for indirectness because data for our selected study population were separately reported in the review. There were no important differences between studies and therefore, we did not downgrade for inconsistency. The evidence for this treatment was from a few, small studies, and the effect estimates included the possibility of both benefit and harm; we downgraded all the evidence for this treatment for imprecision. We did not downgrade the evidence for publication bias; the evidence was based on only a few studies, and the review authors did not formally assess the risk.

We note the distinction between the results of AMSTAR 2 and those of GRADE in this overview. Whilst we used the five GRADE criteria to judge the certainty of the evidence for each outcome, which ranged from moderate to very low, we judged our selected reviews to have methodological flaws such that we were only able to give them an overall rating of low. Therefore, it is reasonable to infer that we could have less confidence in the findings from these reviews than from the reviews that had fewer methodological flaws. However, we also collected the effect estimates from other reviews and compared their findings with those in our selected reviews. Given that the results are largely comparable across all reviews, and any differences could be explained by inclusion criteria, we believed that the differences in methodological quality of all the reviews in this overview was not a reason to reduce our certainty of the evidence for each outcome.

## Potential biases in the overview process

We planned to include systematic reviews of studies that evaluated the effects of interventions for preventing or minimising blood loss, for treating the effects of anaemia by improving the oxygen-carrying potential of the blood, and for reducing the need for allogeneic blood transfusion. We found that it was sometimes difficult to determine eligibility of reviews against these criteria. We excluded some reviews that we expected would meet these eligibility criteria (e.g. [Lewis 2016](#), which evaluated perioperative fluid volume optimisation), because the reviews did not include blood transfusion as an outcome, and therefore, the aim of the review, rather than the studies within the review, did not meet the criteria.

We found many reviews that compared different surgical implants for hip fracture repair or different surgical approaches. We were aware that many of these reviews reported blood loss or ABT risks, but did so as a secondary outcome measure, and therefore, again, we judged that the review aim did not meet our criteria. In addition, we expected that the primary aim of the included studies within these reviews was unlikely to be about minimising blood loss or the effects of anaemia. This opinion was reached based on our own experience of conducting systematic reviews about the effectiveness of surgical treatments for hip fracture repair in which the primary aim of included studies was not related to minimising blood loss ([Lewis 2021](#); [Lewis 2022a](#); [Lewis 2022b](#); [Lewis 2022c](#); [Lewis 2022d](#)). However, we did not explore these eligibility decisions further, for example, by assessing the full texts of individual studies within other similar reviews, and therefore, we cannot rule out the possibility that we incorrectly assessed eligibility for some reviews. We could also not rule out the possibility that we excluded reviews that had mixed surgical populations but did not clearly report whether their results included studies that exclusively recruited people with hip fracture.

We were largely guided by [Shea 2017](#) when conducting assessment of the methodological quality of the included reviews. As noted above, we could not rule out the possibility that our judgements were based on lack of reporting rather than methodological flaws. For example, we found that many reviews did not justify their reason for including only RCTs, or did not cite all excluded studies. For this latter methodological issue, deemed to be critical in a high-quality review according to AMSTAR 2 guidance, we took a more lenient approach; we did not downgrade our overall judgement if review authors reported numbers of excluded studies with reasons in their flow chart or main text, but did not cite excluded studies. However, on other occasions, we adhered strictly to the questions and answers in the AMSTAR 2 checklist.

We also noted that the AMSTAR 2 tool did not always account for review author competency. For example, whilst we judged whether a review conducted a risk of bias assessment, and whether a Cochrane risk of bias tool was used, we did not determine whether review authors had used the tool correctly; it is possible that some review authors were more generous than others in their judgements. It was outside the scope of this overview to check all risk of bias judgements, reporting of publication bias, and indeed, the accuracy of meta-analysis within included reviews. As we were limited by the information in published reviews, we could not rule out the possibility that this may have impacted our GRADE judgements.



Rather than follow a systematic order for prioritising a single review from a series of reviews with overlapping studies, we adapted our priority order to ensure that we selected the review that was predominantly the most relevant to the overview question (in terms of participant and intervention characteristics). We acknowledge that this meant we did not always select the review with the highest methodological quality, or with the most recent search. However, we found that the findings in most reviews were comparable to those in our selected reviews.

## Agreements and disagreements with other studies or reviews

We are not aware of any overviews of systematic reviews for this topic. We found that reviews for each type of intervention were largely consistent in their meta-analyses and interpretation of their findings. For tranexamic acid, reviews in other populations also indicated a benefit in favour of tranexamic acid (e.g. [Henry 2011](#); [Novikova 2015](#)). Whilst we are aware of reviews for iron in other populations, we could not always determine the effectiveness of this treatment. For example, [Gurusamy 2014](#) evaluated iron therapy to treat anaemia, but the evidence of a reduction in blood transfusion after iron use was very low-certainty.

## AUTHORS' CONCLUSIONS

### Implications for practice

Based on evidence from systematic reviews of tranexamic acid, this treatment likely reduces the need for allogeneic blood transfusion in adults undergoing hip fracture surgery. It likely also reduces the volume of transfused packed red blood cells. It probably does not impact the risks of adverse events, such as thromboembolic events or mortality. There were no data to support an estimate of the effect of tranexamic acid on postoperative delirium, health-related quality of life, or activities of daily living four months after surgery.

Based on evidence from systematic reviews of iron, this treatment may make little or no difference to the risk of allogeneic blood transfusion, the volume of transfused PRC, the incidence of infection, or mortality. It is very uncertain whether the treatment affected health-related quality of life four months after surgery. There were no data to support an estimate of the effect of iron on postoperative delirium or activities of daily living after four months.

### Implications for research

This overview lacks evidence of the effectiveness of many pharmacological interventions (such as fibrinogen, factor VIIa and factor XIII, desmopressin, fibrin and non-fibrin sealants and glues, and agents to reverse the effect of anticoagulants), and of all non-pharmacological interventions (such as surgical approaches or temperature management). Whilst the effectiveness of these treatments may have been evaluated in systematic reviews with other objectives, it is apparent that they were not evaluated in systematic reviews for their impact on minimising the need for allogeneic blood transfusion in adults undergoing hip fracture. Therefore, we recommend the production of systematic reviews to evaluate these treatments. Whilst it was beyond the scope of this overview to systematically search for randomised trials for each of these interventions, we are aware of ongoing trials (for example, an evaluation of cell salvage ([Griffin 2022](#))). We are also aware of

ongoing trials evaluating the interventions included in this review (for example, an evaluation of iron and erythropoietin, with a target sample size of 2400 participants ([Moppett 2020](#))). We cannot say with certainty whether future systematic reviews would provide a sufficiently comprehensive evaluation to inform clinical practice, or act as a means to identify significant gaps in the primary research.

The evidence in this overview for tranexamic acid shows that it is likely an effective treatment for reducing the need for blood transfusion, and it is possible to infer that the evidence is sufficient, and no further systematic reviews are required. However, there remains uncertainty about the route of administration for tranexamic acid. Further work is needed to understand the relative effectiveness of intravenous and topical tranexamic acid, as well as intramuscular administration, which was missing from this overview. For iron use, it is also necessary to explore whether there is any role for oral iron, as well as establishing the optimal timing for iron.

We were unable to determine the impact of tranexamic acid or iron on self-reported outcome measures. We did not check if primary studies reported these outcomes, and we cannot state with confidence whether the lack of reporting by review authors was influenced by lack of reporting in the primary studies. We encourage future review authors to include these outcomes alongside an evaluation of any treatment; outcomes should be based on the core outcome set for this surgical population ([Haywood 2014](#)).

## ACKNOWLEDGEMENTS

We would like to thank Carolyn Doree (Information Specialist; NHS Blood and Transplant, University of Oxford, UK) for her contribution in preparing the search strategies during the protocol for this overview.

The following people conducted the editorial process for this article:

- Sign-off Editor (final editorial decision): Nicole Skoetz, University of Cologne and University Hospital Cologne, Germany.
- Managing Editor (selected peer reviewers, collated peer-reviewer comments, provided editorial guidance to authors, edited the article): Sam Hinsley, Cochrane Central Editorial Service
- Editorial Assistant (conducted editorial policy checks and supported editorial team): Leticia Rodrigues, Cochrane Central Editorial Service
- Copy Editor (copy editing and production): Victoria Pennick, Copy-editing Group
- Peer-reviewers (provided comments and recommended an editorial decision): Jennifer Hilgart, Cochrane Evidence Production and Methods Directorate (methods), Kenichi Tanaka, MD, University of Oklahoma Health Sciences Center (clinical), Prof Sigismond Lasocki, Département anesthésie réanimation, CHU Angers, ANgers, France (clinical), Aditi Bauskar, Department of Medical Affairs, Ocular Therapeutix Inc, Bedford, MA, USA (consumer). One additional peer reviewer provided search peer review but chose not to be publicly acknowledged.

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## ADDITIONAL TABLES

**Table 1. Summary of systematic review characteristics evaluating tranexamic acid**

Review	Date of search	Study designs	Number of RCTs (participants)	Participants	Intervention/ comparison	Relevant outcomes	Risk of bias assessment	Certainty of evidence assessment
<a href="#">Agius 2022</a>	February 2021	RCTs	13 (1194)	Hip fracture surgery (type of fracture specified)	IV TXA/ control (placebo or no treatment)	Blood transfusion; adverse events (thomboembolic events)	Cochrane risk of bias tool ( <a href="#">Sterne 2019</a> )	GRADE
<a href="#">Baskaran 2018</a>	July 2016	RCTs NRS	6 (479)	Hip fracture surgery (any type)	IV TXA/ control (placebo or no treatment)	Blood transfusion; adverse events (thomboembolic events)	Cochrane RoB 1 ( <a href="#">Higgins 2011</a> )	None
<a href="#">Farrow 2016</a>	June 2016	RCTs NRS	6 (499)	Hip fracture surgery (any type)	IV and topical TXA/ control (type not specified)	Blood transfusion; adverse events (thomboembolic events, CVA, PE, DVT); mortality	Cochrane RoB 1 ( <a href="#">Higgins 2011</a> )	GRADE
<a href="#">Haj-Younes 2020</a>	March 2019	RCTs	10 (842)	Hip/proximal femoral fractures (AO types 31-A and 31-B)	IV TXA/ placebo or no control	Blood transfusion; adverse events (DVT, PE, acute coronary syndrome, CVA, wound complications)	Cochrane risk of bias tool <sup>a</sup>	None
<a href="#">Jiang 2019</a>	October 2017	RCTs	5 (584)	Intertrochanteric hip fractures	IV and topical TXA/ placebo	Blood transfusion; adverse events (DVT, PE, infection, haematoma)	Cochrane RoB 1 ( <a href="#">Higgins 2011</a> )	None
<a href="#">Liu 2022</a>	February 2021	RCTs NRS	24 (2340)	Hip fractures (type not specified)	IV, topical, or combined IV and topical TXA/ placebo or no treatment	Blood transfusion; adverse events (DVT, PE, MI, CVA)	Cochrane RoB 1 ( <a href="#">Higgins 2011</a> )	None
<a href="#">Luo 2020</a>	December 2018	RCTs	5 (552)	Intertrochanteric fractures treated with intramedullary fixation	IV and topical TXA/ placebo or no treatment	Blood transfusion (number of people, and volume); adverse events (thrombotic events); mortality	Cochrane risk of bias tool <sup>a</sup>	None
<a href="#">Masouros 2022</a>	February 2021	RCTs	10 (1123)	Intra-or extra-capsular hip fractures	IV TXA/ placebo	Blood transfusion (number of people, and volume); adverse events (thrombotic events)	Cochrane risk of bias tool <sup>a</sup>	None

**Table 1. Summary of systematic review characteristics evaluating tranexamic acid** (Continued)

<a href="#">Qi 2019</a>	March 2018	RCTs	10 (854)	Hip fracture	IV TXA/ placebo	Blood transfusion; adverse events (thromboembolic events)	Cochrane risk of bias tool ( <a href="#">Higgins 2011</a> )	None
<a href="#">Wang 2017a</a>	September 2017	RCTs	4 (514)	Intertrochanteric fractures with internal fixation	IV and topical TXA/ placebo	Blood transfusion; Adverse events (DVT, PE, infection)	Cochrane RoB 1 ( <a href="#">Higgins 2011</a> )	GRADE
<a href="#">Xiao 2019</a>	May 2018	RCTs	11 (892)	Hip fractures	IV TXA/ control (placebo, saline, or no treatment)	Blood transfusion; adverse events (DVT, total thromboembolic events)	Cochrane risk of bias tool and Jadad <sup>a</sup>	None
<a href="#">Xing 2020</a>	April 2019	RCTs	5 (539)	Intertrochanteric fractures with intramedullary nailing	IV and topical TXA/ control (placebo, saline, or no treatment)	Blood transfusion; adverse events (DVT, PE, haematoma, wound infection, respiratory infection, renal failure, CVA); mortality	Cochrane RoB 1 ( <a href="#">Higgins 2011</a> )	None
<a href="#">Yu 2020</a>	October 2019	RCTs	11 (1202)	Intertrochanteric fractures	IV and topical TXA/ control (placebo, saline, or no treatment)	Blood transfusion; adverse events (DVT, PE, CVA, MI, wound complications); mortality	Cochrane RoB 1 ( <a href="#">Higgins 2011</a> )	None
<a href="#">Zhang 2017</a>	December 2016	RCTs	8 (598)	Hip fracture	IV TXA/ control (placebo or saline)	Blood transfusion; adverse events (thromboembolic events)	12-item tool ( <a href="#">Furlan 2009</a> )	GRADE
<a href="#">Zhang 2018</a>	January 2018	RCTs NRS	12 (1129)	Hip fracture	IV and topical TXA/ control (placebo or saline)	Blood transfusion; adverse events (thromboembolic events); mortality (3 months)	12-item tool ( <a href="#">Furlan 2009</a> )	None
<a href="#">Zhou 2019a</a>	October 2018	RCTs	8 (836)	Intertrochanteric fractures with internal fixation	IV and topical TXA/ control (placebo, saline, or no treatment)	Blood transfusion; adverse events (DVT)	Cochrane RoB 1 ( <a href="#">Higgins 2011</a> )	GRADE
<a href="#">Zhu 2018</a>	February 2018	RCTs	7 (746)	Intertrochanteric fractures with internal fixation	IV and topical TXA/ control (placebo, saline, or no treatment)	Blood transfusion; adverse events (DVT, PE)	Cochrane risk of bias tool <sup>a</sup>	GRADE

<sup>a</sup>review reported no citation for the Cochrane risk of bias tool and we could not be certain which version of the tool was used in the review

CVA: cerebrovascular accident; DVT: deep vein thrombosis; IV: intravenous(ly); MI: myocardial infarction; NRS: non-randomised study; RCT: randomised controlled trial; PE: pulmonary embolism; TXA: tranexamic acid

**Table 2. Overlapping studies in systematic reviews evaluating tranexamic acid**

	Ag- ius 2022	Liu 2022	Ma- souros 2022	Haj- Younes 2020	Yu 2020	Xing 2020	Luo 2020	Jiang 2019	Zhou 2019a	Xiao 2019Xi- ao 2019	Qi 2019	Zhu 2018	Zhang 2018	Wang 2017a	Zhang 2017	Baskara 2018	Far- row 2016
Ahmed 2020		Y															
Baruah 2016	Y	Y		Y	Y				Y	Y	Y	Y	Y				
Chen 2019	Y	Y	Y		Y												
Drakos 2016		Y			Y	Y	Y	Y	Y			Y	Y	Y			
Emara 2014	Y	Y								Y	Y		Y		Y	Y	Y
Haghighi 2017	Y			Y						Y			Y				
Ji 2015															Y		
Jordan 2019		Y															
Lei 2017	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y			
Li 2015		Y															
Luo 2018	Y	Y															
Luo 2019		Y	Y	Y	Y	Y	Y										
Mohib 2015	Y	Y			Y			Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Nikolaou 2021			Y														
Sadeghi 2007		Y		Y						Y	Y		Y		Y	Y	Y
Schiavone 2018		Y			Y				Y								
Shi 2018		Y															



**Table 2. Overlapping studies in systematic reviews evaluating tranexamic acid** (Continued)

Tengberg 2016	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y
Tian 2018	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y					
Vijay 2013	Y	Y		Y					Y	Y		Y			Y	Y	
Virani 2016		Y			Y		Y	Y			Y	Y	Y				
Wang 2021		Y															
Wang 2017b							Y										
Wang 2013														Y			
Watts 2017	Y	Y	Y	Y					Y	Y		Y					
Zhang 2022		Y	Y														
Zhang 2020b		Y															
Zhou 2019b	Y	Y	Y		Y												
Zufferey 2009	Y	Y	Y	Y					Y	Y		Y	Y	Y	Y	Y	Y

Systematic reviews are in columns (ordered by date of publication). Included studies in the systematic reviews are in rows (ordered alphabetically). Study overlap = 65.5%; covered area (CA) for overlap = 31.2%; corrected covered area (CCA) for overlap = 26.9%

**Table 3. Characteristics of RCTs in Liu 2021 and Masouros 2021 (tranexamic acid)**

Study ID <sup>a</sup>	N (TXA; control)	Age (in years), mean (SD) (TXA; control)	M/F (TXA; control)	Fracture type	Surgery	Route, dose, number of doses (TXA; control)	Timing	Transfusion criteria
Ahmed 2020	60; 60	NS	NS	trochanteric	DHS	IV 15 mg/kg; normal saline, given once	Prior to surgery	NS
Baruah 2016	30; 30	57.7 (± 14.5); 55.3 (± 15.2)	24/6; 25/5	stable trochanteric	ORIF with DHS	IV 15 mg/kg; normal saline, given once	15 min prior to surgery	Hb < 8.5 g/dL or HCT < 27%

**Table 3. Characteristics of RCTs in Liu 2021 and Masouros 2021 (tranexamic acid)** (Continued)

Chen 2019	88; 88	76.8 ( $\pm$ 7); 77.4 ( $\pm$ 6.8)	39/49; 37/51	trochanteric	DHS, PFNA	IV 15 mg/kg in 100 mL of saline, given 3 times; normal saline	10 min before incision, continuously through surgery, 3 h after surgery	Hb < 7 g/dL; Hb < 10 g/dL at risk
Drakos 2016	100; 100	81 (65 to 96); 80.7 (65 to 97) <sup>b</sup>	27/73; 21/79	trochanteric	IMN	Topical 3 g, 30 mL (500 mg/5 mL $\times$ 6 amps)	At the end of surgery	Hb < 8 g/dL or HCT < 25%, unless at risk
Emara 2014	TXA: 20; 20; control: 20	TXA: 56.5 ( $\pm$ 2.8); TXA: 55 ( $\pm$ 2.6); Control: 56 ( $\pm$ 3.1)	TXA: 12/8; TXA: 10/10; Control: 14/6	femoral	HA	TXA: topical 10 mg/kg in 20 mL saline; 5 mg/kg/h in the form of 500 mg TXA in 250 mL at rate of 80 mL/h, given twice; topical 1.5 g in 100 mL saline, given once; control: normal saline	TXA: a bolus dose prior to skin incision; Topical: prior to wound closure	NS
Jordan 2019	51; 50	84.1 ( $\pm$ 6.9); 84.6 ( $\pm$ 10.4)	9/43; 13/37	sub-capital femoral	THA or PHA	Topical 1 g in 10 mL solution, given once; normal saline	Applied on soft tissues and exposed surfaces of femur	Hb < 7 g/dL or Hb < 8 g/dL; Hb 9 to 10 g/dL at risk
Lei 2017	37; 40	77.8 ( $\pm$ 9.8); 79.2 ( $\pm$ 6.5)	5/32; 7/33	trochanteric	PFNA	IV 1 g in 200 mL saline, given once; normal saline	After anaesthesia, but before surgery	Hb < 9 g/dL
Li 2015	30; 30	77.9 ( $\pm$ 3.9); 77.4 ( $\pm$ 3.4)	15/15; 13/17	femoral head	THA	IV 10 mg/kg, given once; normal saline	A bolus after anaesthesia, but before surgery	Hb < 7 g/dL; Hb 7 to 10 g/dL at risk
Luo 2018	TXA: 21; TXA: 18; TXA: 19; control: 19	TXA: 77.1 ( $\pm$ 7); TXA: 73.8 ( $\pm$ 6.6); TXA: 74.2 ( $\pm$ 6); Control: 76.7 ( $\pm$ 9.2)	TXA: 0/21; TXA: 0/18; TXA: 0/19; Control: 0/19	femoral neck	THA	TXA: IV 15 mg/kg, given once; TXA: topical 3 g, once; TXA: IV + topical 15 mg/kg; 1.5 g, twice; control: normal saline	TXA: 5 min before skin incision; TXA: topical: into the joint cavity; TXA: IV + topical: 5 min before skin incision, into the joint cavity	Hb < 7 g/dL or HCT < 25%

**Table 3. Characteristics of RCTs in Liu 2021 and Masouros 2021 (tranexamic acid)** (Continued)

Luo 2019	44; 46	75.1 ( $\pm$ 8); 76.1 ( $\pm$ 9.3)	23/21; 20/26	trochanteric	PFNA	IV 15 mg/kg, given twice; normal saline	15 min before incision and 3 h later	Hb < 8 g/dL; Hb > 8 g/dL at risk
Mohib 2015	50; 50	69 ( $\pm$ 10); 70 ( $\pm$ 9.4)	21/29; 24/26	trochanteric	NS	IV 15 mg/kg, given twice; normal saline	Just before surgery and 3 h later	Hb < 7 g/dL
Nikolaou 2021	68; 70	82.9; 83.4	10/58; 18/52	trochanteric; femoral neck	IMN; HA	IV 15 mg/kg; normal saline	5 mins before surgery	NS
Sadeghi 2007	32; 35	51.8 ( $\pm$ 25.7); 44.4 ( $\pm$ 26.2)	17/15; 24/11	intracapsu- lar; extra- capsular	HA, IMN, DHS	IV 15 mg/kg, given once; normal saline	A bolus at induction of anaesthesia	Case by case Hb 8 to 10 g/ dL
Schiavone 2018	47; 43	84.3 ( $\pm$ 8.3); 84.3 ( $\pm$ 8.3)	12/35; 15/28	pertrochanteric	DHS	IV 15 mg/kg, given once; normal saline	A bolus at surgical inci- sion	Hb < 8.5 g/ dL; Hb < 9 g/ dL at risk
Shi 2018	24; 24	88.1 ( $\pm$ 6.2); 89.2 ( $\pm$ 7.1)	NS	trochanteric	PFNA	Topical 2 g in 20 mL saline, giv- en once; normal saline	Into the joint cavity	NS
Tengberg 2016	33; 39	79.8 ( $\pm$ 11.5); 70 ( $\pm$ 12.6)	7/26; 14/25	intracapsu- lar; extra- capsular	IM	IV 1 g; 3 g in 1 L of saline, given twice; placebo	A bolus during drap- ing, just prior to surgery, and postoper- ative 24 h infusion	Hb < 9.67 g/ dL
Tian 2018	50; 50	77.7 ( $\pm$ 6.5); 79.3 ( $\pm$ 6.6)	19/31; 14/36	trochanteric	PFNA	IV 10 mg/kg, given twice; normal saline	10 min preoperatively and 5 h postoperative- ly	Hb < 9 g/dL
Vijay 2013	45; 45	48.8 ( $\pm$ 16.2); 49.3 ( $\pm$ 19.5)	10/35; 10/35	femoral	ORIF, HA, THA	IV 10 mg/kg (500 mg in 50 mL saline; 1 mg/kg/h dissolved in 1 L saline), given twice; normal saline	A bolus 15 min before incision, a continuous infusion until the com- pletion of surgery	Reduction of Hb > 25%
Virani 2016	67; 70	67; 69.1	25/42; 24/43	per- itrochanteric	DHS	Topical 2 g, given once; normal saline	In the proximal lateral thigh before closure	Hb < 9 g/dL

**Table 3. Characteristics of RCTs in Liu 2021 and Masouros 2021 (tranexamic acid)** (Continued)

Wang 2021	TXA: 33; TXA: 35; control: 32	TXA: 75.2 ( $\pm$ 9.4); TXA: 74.3 ( $\pm$ 7.1); control: 72.3 ( $\pm$ 7.7)	TXA: 10/23; TXA: 9/26; control: 10/22	trochanteric	PFNA	TXA: IV 1 g, given once; TXA: IV 1g, given 3 times; control: normal saline	Half-hour before operation; before operation; and at 3 and 6 h after operation	Hb < 7 g/dL; Hb 7 to 10 g/dL at risk
Watts 2017	69; 69	81 ( $\pm$ 10); 82.2 ( $\pm$ 10)	21/48; 22/47	femoral neck	HA, THA	IV 15 mg/kg in 100 mL of saline, given twice; normal saline	Before incision, and at wound closure	Hb < 7 g/dL; Hb < 8 g/dL at risk
Zhang 2022	61; 61	79.1 ( $\pm$ 11.9); 76.1 ( $\pm$ 16.6)	33/28; 34/27	trochanteric	PFNA	IV 1 g in 100 mL saline, given twice; normal saline	10 min before incision, and at 3 h later	Hb < 7 g/dL; Hb 7 to 10 g/dL at risk
Zhang 2020b	TXA: 15; TXA: 15; control: 15	TXA: 71.2 (65 to 89); TXA: 71.6 (67 to 84); control: 73.1 (65 to 86) <sup>a</sup>	TXA: 7/8; TXA: 6/9; control: 8/7	trochanteric	PFNA	TXA: IV 1 g in 100 mL saline, given once; TXA: IV + topical 1 g in 100 mL saline, 1 g in 50 mL saline, twice; control: normal saline	TXA: 15 min before incision; TXA: 15 min before incision, into the joint cavity	Hb < 7 g/dL
Zhou 2019b	50; 50	75.1 ( $\pm$ 8.3); 77.8 ( $\pm$ 6.4)	15/35; 22/28	trochanteric	PFNA	IV 1 g in 100 mL saline, given once; normal saline	15 min prior to surgery	Hb < 7 g/dL
Zufferey 2009	57; 53	Mean (range): 81 (51 to 99); 82 (56 to 95)	10/47; 4/49	cervical only; stable/unstable trochanteric transtrochanteric, sub-trochanteric	THA, HA, DHS, IMN	IV 15 mg/kg, given twice; placebo	Before surgery and 3 h later	Hb < 9 g/dL; Hb < 10 g/dL at risk

<sup>a</sup>All information for individual studies is taken from Liu 2022; except for Nikolaou 2021, which is taken from Masouros 2022.

<sup>b</sup>Average (mean or median) and distribution type was not specified in Liu 2022, or in the original study reports.

CHS: cannulated hip screw; DHS: dynamic hip screw; DVT: deep vein thrombosis; h: hours; Hb: haemoglobin; HA: hemiarthroplasty; IMN: intramedullary nail; IV: intravenous(ly); LMWH: low-molecular-weight heparin; M/F: male/female; min: minute(s); N: number of participants; NS: not specified; ORIF: open reduction and internal fixation; PFNA: proximal femoral nail antirotation; PHA: partial hip arthroplasty; SD: standard deviation; THA: total hip arthroplasty; TXA: tranexamic acid

**Table 4. Summary of systematic review characteristics evaluating iron and iron with EPO**

Review	Date of search	Study designs	Number of RCTs (participants)	Participants	Intervention Comparison	Relevant outcomes	Risk of bias assessment	Certainty of evidence assessment
<a href="#">Chen 2021</a>	April 2019	RCTs and NRS	3 (803)	Femoral neck fractures, trochanteric fractures, or subtrochanteric fractures	Iron or iron + EPO (included studies used iron sucrose and ferrous sulphate) <i>Control:</i> placebo or standard care	Blood transfusion (rate and volume); adverse events (infection); mortality	Jadad <sup>a</sup>	None
<a href="#">Gomez-Ramirez 2019</a>	2018	RCTs and NRS	5 (948)	Major orthopaedic surgery (including hip fracture)	Iron or iron + EPO (included studies used iron sucrose or FCM) <i>Control:</i> placebo or standard care	Blood transfusion; adverse events (gastrointestinal symptoms, hypotension, headache, general discomfort, skin rash, flushing and tingling in the lips, infection); mortality	None	None
<a href="#">Lin 2013</a>	July 2012	RCTs and NRS	2 (279)	Mixed surgery (including hip fracture)	Iron + EPO <i>Control:</i> autologous blood donation, oral iron, or placebo	Blood transfusion (rate and volume); adverse events (infection, thromboembolic events); mortality	Cochrane risk of bias tool <sup>a</sup>	None
<a href="#">Schack 2019</a>	November 2017	RCTs and NRS	3 (485)	Major non-cardiac surgery (including hip fracture)	Oral or IV iron with or without EPO <i>Control:</i> no intervention, active comparator, or another iron treatment	Blood transfusion; adverse events (mild and severe); mortality	RoB 1 ( <a href="#">Higgins 2011</a> )	None
<a href="#">Shah 2018</a>	June 2018	RCTs	2 (503)	Non-elective surgery (including hip fracture)	IV iron with and without EPO <i>Control:</i> placebo or standard care	Blood transfusion (rate and volume); delirium; adverse events (nausea, gastrointestinal symptoms, cholestasis, peripheral phlebitis, hypotension, low-grade fever, skin rash, general discomfort, acute coronary disease, CVA, COPD exacerbation, heart failure,	RoB 1 ( <a href="#">Higgins 2011</a> )	None



**Table 4. Summary of systematic review characteristics evaluating iron and iron with EPO** (Continued)

						renal function deterioration, skin pressure ulcer); HRQoL; mortality		
<a href="#">Shin 2019</a>	September 2018	RCTs and NRS	2 (491)	Orthopaedic surgery (including hip fracture)	Iron <i>Control</i>	Blood transfusion (rate and volume); adverse events (infection); mortality	RoB 1 ( <a href="#">Higgins 2011</a> )	None
<a href="#">Sinclair 2020<sup>b</sup></a>	January 2021	RCTs and NRS	4 (832)	Hip fracture surgery	IV iron (any preparation)  <i>Control: placebo or standard care</i>	Blood transfusion; HRQoL; mortality; ADL	RoB 1 ( <a href="#">Higgins 2011</a> )	GRADE
<a href="#">Smith 2020</a>	September 2019	RCTs and NRS	3 (579)	Major orthopaedic surgery (including hip fracture)	IV iron or iron with EPO, given preoperatively  <i>Control: placebo or standard care</i>	Blood transfusion (rate and volume); adverse events (serious adverse events, cardiovascular events, infection); HRQoL; mortality	RoB 1 ( <a href="#">Higgins 2011</a> )	None
<a href="#">Yang 2011</a>	May 2011	RCTs	3 (568)	Hip or knee surgery (including hip fracture)	Oral or IV iron  <i>Control: placebo or no treatment</i>	Blood transfusion (rate and volume); adverse events <sup>c</sup> ; mortality	Cochrane risk of bias tool ( <a href="#">van Tulder 2003</a> )	None

<sup>a</sup>Review authors did not report a citation for this tool and we could not be certain which version was used

<sup>b</sup>We used only unpublished data for this review, which were supplied by personal communication with the review author (by email)

<sup>c</sup>Type of adverse events not specified in the study; because not all studies were eligible for inclusion in our review, we could not determine which of the reported adverse events were relevant.

ADL: activities of daily living; EPO: erythropoietin; HRQoL: health-related quality of life; IV: intravenous(ly); NRS: non-randomised studies; RCTs: randomised controlled trials

**Table 5. Overlapping studies in systematic reviews evaluating iron and iron with erythropoietin (EPO)**

	<a href="#">Chen 2021</a>	<a href="#">Gomez-Ramirez 2019</a>	<a href="#">Lin 2013</a>	<a href="#">Schack 2019</a>	<a href="#">Shah 2018</a>	<a href="#">Shin 2019</a>	<a href="#">Sinclair 2020</a>	<a href="#">Smith 2020</a>	<a href="#">Yang 2011</a>
<a href="#">Bernabeu-Wittel 2016</a>	Y	Y			Y	Y	Y	Y	
<a href="#">Bielza 2021</a>							Y		
<a href="#">Kateros 2010</a>		Y	Y						

**Table 5. Overlapping studies in systematic reviews evaluating iron and iron with erythropoietin (EPO)** (Continued)

Moppett 2019								Y	Y	
Parker 2010	Y	Y			Y					Y
Prasad 2009		Y			Y					Y
Serrano-Trenas 2011	Y	Y	Y	Y	Y	Y	Y	Y	Y	Y

Systematic reviews are in columns (ordered by date of publication). Included studies in the systematic reviews are in rows (ordered alphabetically). Study overlap = 85.7%; covered area (CA) for overlap = 42.9%; corrected covered area (CCA) for overlap = 35.7%

**Table 6. Characteristics of RCTs in Shah 2018 (iron)**

Study ID	Participant criteria	N	Years of age, mean (SD)	M/F	Fracture type	Surgery	Administration dose, route, and number of doses	Timing	Transfusion criteria
Bernabeu-Wittel 2016	> 65 years, osteoporotic hip fracture, Hb 90 to 120 g/L	<i>Iron</i> : 103; <i>Iron + EPO</i> : 100 <i>Control</i> : 100	<i>Iron</i> : 84.6 ( $\pm$ 6.2) <i>Iron + EPO</i> : 83.4 ( $\pm$ 6.4) <i>Control</i> : 82.3 ( $\pm$ 6.9)	<i>Iron</i> : 19/84 <i>Iron + EPO</i> : 13/87 <i>Control</i> : 13/87	Pertrochanteral, subcapital, others	IF, HA or THA	<i>Iron</i> : 1000 mg of IV ferric carboxymaltose (2 x 500 mg vials diluted in 250 mL saline) in 20 min infusion  <i>Iron + EPO</i> : 1000 mg of IV ferric carboxymaltose (2 x 500 mg vials diluted in 250 mL saline) in 20 min infusion; subcutaneous single dose of 40,000 IU or EPO in prefilled 1 mL syringe  <i>Control</i> : IV placebo (250 mL saline) in 20 min infusion	Prior to surgery	Hb < 70 g/L: 3 RBC transfusions (independent of symptoms)  Hb 71 to 89 g/L with severe symptoms: 2 RBC transfusions
Serrano-Trenas 2011	> 65 years, hip fracture	<i>Iron</i> : 99 <i>Control</i> : 97	<i>Iron</i> : 83.46 ( $\pm$ 7.11) <i>Control</i> : 82.53 ( $\pm$ 6.37)	<i>Iron</i> : 20/79 <i>Control</i> : 20/77	Extracapsular, intracapsular	IF, HA	<i>Iron</i> : standard protocol treatment; plus 600 mg iron sucrose IV (3 x 200 mg over 48 hour period, in 90-min infusion)  <i>Control</i> : standard protocol treatment <sup>a</sup>	<i>Iron</i> : first dose 24 hours after admission and before surgery; other doses given before or after surgery, all within 48 hours	Assumed to follow standard protocol <sup>a</sup>

<sup>a</sup>criteria for RBC transfusion: preoperative Hb < 10 g/dL; postoperative Hb < 8 g/dL, or < 9 g/dL if participant had history of cardiorespiratory conditions; or any Hb with symptoms of untreated anaemia

EPO: erythropoietin; Hb: haemoglobin levels; IV: intravenous(ly); M/F: male/female; N: number of participants randomised to group; RBC: red blood cell

**Table 7. AMSTAR 2 summary for reviews evaluating tranexamic acid**

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Overall confidence in the results of the review
<a href="#">Agius 2022</a>	Y	Y	N	PY	Y	N	N	PY	Y	N	Y	N	N	Y	Y	Y	Very low
<a href="#">Baskaran 2018</a>	Y	N	N	PY	Y	Y	N	PY	Y	N	N	Y	Y	Y	N <sup>a</sup>	Y	Very low
<a href="#">Farrow 2016</a>	Y	Y	N	PY	Y	N	N <sup>b</sup>	Y	Y	N	Y	Y	Y	Y	N <sup>a</sup>	Y	Moderate
<a href="#">Haj-Younes 2020</a>	Y	N	N	PY	N	N	N <sup>b</sup>	PY	Y	N	N	N	N	N	N	Y	Very low
<a href="#">Jiang 2019</a>	Y	Y	N	PY	Y	Y	N <sup>c</sup>	Y	Y	N	Y <sup>d</sup>	N	Y	N	N <sup>a</sup>	Y	Moderate
<a href="#">Liu 2022</a>	Y	N	N	PY	Y	Y	N <sup>b</sup>	Y	Y	N	Y	Y	Y	Y	Y	Y	Low
<a href="#">Luo 2020</a>	Y	N	N	PY	Y	Y	N	Y	Y	N	Y	N	Y	Y	Y	Y	Very low
<a href="#">Masouros 2022</a>	Y	PY	N	PY	Y	N	Y	Y	Y	N	Y	N	Y	Y	N	N	Low
<a href="#">Qi 2019</a>	Y	N	N	PY	Y	Y	N <sup>b</sup>	Y	Y	N	Y	N	N	Y	Y	Y	Very low
<a href="#">Wang 2017a</a>	Y	N	N	PY	Y	Y	N <sup>b</sup>	Y	Y	Y	Y	N	N	N	Y	Y	Very low
<a href="#">Xiao 2019</a>	Y	N	N	PY	N	N	Y	Y	Y	N	N	Y	Y	Y	Y	Y	Very low
<a href="#">Xing 2020</a>	Y	N	N	PY	Y	Y	N <sup>b</sup>	Y	Y	N	Y	N	N	Y	N <sup>a</sup>	Y	Very low
<a href="#">Yu 2020</a>	Y	N	N	PY	Y	Y	N <sup>b</sup>	Y	Y	N	Y	N	Y	Y	Y	Y	Low
<a href="#">Zhang 2017</a>	Y	N	N	PY	N	Y	Y	Y	Y	N	Y	N	Y	Y	N <sup>a</sup>	Y	Low
<a href="#">Zhang 2018</a>	Y	N	N	PY	Y	Y	Y	Y	Y	N	Y	N	N	N	N	Y	Very low

**Table 7. AMSTAR 2 summary for reviews evaluating tranexamic acid** (Continued)

<a href="#">Zhou 2019a</a>	Y	N	N	PY	N	Y	N <sup>b</sup>	Y	Y	N	Y	N	N	Y	N <sup>a</sup>	Y	Very low
<a href="#">Zhu 2018</a>	Y	N	N	PY	Y	N	N <sup>b</sup>	Y	Y	N	Y	N	Y	Y	N <sup>a</sup>	Y	Low

Scores from the 16 questions in the AMSTAR 2 critical appraisal tool (see [Appendix 2](#)). N: no; PY: partial yes; Y: yes

<sup>a</sup>Funnel plot not performed, but we noted that fewer than 10 trials were included

<sup>b</sup>Although citations for individual studies were not given, reasons for exclusion were enumerated

<sup>c</sup>No studies excluded at full-text review

<sup>d</sup>Protocol did not clearly state a rationale for choosing to combine studies; however, we judged the studies to be sufficiently similar

**Table 8. AMSTAR 2 summary for reviews evaluating iron or iron with erythropoietin (EPO)**

	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	Overall confidence in the results of the review
<a href="#">Chen 2021</a>	Y	Y	N	PY	Y	Y	N <sup>a</sup>	PY	Y	N	Y	Y	Y	Y	N <sup>b</sup>	Y	Moderate
<a href="#">Gomez-Ramirez 2019</a>	Y	N	N	N	Y	N	Y	PY	N	N	N/A	N/A	Y	Y	N/A	Y	Very low
<a href="#">Lin 2013</a>	Y	Y	N	PY	Y	Y	N <sup>a</sup>	PY	Y	Y	N/A	N/A	Y	Y	N/A	Y	High
<a href="#">Schack 2019</a>	Y	Y	N	PY	Y	N	N <sup>a</sup>	PY	Y	N	Y	Y	Y	Y	Y	N	Moderate
<a href="#">Shah 2018</a>	Y	Y	N	PY	Y	Y	N <sup>a</sup>	PY	Y	N	Y	Y	N	Y	N <sup>b</sup>	Y	Low
<a href="#">Shin 2019</a>	Y	Y	N	PY	Y	Y	N <sup>a</sup>	PY	Y	N	Y	Y	Y	Y	Y	Y	Moderate
<a href="#">Sinclair 2020</a>	Y	Y	N	PY	Y	Y	Y	PY	Y	N	Y	Y	Y	Y	Y	Y	Moderate
<a href="#">Smith 2020</a>	Y	Y	N	PY	N	N	N <sup>a</sup>	PY	Y	N	N/A	N/A	Y	Y	N/A	Y	Moderate
<a href="#">Yang 2011</a>	Y	N	N	PY	Y	Y	Y	PY	Y	N	Y	N	Y	Y	N <sup>b</sup>	N	Low

Scores from the 16 questions in the AMSTAR 2 critical appraisal tool (see [Appendix 2](#)). N: no; N/A: not applicable, as no meta-analysis was conducted; PY: partial yes; Y: yes

<sup>a</sup>Although citations for individual studies were not given, reasons for exclusion were enumerated

<sup>b</sup>Funnel plot not performed, but we noted that analysis included fewer than 10 trials



**Table 9. Summary of findings table: tranexamic acid versus control for reducing blood cell transfusion in adults undergoing hip fracture surgery**

Tranexamic acid versus control for reducing blood cell transfusion in adults undergoing hip fracture surgery						
<b>Population:</b> people undergoing surgery for hip fracture						
<b>Setting:</b> hospital settings						
<b>Intervention:</b> tranexamic acid, given at any dose by any route of administration; studies included in these reviews gave tranexamic acid intravenously, topically, or both						
<b>Comparison:</b> placebo or no treatment						
Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with control	Risk with TXA				
<b>Number of people requiring ABT<sup>a</sup></b> <i>during perioperative period</i>	Study population 451 per 1000 <sup>b</sup>	<b>257 per 1000</b> (207 to 307)	<b>RR 0.56</b> (0.46 to 0.68)	2148 participants (21 studies)	Moderate <sup>c</sup>	
<b>Volume of transfused allogeneic blood (measured as units of PRC)<sup>d</sup></b> <i>during perioperative period</i>	Mean volume of transfused PRC in the control group ranged from <b>0.53 to 2.4 units</b>	<b>0.53 units lower</b> (0.27 lower to 0.80 lower)	-	813 participants (7 studies)	Moderate <sup>e</sup>	
<b>Postoperative delirium</b>	-	-	Not estimable	-	-	No data reported
<b>Adverse events<sup>a</sup></b> DVT	Study population 79 per 1000 <sup>f</sup>	<b>92 per 1000</b> (58 to 142)	<b>RR 1.16</b> (0.74 to 1.81)	(22 studies) <sup>g</sup>	Moderate <sup>h</sup>	Effects of other adverse events were:  PE: RR 1.01, 95% CI 0.36 to 2.86; 9 studies  MI: RR 1.00, 95% CI 0.23 to 4.33; 8 studies  CVA: RR 1.45, 95% CI 0.56 to 3.70; 8 studies
<b>Activities of daily living</b>	-	-	Not estimable	-	-	No data reported
<b>Health-related quality of life</b>	-	-	Not estimable	-	-	No data reported
<b>All-cause mortality<sup>a</sup></b> <i>within 1 month of surgery</i>	Study population 67 per 1000 <sup>i</sup>	<b>67 per 1000</b> (47 to 98)	<b>RR 1.01</b> (0.70 to 1.46)	(10 studies) <sup>g</sup>	Moderate <sup>h</sup>	Time point was not reported; we assumed from other information that this effect

**Table 9. Summary of findings table: tranexamic acid versus control for reducing blood cell transfusion in adults undergoing hip fracture surgery** (Continued)

estimate includes data from  
< 3 months and ≥ 3 months

\***The risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**ABT:** allogenic blood transfusion; **CI:** confidence interval; **CVA:** cerebrovascular accident; **DVT:** deep vein thrombosis; **MI:** myocardial infarction; **PE:** pulmonary embolism; **PRC:** packed red blood cells; **RR:** risk ratio

#### GRADE Working Group grades of evidence

**High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect

**Moderate certainty:** we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

**Low certainty:** our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect

**Very low certainty:** we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect

<sup>a</sup>The data for this outcome were reported in [Liu 2022](#), which did not include a summary of findings table. We judged the certainty of the evidence based on the information presented in the published report. We did not re-analyse the data, or re-assess any risk of bias judgements in the published report.

<sup>b</sup>Derived from the pooled estimate of the control groups in the included studies in [Liu 2022](#)

<sup>c</sup>Downgraded by one level for publication bias. Review authors noted evidence of publication bias from funnel plot investigation and Eggers test ( $P = 0.001$ )

<sup>d</sup>The data for this outcome were reported in [Masouros 2022](#), which did not include a summary of findings table. We judged the certainty of the evidence based on the information presented in the published report. We did not re-analyse the data, or re-assess any risk of bias judgements in the published report.

<sup>e</sup>Downgraded by one level for inconsistency, owing to statistical heterogeneity ( $I^2 = 78\%$ )

<sup>f</sup>We were unable to determine a pooled estimate of the control group in [Liu 2022](#), because these data were not reported by the study authors; therefore, we derived the control group risk of DVT from [Masouros 2022](#).

<sup>g</sup>Number of participants included in this effect estimate was not reported in [Liu 2022](#)

<sup>h</sup>Downgraded by one level for imprecision, owing to wide CI that includes both benefit and harm

<sup>i</sup>Risk in the control group taken from the National Hip Fracture Database (NHFD) for England, Wales and Northern Island for 2016

**Table 10. Summary of findings table: iron versus control for reducing blood cell transfusion in adults undergoing hip fracture surgery**

#### Iron versus control for reducing blood cell transfusion in adults undergoing hip fracture surgery

**Population:** people undergoing surgery for hip fracture

**Setting:** hospitals

**Intervention:** iron or iron with EPO, given at any dose for any duration; studies in the review used intravenous administration, starting preoperatively

**Comparison:** placebo control or standard care treatment

Outcomes	Anticipated absolute effects* (95% CI)		Relative effect (95% CI)	Number of participants (studies)	Certainty of the evidence (GRADE)	Comments
	Risk with control	Risk with iron				
<b>Number of people requiring ABT<sup>a</sup></b>	Study population 475 per 1000 <sup>b</sup>	<b>428 per 1000</b>	<b>RR 0.90</b> (0.73 to 1.11)	403 participants (2 studies)	Low <sup>c</sup>	

**Interventions for reducing red blood cell transfusion in adults undergoing hip fracture surgery: an overview of systematic reviews (Review)**

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**Table 10. Summary of findings table: iron versus control for reducing blood cell transfusion in adults undergoing hip fracture surgery** (Continued)  
during perioperative period (347 to 527)

<b>Volume of transfused allogeneic blood (measured as units of PRC)<sup>a</sup></b>  during perioperative period	Mean volume of transfused PRC in the control group ranged from <b>0.87 to 1.28 units</b>	<b>0.07 fewer units</b>  (0.31 fewer to 0.17 more)	-	403 participants (2 studies)	Low <sup>c</sup>	
<b>Postoperative delirium</b>	-	-	Not estimable	303 participants (1 study)	-	No effect estimate reported; however, review authors reported that 25 participants in the iron group had delirium compared to 26 participants in the control group.
<b>Adverse events<sup>a</sup></b>	Study population	<b>RR 0.99</b>	403 participants (2 studies)	Low <sup>c</sup>		
Infection	110 per 1000 <sup>b</sup>	<b>111 per 1000</b>  (61 to 198)	0.55 to 1.80			
<b>Activities of daily living</b>	-	-	Not estimable	-	-	No effect estimate or data reported
<b>Health-related quality of life<sup>a</sup></b>	-	-	Not estimable	-	-	No effect estimate or data reported. Review authors reported that there were no significant differences between groups
<b>All-cause mortality<sup>a</sup></b>	Study population	<b>RR 1.06</b>	403 participants (2 studies)	Low <sup>c</sup>		
1-month follow-up	70 per 1000 <sup>b</sup>	<b>70 per 1000</b>  (37 to 149)	(0.53 to 2.13)			

\***The risk in the intervention group** (and its 95% CI) is based on the assumed risk in the comparison group and the **relative effect** of the intervention (and its 95% CI).

**ABT:** allogeneic blood transfusion; **CI:** confidence interval; **EPO:** erythropoietin; **PRC:** packed red blood cells; **RR:** risk ratio

#### GRADE Working Group grades of evidence

**High certainty:** we are very confident that the true effect lies close to that of the estimate of the effect

**Moderate certainty:** we are moderately confident in the effect estimate; the true effect is likely to be close to the estimate of the effect, but there is a possibility that it is substantially different

**Low certainty:** our confidence in the effect estimate is limited; the true effect may be substantially different from the estimate of the effect

**Very low certainty:** we have very little confidence in the effect estimate; the true effect is likely to be substantially different from the estimate of effect

<sup>a</sup>The data for this outcome were reported in [Shah 2018](#), which did not include a summary of findings table. We judged the certainty of the evidence based on the information presented in the published report. We did not re-analyse the data or re-assess any risk of bias judgements in the published report.

<sup>b</sup>Derived from the pooled estimate in the control groups in [Shah 2018](#)

<sup>c</sup>We downgraded the evidence by two levels for imprecision, because the effect estimate was imprecise, and because the evidence was derived from a few participants in only two studies.

## APPENDICES

### Appendix 1. Search strategies

#### Cochrane Database of Systematic Reviews

#1 MeSH descriptor: [Arthroplasty, Replacement, Hip] this term only (2025)  
 #2 MeSH descriptor: [Hip] this term only and with qualifier(s): [surgery - SU] (61904)  
 #3 MeSH descriptor: [Osteoarthritis, Hip] this term only and with qualifier(s): [surgery - SU] (412)  
 #4 MeSH descriptor: [Hip Prosthesis] this term only (1153)  
 #5 MeSH descriptor: [Acetabuloplasty] this term only (0)  
 #6 MeSH descriptor: [Hemiarthroplasty] this term only (65)  
 #7 MeSH descriptor: [Fracture Fixation, Internal] explode all trees (1480)  
 #8 MeSH descriptor: [Open Fracture Reduction] this term only (40)  
 #9 acetabuloplast\* or acetabulum arthroplast\* (289)  
 #10 ((hip or hips or femur\* or femoral or acetabul\*) near/6 (replac\* or operat\* or postop\* or periop\* or surg\* or arthroplast\* or hemiarthroplast\* or reconstruct\* or reduction\* or repair\* or osteotom\* or alloplast\* or plast\* or resurfac\* or implant\* or prosthes\* or pinning\* or revision\*)) (13485)  
 #11 ((joint\* near/3 (replac\* or prosthes\* or implant\*)) and (hip or hips or femur\* or femoral\* or acetabul\*)) (1267)  
 #12 MeSH descriptor: [Internal Fixators] explode all trees (1813)  
 #13 (pin or pins or nail or nails or screw or screws or plate or plates or rod or rods) (14218)  
 #14 ((static\* or dynamic\*) next (device\* or implant\*)) (26)  
 #15 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11 or #12 or #13 or #14 (84122)  
 #16 MeSH descriptor: [Femoral Fractures] explode all trees (2090)  
 #17 ((hip or hips or cervical or femur\* or femoral\* or acetabul\*) near/5 (fracture\* or trauma\* or break\* or broke\* or crack\*)) (7813)  
 #18 (((head or neck or proximal) near/5 (fracture\* or trauma\* or break\* or broke\* or crack\*)) and (femoral\* or femur\*)) (2435)  
 #19 ((intracapsular or intra-capsular or subcapital or sub-capital or transcervical or trans-cervical or basicervical or basi-cervical) near/5 (fracture\* or trauma\* or break\* or broke\* or crack\*)) (287)  
 #20 ((extracapsular or extra-capsular or trochant\* or subtrochant\* or pertrochant\* or intertrochant\*) near/5 (fracture\* or trauma\* or break\* or broke\* or crack\*)) (1030)  
 #21 (hip or hips or femur\* or femoral\* or acetabul\*) (38384)  
 #22 MeSH descriptor: [Fractures, Bone] this term only (2379)  
 #23 MeSH descriptor: [Fracture Dislocation] explode all trees (12)  
 #24 MeSH descriptor: [Fractures, Closed] this term only (138)  
 #25 MeSH descriptor: [Fractures, Comminuted] this term only (56)  
 #26 MeSH descriptor: [Fractures, Compression] this term only (165)  
 #27 MeSH descriptor: [Fractures, Malunited] this term only (44)  
 #28 MeSH descriptor: [Fractures, Multiple] this term only (17)  
 #29 MeSH descriptor: [Fractures, Open] this term only (132)  
 #30 MeSH descriptor: [Fractures, Spontaneous] this term only (133)  
 #31 MeSH descriptor: [Fractures, Stress] this term only (105)  
 #32 MeSH descriptor: [Fractures, Ununited] this term only (133)  
 #33 MeSH descriptor: [Intra-Articular Fractures] this term only (56)  
 #34 MeSH descriptor: [Osteoporotic Fractures] this term only (376)  
 #35 MeSH descriptor: [Periprosthetic Fractures] this term only (21)  
 #36 #22 or #23 or #24 or #25 or #26 or #27 or #28 or #29 or #30 or #31 or #32 or #33 or #34 or #35 (3413)  
 #37 #21 and #36 (1074)  
 #38 #16 or #17 or #18 or #19 or #20 or #37 (8223)  
 #39 #15 and #38 (4229)  
 #40 MeSH descriptor: [Femoral Fractures] explode all trees and with qualifier(s): [surgery - SU] (1048)  
 #41 ((hip or hips or femur\* or femoral or acetabul\* or joint\*) near/6 (replac\* or operat\* or postop\* or periop\* or surg\* or arthroplast\* or hemiarthroplast\* or reconstruct\* or reduction\* or repair\* or osteotom\* or alloplast\* or plast\* or resurfac\* or implant\* or prosthes\* or pinning\* or revision\*)) :ti and (fracture\* or trauma\*) (2033)  
 #42 #39 or #40 or #41 (4734)  
 Cochrane Reviews (139), Cochrane Protocols (33). Total: 172

#### MEDLINE

**Interventions for reducing red blood cell transfusion in adults undergoing hip fracture surgery: an overview of systematic reviews (Review)**

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1 Arthroplasty, Replacement, Hip/ (31155)  
2 Hip/su (2978)  
3 Osteoarthritis, Hip/su (4888)  
4 Hip Prosthesis/ (24468)  
5 Acetabuloplasty/ or Hemiarthroplasty/ or exp Fracture Fixation, Internal/ or Open Fracture Reduction/ (49071)  
6 (acetabuloplast\* or acetabulum arthroplast\*).tw,kf. (397)  
7 ((hip or hips or femur\* or femoral or acetabul\*) adj6 (replac\* or operat\* or postop\* or periop\* or surg\* or arthroplast\* or hemiarthroplast\* or reconstruct\* or reduction\* or repair\* or osteotom\* or alloplast\* or plast\* or resurfac\* or implant\* or prosthes\* or pinning\* or revision\*)).mp. (99223)  
8 ((joint\* adj3 (replac\* or prosthes\* or implant\*)) and (hip or hips or femur\* or femoral\* or acetabul\*)).tw,kf. (5174)  
9 Internal Fixators/ or Bone Nails/ or Bone Plates/ or exp Bone Screws/ (53387)  
10 (pin or pins or nail or nails or screw or screws or plate or plates or rod or rods).tw,kf. (310605)  
11 ((static\* or dynamic\*) adj (device\* or implant\*)).tw,kf. (230)  
12 or/1-11 (434391)  
13 exp Femoral Fractures/ (42326)  
14 ((hip or hips or cervical or femur\* or femoral\* or acetabul\*) adj5 (fracture\* or trauma\* or break\* or broke\* or crack\*)).tw,kf. (58805)  
15 (((head or neck or proximal) adj5 (fracture\* or trauma\* or break\* or broke\* or crack\*)) and (femoral\* or femur\*)).tw,kf. (14775)  
16 ((intracapsular or intra-capsular or subcapital or sub-capital or transcervical or trans-cervical or basicervical or basi-cervical) adj5 (fracture\* or trauma\* or break\* or broke\* or crack\*)).tw,kf. (1840)  
17 ((extracapsular or extra-capsular or trochant\* or subtrochant\* or pertrochant\* or intertrochant\*) adj5 (fracture\* or trauma\* or break\* or broke\* or crack\*)).tw,kf. (6622)  
18 (hip or hips or femur\* or femoral\* or acetabul\*).tw,kf. and (fractures, bone/ or exp fracture dislocation/ or fractures, closed/ or fractures, comminuted/ or fractures, compression/ or fractures, malunited/ or fractures, multiple/ or fractures, open/ or fractures, spontaneous/ or exp fractures, stress/ or fractures, ununited/ or intra-articular fractures/ or osteoporotic fractures/ or periprosthetic fractures/) (18249)  
19 or/13-18 (75049)  
20 12 and 19 (34459)  
21 exp Femoral Fractures/su (21458)  
22 ((hip or hips or femur\* or femoral or acetabul\* or joint\*) adj6 (replac\* or operat\* or postop\* or periop\* or surg\* or arthroplast\* or hemiarthroplast\* or reconstruct\* or reduction\* or repair\* or osteotom\* or alloplast\* or plast\* or resurfac\* or implant\* or prosthes\* or pinning\* or revision\*)).ti,kf. and (fracture\* or trauma\*).tw,kf. (13453)  
23 20 or 21 or 22 (41172)  
24 Meta-Analysis/ or Network Meta-Analysis/ (151162)  
25 Systematic Review/ (181023)  
26 "Systematic Reviews as Topic"/ (7233)  
27 ((meta analy\* or metaanaly\*) and (trials or studies)).ab. (170466)  
28 (meta analy\* or metaanaly\* or evidence-based).ti. (176422)  
29 ((systematic\* or evidence-based) adj2 (review\* or overview\*)).tw,kf. (251987)  
30 (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. (340489)  
31 Cochrane Database of systematic reviews.jn. (15714)  
32 ((additional adj (papers or articles or sources)) or (relevant adj (journals or articles))).ab. (17504)  
33 \*Evidence Based Medicine/ (26730)  
34 ((electronic\* or online) adj (sources or resources or databases)).ab. (36686)  
35 network meta-analys\*.tw,kf. (6450)  
36 or/24-35 (551679)  
37 Review.pt. (2917485)  
38 Randomized Controlled Trials as Topic/ (151648)  
39 selection criteria.ab. or critical appraisal.ti. (36713)  
40 (data adj (abstraction or extraction or analys\*)).ab. (113420)  
41 Randomized Controlled Trial/ (554956)  
42 or/38-41 (827579)  
43 37 and 42 (92385)  
44 36 or 43 (590397)  
45 (Animals/ or exp Animal Experimentation/ or exp Models, Animal/) not Humans/ (4907706)  
46 Editorial.pt. (591670)  
47 45 or 46 (5487429)  
48 44 not 47 (576554)  
49 23 and 48 (1372)

## PubMed



#1 (((hip OR hips OR femur\* OR femoral OR acetabul\*) AND (replac\* OR operating OR operated OR operation OR operations OR postop\* OR periop\* OR surger\* OR surgical\* OR arthroplast\* OR hemiarthroplast\* OR reconstruct\* OR reduction\* OR repair\* OR osteotom\* OR alloplast\* OR plasty OR plasties OR resurfac\* OR implant OR implants OR implanted OR implantation\* OR prosthes\* OR pinning\* OR revision\*)) OR ((joint\* AND (replac\* OR prosthes\* OR implant OR implants OR implanted OR implantation\* OR prosthes\*)) AND (hip OR hips OR femur\* OR femoral\* OR acetabul\*)) OR (acetabuloplast\* OR acetabulum arthroplast\* OR pin OR pins OR nail OR nails OR screw OR screws OR plate OR plates OR rod OR rods) OR ((static\* OR dynamic\*) AND (device\* OR implant OR implants OR implanted OR implantation\*)) (614,956)  
#2 ((hip OR hips OR cervical OR femur\* OR femoral\* OR acetabul\*) AND (fracture\* OR trauma OR traumas OR traumatic\* OR break\* OR broke\* OR crack\*)) OR (((head OR neck OR proximal) AND (fracture\* OR trauma OR traumas OR traumatic\* OR break\* OR broke\* OR crack\*)) AND (femoral\* OR femur\*)) OR ((intracapsular OR intra-capsular OR subcapital OR sub-capital OR transcervical OR trans-cervical OR basicervical OR basi-cervical) AND (fracture\* OR trauma OR traumas OR traumatic\* OR break\* OR broke\* OR crack\*)) OR ((extracapsular OR extra-capsular OR trochant\* OR subtrochant\* OR pertrochant\* OR intertrochant\*) AND (fracture\* OR trauma OR traumas OR traumatic\* OR break\* OR broke\* OR crack\*)) (190,843)  
#3 #1 AND #2 (89,207)  
#4 ((hip OR hips OR femur\* OR femoral OR acetabul\* OR joint\*) AND (replac\* OR operating OR operated OR operation OR operations OR postop\* OR periop\* OR surger\* OR surgical\* OR arthroplast\* OR hemiarthroplast\* OR reconstruct\* OR reduction\* OR repair\* OR osteotom\* OR alloplast\* OR plasty OR plasties OR resurfac\* OR implant OR implants OR implanted OR implantation\* OR prosthes\* OR pinning\* OR revision\*)) AND (fracture\* OR trauma OR traumas OR traumatic\*) (164,368)  
#5 #3 OR #4 (170,319)  
#6 systematic[sb] AND (publisher[sb] OR inprocess[sb] OR pubmednotmedline[sb]) (36142)  
#7 #5 AND #6 (380)  
#8 pubstatusaheadofprint (282,639)  
#9 #7 and #8 (94)

## Embase

1 exp hip arthroplasty/ (31426)  
2 hip/su (1517)  
3 hip osteoarthritis/su (4392)  
4 hip prosthesis/ (11866)  
5 hemiarthroplasty/ or exp fracture treatment/ (120776)  
6 (acetabuloplast\* or acetabulum arthroplast\*).tw,kw. (439)  
7 ((hip or hips or femur\* or femoral or acetabul\*) adj6 (replac\* or operat\* or postop\* or periop\* or surg\* or arthroplast\* or hemiarthroplast\* or reconstruct\* or reduction\* or repair\* or osteotom\* or alloplast\* or plast\* or resurfac\* or implant\* or prosthes\* or pinning\* or revision\*)).mp. (127546)  
8 ((joint\* adj3 (replac\* or prosthes\* or implant\*)) and (hip or hips or femur\* or femoral\* or acetabul\*)).tw,kw. (6899)  
9 exp bone plate/ or bone implant/ or exp bone nail/ or exp bone pin/ or exp femoral fixation device/ or exp bone prosthesis/ or exp bone screw/ (75602)  
10 (pin or pins or nail or nails or screw or screws or plate or plates or rod or rods).tw,kw. (367227)  
11 ((static\* or dynamic\*) adj (device\* or implant\*)).tw,kw. (328)  
12 or/1-11 (578854)  
13 exp hip fracture/ or exp femur fracture/ (63790)  
14 ((hip or hips or cervical or femur\* or femoral\* or acetabul\*) adj5 (fracture\* or trauma\* or break\* or broke\* or crack\*)).tw,kw. (72455)  
15 (((head or neck or proximal) adj5 (fracture\* or trauma\* or break\* or broke\* or crack\*)) and (femoral\* or femur\*)).tw,kw. (16634)  
16 ((intracapsular or intra-capsular or subcapital or sub-capital or transcervical or trans-cervical or basicervical or basi-cervical) adj5 (fracture\* or trauma\* or break\* or broke\* or crack\*)).tw,kw. (2032)  
17 ((extracapsular or extra-capsular or trochant\* or subtrochant\* or pertrochant\* or intertrochant\*) adj5 (fracture\* or trauma\* or break\* or broke\* or crack\*)).tw,kw. (7785)  
18 (hip or hips or femur\* or femoral\* or acetabul\*).tw,kw. and (fracture/ or fragility fracture/ or intraarticular fracture/ or joint fracture/ or multiple fracture/ or open fracture/ or pathologic fracture/ or periprosthetic fracture/) (28650)  
19 or/13-18 (103244)  
20 12 and 19 (46982)  
21 exp hip fracture/su or exp femur fracture/su (20669)  
22 ((hip or hips or femur\* or femoral or acetabul\* or joint\*) adj6 (replac\* or operat\* or postop\* or periop\* or surg\* or arthroplast\* or hemiarthroplast\* or reconstruct\* or reduction\* or repair\* or osteotom\* or alloplast\* or plast\* or resurfac\* or implant\* or prosthes\* or pinning\* or revision\*)).ti,kw. and (fracture\* or trauma\*).tw,kw. (14759)  
23 20 or 21 or 22 (52020)  
24 Meta Analysis/ (233623)  
25 Systematic Review/ (326774)  
26 (meta analy\* or metaanalys\*).tw,kw. (288462)  
27 ((systematic\* or literature) adj2 (review\* or overview\* or search\*)).tw,kw. (566397)

28 (evidence syntheses\* or scopus or cochrane or embase or EBSCO or cinahl or cinhal or lilacs or BIDS or Google Scholar or Google database or Wanfang or science citation index or psyclit or psychlit or psycinfo or psychinfo or cancerlit or "web of science" or grey literature or gray literature or evidence library or trip database).tw. (284888)

29 ((additional adj (articles or papers or sources)) or (relevant adj (journals or articles))).ab. (21579)

30 (reference lists or bibliograph\* or handsearch\* or hand search\* or manual\* search\* or search term\* or published articles or search strateg\*).ab. (104520)

31 or/24-30 (865126)

32 (data extraction or selection criteria or (critical\* adj1 apprais\*)).tw,kw. (87692)

33 review.pt. or review/ (2929698)

34 32 and 33 (40102)

35 31 or 34 (871150)

36 Animal experiment/ not (human experiment/ or human/) (2378886)

37 35 not 36 (868653)

38 23 and 37 (2263)

## Epistemonikos

Study Type: Systematic Review

Title/Abstract: (((hip OR hips OR femur\* OR femoral OR acetabul\*) AND (replac\* OR operat\* OR postop\* OR periop\* OR surg\* OR arthroplast\* OR hemiarthroplast\* OR reconstruct\* OR reduction\* OR repair\* OR osteotom\* OR alloplast\* OR plast\* OR resurfac\* OR implant\* OR prosthes\* OR pinning\* OR revision\*)) OR ((joint\* AND (replac\* OR prosthes\* OR implant\*)) AND (hip OR hips OR femur\* OR femoral\* OR acetabul\*)) OR (acetabuloplast\* OR acetabulum arthroplast\* OR pin OR pins OR nail OR nails OR screw OR screws OR plate OR plates OR rod OR rods) OR ((static\* OR dynamic\*) AND (device\* OR implant\*)))

AND  
Title/Abstract: ((hip OR hips OR cervical OR femur\* OR femoral\* OR acetabul\*) AND (fracture\* OR trauma\* OR break\* OR broke\* OR crack\*)) OR (((head OR neck OR proximal) AND (fracture\* OR trauma\* OR break\* OR broke\* OR crack\*)) AND (femoral\* OR femur\*)) OR ((intracapsular OR intra-capsular OR subcapital OR sub-capital OR transcervical OR trans-cervical OR basicervical OR basi-cervical) AND (fracture\* OR trauma\* OR break\* OR broke\* OR crack\*)) OR ((extracapsular OR extra-capsular OR trochant\* OR subtrochant\* OR pertrochant\* OR intertrochant\*) AND (fracture\* OR trauma\* OR break\* OR broke\* OR crack\*))

OR  
Abstract/Title: ((hip OR hips OR femur\* OR femoral OR acetabul\* OR joint\*) AND (replac\* OR operat\* OR postop\* OR periop\* OR surg\* OR arthroplast\* OR hemiarthroplast\* OR reconstruct\* OR reduction\* OR repair\* OR osteotom\* OR alloplast\* OR plast\* OR resurfac\* OR implant\* OR prosthes\* OR pinning\* OR revision\*)) AND Title/Abstract: (fracture\* OR trauma\*)

Total: 1652

## PROSPERO

#1 MeSH DESCRIPTOR Femoral Fractures EXPLODE ALL TREES (188)

#2 ((hip or hips or femur or femoral or acetabular) AND (fracture\* OR trauma\* OR break\* OR broke\* OR crack\*)) (1451)

#3 #1 OR #2 (1456)

#4 MeSH DESCRIPTOR Arthroplasty, Replacement, Hip EXPLODE ALL TREES (239)

#5 MeSH DESCRIPTOR Fracture Fixation EXPLODE ALL TREES (145)

#6 ((hip or hips or femur or femoral or acetabular) AND (replac\* or operat\* or postop\* or periop\* or surg\* or arthroplast\* or hemiarthroplast\* or reconstruct\* or reduction\* or repair\* or osteotom\* or alloplast\* or plast\* or resurfac\* or implant\* or prosthes\* or pinning\* or revision\*)) (2540)

#7 #4 OR #5 OR #6 (2657)

#8 #3 AND #7 (1114)

## Transfusion Evidence Library

Clinical Speciality: Surgery / Orthopaedic Surgery

Study Design: Systematic Review

OR

Search terms: hip fracture OR femur fracture OR femoral fracture OR acetabular fracture

Study Design: Systematic Review

Total: 20

## Web of Science

#1 TS=((hip or hips or femur\* or femoral or acetabul\*) near/6 (replac\* or operat\* or postop\* or periop\* or surg\* or arthroplast\* or hemiarthroplast\* or reconstruct\* or reduction\* or repair\* or osteotom\* or alloplast\* or plast\* or resurfac\* or implant\* or prosthes\* or pinning\* or revision\*)) (90,240)

#2 TS=((joint\* near/3 (replac\* or prothes\* or implant\*)) and (hip or hips or femur\* or femoral\* or acetabul\*)) (8,134)  
#3 TS=(pin or pins or nail or nails or screw or screws or plate or plates or rod or rods) (950,364)  
#4 TS=((static\* or dynamic\*) near/1 (device\* or implant\*)) (4,277)  
#5 #4 OR #3 OR #2 OR #1 (1,037,729)  
#6 TS=((hip or hips or cervical or femur\* or femoral\* or acetabul\*) near/5 (fracture\* or trauma\* or break\* or broke\* or crack\*)) (63,772)  
#7 TS=((((head or neck or proximal) near/5 (fracture\* or trauma\* or break\* or broke\* or crack\*)) and (femoral\* or femur\*)) (12,904)  
#8 TS=((intracapsular or intra-capsular or subcapital or sub-capital or transcervical or trans-cervical or basicervical or basi-cervical) near/5 (fracture\* or trauma\* or break\* or broke\* or crack\*)) (1,892)  
#9 TS=((extracapsular or extra-capsular or trochant\* or subtrochant\* or pertrochant\* or intertrochant\*) near/5 (fracture\* or trauma\* or break\* or broke\* or crack\*)) (5,410)  
#10 #9 OR #8 OR #7 OR #6 (65,550)  
#11 #10 AND #5 (23,384)  
#12 TI=((hip or hips or femur\* or femoral or acetabul\* or joint\*) near/6 (replac\* or operat\* or postop\* or periop\* or surg\* or arthroplast\* or hemiarthroplast\* or reconstruct\* or reduction\* or repair\* or osteotom\* or alloplast\* or plast\* or resurfac\* or implant\* or prothes\* or pinning\* or revision\*)) and TS=(fracture\* or trauma\*) (11,857)  
#13 #12 OR #11 (26,760)  
#14 TS=("systematic review" OR "systematic reviews" OR "review of reviews" OR "systematic overview" OR meta-analysis OR metaanalysis) OR TI=(systematic\*) (644,598)  
#15 TS=("evidence synthesis" or scopus or cochrane or embase or EBSCO or cinahl or cinhal or lilacs or BIDS or "Google Scholar" or "Google database" or Wanfang or "science citation index" or psyclit or psychlit or psycinfo or psychinfo or cancerlit or "web of science" or "grey literature" or "gray literature" or "evidence library" or "trip database") (258,186)  
#16 #15 OR #14 (751,842)  
#17 #16 AND #13 (1,422)

## Appendix 2. AMSTAR 2: questions from the critical appraisal tool

1. Did the research questions and inclusion criteria for the review include the components of the criteria for participants, intervention, comparison, and outcomes (PICO)?
2. Did the report of the review contain an explicit statement that the review methods were established prior to the conduct of the review and did the report justify any significant deviations from the protocol?
3. Did the review authors explain their selection of the study designs for inclusion in the review?
4. Did the review authors use a comprehensive literature search strategy?
5. Did the review authors perform study selection in duplicate?
6. Did the review authors perform data extraction in duplicate?
7. Did the review authors provide a list of excluded studies and justify the exclusions?
8. Did the review authors describe the included studies in adequate detail?
9. Did the review authors use a satisfactory technique for assessing the risk of bias in individual studies that were included in the review?
10. Did the review authors report on the sources of funding for the studies included in the review?
11. If meta-analysis was performed did the review authors use appropriate methods for statistical combination of results?
12. If meta-analysis was performed, did the review authors assess the potential impact of risk of bias in individual studies on the results of the meta-analysis or other evidence synthesis?
13. Did the review authors account for RoB in individual studies when interpreting/ discussing the results of the review?
14. Did the review authors provide a satisfactory explanation for, and discussion of, any heterogeneity observed in the results of the review?
15. If they performed quantitative synthesis did the review authors carry out an adequate investigation of publication bias (small study bias) and discuss its likely impact on the results of the review?
16. Did the review authors report any potential sources of conflict of interest, including any funding they received for conducting the review?

## Appendix 3. Excluded reviews

Review ID	Review title	Review characteristics and reason for exclusion
<a href="#">Alcock 2021</a>	Reversal of direct oral anti-coagulants (DOACs) in hip fracture patients. A systematic review and meta-analysis	No RCTs in the review

(Continued)

<a href="#">Brunskill 2015</a>	Red blood cell transfusion for people undergoing hip fracture surgery	Review compares RBC transfusion versus no transfusion or an alternative to transfusion, different transfusion protocols or different transfusion thresholds
<a href="#">Charity 2015</a>	The use of intravenous tranexamic acid in hip fracture surgery	Unpublished due to similarity to other review ( <a href="#">Farrow 2016</a> )
<a href="#">Chawla 2018</a>	Cell salvage and auto-transfusion in patients undergoing surgical treatment for fractured neck of femur: a systematic review	Review incomplete and review authors have no plans to resume
<a href="#">Chen 2020</a>	Meta-analysis of the efficacy of platelet-rich plasma combined with cannulated screw fixation for the treatment of femoral neck fracture	Review evaluates the effect of platelet-rich plasma combined with cannulated screw fixation on healing rate and does not measure outcomes related to blood loss
<a href="#">Gausden 2017</a>	Tranexamic acid in orthopaedic trauma surgery: a meta-analysis	RCTs and NRS are not separated
<a href="#">Kates 2016</a>	Hip fracture programs: are they effective?	Review compares care programmes on length of hospital stay, mortality, and readmittance rates and does not measure outcomes related to blood loss
<a href="#">Krishnan 2015</a>	Comparison of staples versus sutures for skin closure after orthopedic surgery	Review compares staples with sutures on the incidence of infection and does not measure outcomes related to blood loss
<a href="#">Kristan 2021</a>	Does preoperative therapy with direct oral anti-coagulants affect the length of stay in patients with hip fracture?	Review compares preoperative therapy with direct oral anticoagulants with patients who did not receive such treatment and does not measure outcomes related to blood loss
<a href="#">Lewis 2016</a>	Perioperative fluid volume optimization following proximal femoral fracture	Review compares the safety and effectiveness of perioperative fluid optimization and does not measure outcomes related to blood loss
<a href="#">Martinez 2013</a>	Preventing delirium: should non-pharmacological interventions be used? A systematic review.	Review compares the effectiveness of non-pharmacological interventions on the development of delirium and does not measure outcomes related to blood loss
<a href="#">Moppett 2015</a>	LiDCO-based fluid management in patients undergoing hip fracture surgery under spinal anaesthesia: a randomized trial and systematic review	Review compares the effectiveness of perioperative fluid management and does not measure outcomes related to blood loss
<a href="#">Perel 2013</a>	Tranexamic acid for reducing mortality in emergency and urgent surgery	Review included a mixed population and we had sufficient evidence from other reviews of TXA
<a href="#">Prodromidis 2021</a>	Is perioperative hypothermia associated with increased 30-day mortality in hip fracture patients in the UK? A systematic review and meta-analysis	Review compares perioperative body temperatures in patients and does not measure outcomes related to blood loss
<a href="#">Reale 2021</a>	Complications of tranexamic acid in orthopedic lower limb surgery: a meta-analysis of randomized controlled trials	Review does not measure outcomes related to blood loss

(Continued)

<a href="#">Sukeik 2010</a>	Tranexamic acid in total hip replacements: a meta-analysis	Publication does not contain enough information to determine whether participants have hip fractures
<a href="#">Virsooe-Frandsen 2019</a>	Preoperative interventions for the prevention of delirium in hip fracture patients: a systematic review	Review compares pre-operative interventions on delirium and does not measure outcomes related to blood loss
<a href="#">Wang 2018</a>	The efficacy of oral versus intravenous tranexamic acid in reducing blood loss after primary total knee and hip arthroplasty: A meta-analysis	Review had the wrong comparator
<a href="#">Ye 2021</a>	Meta analysis of the effect of recombinant human erythropoietin combined with iron in the treatment of senile hip fracture with perioperative anemia	The review incorrectly categorised included studies. In addition, there is no overlap of any of the studies in the other iron/EPO reviews. Therefore, we excluded this review because we could not be certain of its integrity

EPO: erythropoietin; NRS: non-randomised studies; RBC: red blood cell; RCT: randomised controlled trial; TXA: tranexamic acid

#### Appendix 4. Ongoing reviews

Review ID	Review title	Review characteristics
<a href="#">Gibbs 2020</a>	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	Hip, pelvic, and long bone fractures; RCTs; pharmacological interventions (including tranexamic acid) for preventing blood loss in definitive surgical fixation. Review authors have completed data extraction and are writing up the report
<a href="#">Sargazi 2016</a>	Systematic review of the role of tranexamic acid in hip fracture surgery	Neck of femur fractures; RCTs and NRS; use of perioperative IV tranexamic acid (single or multiple doses) compared with no IV tranexamic acid administered (placebo given)
<a href="#">Singh 2021</a>	Tranexamic acid in patients undergoing hip hemiarthroplasty: is it worth using in every patient? An updated systematic review	Femoral neck fractures; RCTs and NRS; tranexamic acid administration during the perioperative period in elderly participants compared with no control, or participants who did not receive tranexamic acid during hemiarthroplasty

IV: intravenous(ly); NRS: non-randomised studies; RCTs: randomised controlled trials

#### Appendix 5. Reviews awaiting classification

Review ID	Review title	Review characteristics
<a href="#">Liu 2020</a>	Efficacy and safety of tranexamic acid in the arthroplasty of femoral neck fractures: a systematic review and meta-analysis	Participants with femoral neck fractures undergoing total hip arthroplasty or hemiarthroplasty; RCTs; IV or topical perioperative administration of tranexamic acid compared with either placebo or no treatment. Listed as completed on PROSPERO (CRD42020184024). We attempted to contact review authors but received no reply

(Continued)

Mianguel 2021	Update on the efficacy and safety of intravenous tranexamic acid in hip fracture surgery: a systematic review and meta-analysis	Participants undergoing hip fracture related surgery; RCTs; IV tranexamic acid compared with placebo. Review in the editorial process with publication pending
Zhang 2020a	Comparison of efficacy and safety in total hip arthroplasty by topical, intravenous application or combined application of tranexamic acid: a meta-analysis	Participants undergoing total hip arthroplasty for hip fracture; RCTs; combined IV and topical tranexamic administration compared to each group separately. Dates on PROSPERO (CRD42020192136) indicate review should be completed; we attempted to contact review authors but received no reply

IV: intravenous(ly); RCTs: randomised controlled trials

## Appendix 6. Characteristics of included systematic reviews evaluating tranexamic acid

Agius 2022	
<b>Review information</b>	<p><b>Comparison:</b> IV TXA vs placebo or no treatment</p> <p><b>Aim:</b> to investigate the effect of IV TXA in hip fracture on blood product utilisation during hip fracture surgery. The secondary aim was to evaluate the safety of TXA in relation to the development of thromboembolic events</p> <p><b>Protocol/trial registration:</b> CRD42021218708</p> <p><b>Sources of funding:</b> none</p> <p><b>Declarations of interest:</b> review authors declare no conflicts of interest</p>
<b>Search methods</b>	<p><b>Date of search:</b> February 2021</p> <p><b>Databases:</b> 4 databases: CENTRAL; MEDLINE; PubMed; Embase</p> <p><b>Additional searches:</b> searched references lists, and contacted authors of studies for which full-text reports were not published</p> <p><b>Any restrictions or limitations on searches:</b> limited to full-text articles published in English from 2010 onwards</p> <p><b>Methods to select studies and extract data:</b> titles and abstracts screened by 2 independent review authors with disagreements resolved by a third person. Did not specify how many review authors conducted data extraction and risk of bias assessment</p> <p><b>Methods to assess risk of bias:</b> Cochrane ROB 2 tool (Sterne 2019)</p> <p><b>Methods to judge certainty of evidence:</b> GRADE</p>
<b>Review criteria</b>	<p><b>Types of study designs:</b> RCTs</p> <p><b>Inclusion criteria:</b> adults (&gt; 18 years of age) with hip/proximal femoral fractures who require surgery</p> <p><b>Exclusion criteria:</b> undergoing elective or planned surgery, administration of oral, subfascial or topical TXA, did not examine review outcomes, observational or cohort studies, case reports or series</p>



(Continued)

## Outcomes

**All outcomes reported in review:** blood transfusion requirements, rates of venous thromboembolism

**Review primary outcome:** number of people with blood transfusion

**Outcomes relevant to this overview:** number of people with blood transfusion; venous thromboembolism

**Data analysis methods:** RR for dichotomous outcomes, and RD for continuous data. Effect model choice dictated by levels of heterogeneity. Sensitivity analysis when  $I^2 > 75\%$

## Baskaran 2018

### Review information

**Comparison:** IV TXA vs placebo or no treatment

**Aim:** to investigate the efficacy of TXA in hip fracture surgery on operative and total blood loss, ABT requirements and VTE incidence

**Protocol/trial registration:** not specified

**Sources of funding:** none

**Declarations of interest:** review authors declared no conflicts

### Search methods

**Date of search:** 1 July 2016

**Databases:** 7 databases: MEDLINE; PubMed, Embase, Cochrane and Controlled Trials Register<sup>a</sup>, Ovid<sup>a</sup>, Trip<sup>a</sup>, and Google<sup>a</sup>

**Additional searches:** not specified

**Any restrictions or limitations on searches:** no language limitations described but non-English studies were excluded

**Methods to select studies and extract data:** standardised checklist to analyse each paper for potential inclusion and exclusion. The searches were then distributed to 2 independent review authors and reviewed for similarities in study design, methodology, participant demographics, and outcomes measured according to the checklist

**Methods to assess risk of bias:** MMAT and Cochrane RoB 1 (Higgins 2011)

**Methods to judge certainty of evidence:** not specified. We assumed certainty was not assessed

### Review criteria

**Types of study designs:** RCTs and NRS

**Inclusion criteria:** people undergoing hip fracture surgery

**Exclusion criteria:** non-English language studies; compared non-IV administration routes of TXA; or not part of complete articles

## Outcomes

**All outcomes reported in review:** blood loss, receipt of ABT, number of blood transfusions per participant, number of participants with a VTE

**Review primary outcome:** not specified. Total blood loss is the first outcome reported

**Outcomes relevant to this overview:** number of people with blood transfusion; adverse events (VTE)

**Data analysis methods:** random effects model for all continuous variables

## Farrow 2016

### Review information

**Comparison:** IV TXA vs control (type of control not specified)

(Continued)

**Aim:** to systematically examine and quantify the efficacy and safety of TXA in hip fracture surgery

**Protocol/trial registration:** PROSPERO CRD42016036806

**Sources of funding:** none

**Declarations of interest:** "no financial relationships with any organizations that might have an interest in the submitted work in the previous 3 years; no other relationships or activities that could appear to have influenced the submitted work"

## Search methods

**Date of search:** 18 June 2016

**Databases:** 5 databases: MEDLINE, Embase, AMED, CINAHL, and the Cochrane Central Registry of Controlled Trials<sup>a</sup>

**Additional searches:** search of unpublished/grey literature databases was undertaken including: OpenGrey, Current Clinical Trials, the WHO registry of clinical trials and clinaltrials.gov.

An additional online search was undertaken using the Google search engine to identify any papers that may have been omitted from the initial search, and to cross-reference against the database search

**Any restrictions or limitations on searches:** no restrictions described, but non-English studies were excluded

**Methods to select studies and extract data:** 2 review authors independently screened titles and abstracts; data were extracted onto a predefined data extraction sheet by one review author and verified by a second review author

**Methods to assess risk of bias:** Cochrane RoB 1 ([Higgins 2011](#))

**Methods to judge certainty of evidence:** GRADE

## Inclusion criteria

**Types of study designs:** RCTs and NRS

**Inclusion criteria:** people undergoing any form of hip fracture surgery, including open reduction internal fixation (cannulated screws, dynamic hip screws, intramedullary devices), hemiarthroplasty, and THA for trauma

**Exclusion criteria:** review articles and studies that included assessment of primary THA (elective), hip arthroscopy or any form of non-trauma hip surgery; non-English language publications

## Outcomes

**All outcomes reported:** frequency of postoperative blood transfusion, post-operative haemoglobin, perioperative blood loss, frequency of thromboembolic events, length of hospital stay, and complications within the initial 90 days postoperatively. Outcomes were assessed as either intra-operative, short-term (hospital admission) or longer-term (post-hospital discharge)

**Review primary outcome:** frequency of postoperative blood transfusion

**Outcomes relevant to this overview:** number of people with blood transfusions; adverse events (thromboembolic events, CVA, PE, DVT)

**Data analysis methods:** meta-analysis when there was clinical homogeneity between studies. When  $I^2$  was  $\leq 20\%$  and  $\text{Chi}^2$  equated to  $P \geq 0.10$ , a fixed-effect model meta-analysis was undertaken; when these were not satisfied, a random-effects meta-analysis was undertaken

## Haj-Younes 2020

### Review information

**Comparison:** IV TXA (any dose or formulation) vs placebo or no TXA

**Aim:** to determine whether TXA reduces transfusion rates in people undergoing surgery for hip fractures; and to assess the effects of TXA on mortality and thromboembolic events

**Protocol/trial registration:** not specified

(Continued)

	<b>Sources of funding:</b> none  <b>Declarations of interest:</b> review authors declared no conflicts of interest
<b>Search methods</b>	<b>Date of search:</b> March 2019  <b>Databases:</b> 4 databases: CENTRAL, MEDLINE, Embase, ISI Web of Science: Science Citation Index Expanded  <b>Additional searches:</b> 1 clinical trials register: WHO International Clinical Trials Registry Portal  <b>Any restrictions or limitations on searches:</b> not limited by date, language, or publication status  <b>Methods to select studies and extract data:</b> systematic search by 2 separate review authors, no other details  <b>Methods to assess risk of bias:</b> Cochrane risk of bias tool <sup>b</sup>  <b>Methods to judge certainty of evidence:</b> not specified. We assumed certainty was not assessed
<b>Inclusion criteria</b>	<b>Types of study designs:</b> RCTs  <b>Inclusion criteria:</b> > 18 years of age, treated surgically for hip/proximal femoral fractures (AO types 31-A and 31-B)  <b>Exclusion criteria:</b> not specified
<b>Outcomes</b>	<b>All outcomes reported:</b> proportion of people requiring a blood transfusion, number of units of blood transfused, mortality, and morbidity (including DVT, PE, acute coronary events, CVA, and wound complications). Initial plan to include blood loss, but not included in meta-analysis because of heterogeneity in the manner of collection and reporting of these data  <b>Review primary outcome:</b> proportion of people requiring a blood transfusion  <b>Outcomes relevant to this overview:</b> number of people with blood transfusion, volume of blood transfusion, adverse events (DVT, PE, acute coronary syndrome, CVA, wound complications)  <b>Data analysis methods:</b> data from the trials were pooled using the generic inverse variance method with random effects model
<b>Jiang 2019</b>	
<b>Review information</b>	<b>Comparison:</b> IV and topical TXA vs placebo  <b>Aim:</b> to evaluate if TXA results in less blood loss and incidence of blood transfusion, but provides similar complication rates than placebo in intertrochanteric fracture surgery  <b>Protocol/trial registration:</b> Research Registry (reviewregistry622)  <b>Sources of funding:</b> not specified  <b>Declarations of interest:</b> review authors declared no conflicts of interest
<b>Search methods</b>	<b>Date of search:</b> October 2017  <b>Databases:</b> Cochrane Library, PubMed, Embase, Google database, and Chinese Wanfang database  <b>Additional searches:</b> reference lists of related review articles and original studies were searched  <b>Any restrictions or limitations on searches:</b> no restriction on language or publication date  <b>Methods to select studies and extract data:</b> 2 independent review authors screened the titles and abstracts of the identified studies after removing duplicates from the search results, with disagreements resolved through discussion or consultation with an expert

(Continued)

**Methods to assess risk of bias:** Cochrane risk of bias tool ([Higgins 2011](#))

**Methods to judge certainty of evidence:** not specified. We assumed certainty was not assessed

**Inclusion criteria**
**Types of study designs:** RCTs

**Inclusion criteria:** people prepared for intertrochanteric fracture surgery

**Exclusion criteria:** not specified

**Outcomes**
**All outcomes reported:** total blood loss, blood loss in drainage, haemoglobin on postoperative day 3, length of hospital stay, need for transfusion, DVT, PE, infection and haematoma

**Review primary outcome:** total blood loss

**Outcomes relevant to this overview:** number of people with blood transfusion, adverse events (DVT, PE, infection, and haematoma)

**Data analysis methods:** when there was no statistical evidence of heterogeneity ( $I^2 < 50\%$ ,  $P > 0.1$ ), a fixed-effects model was adopted; otherwise, a random effects model was chosen

**Liu 2022**
**Review information**
**Comparison:** IV, topical, or combined IV and topical TXA vs placebo or no treatment

**Aim:** to provide a more updated and rigorous analysis of the efficacy and safety of TXA for people undergoing hip fracture surgery, as well as to disclose the optimal route, dosage, and frequency for TXA administration to better guide surgeons in clinical practice

**Protocol/trial registration:** not specified

**Sources of funding:** none

**Declarations of interest:** review authors declared no conflicts of interest

**Search methods**
**Date of search:** February 2021

**Databases:** 5 databases: PubMed, Embase, Web of Science, Cochrane and Controlled Trials Register<sup>a</sup>, and Scopus

**Additional searches:** reference lists of the eligible studies and relevant reviews

**Any restrictions or limitations on searches:** no restrictions on language and status of publication

**Methods to select studies and extract data:** data extracted by 2 independent review authors according to a predefined standardised checklist with any disagreements settled by consensus

**Methods to assess risk of bias:** MMAT, and Cochrane RoB 1 ([Higgins 2011](#))

**Methods to judge certainty of evidence:** not specified. We assumed certainty was not assessed

**Inclusion criteria**
**Types of study designs:** RCTs and NRS

**Inclusion criteria:** people undergoing hip fracture surgery (type not specified)

**Exclusion criteria:** if studies did not satisfy the inclusion criteria, assessed any form of non-trauma hip surgery (e.g. elective arthroplasty for osteoarthritis), or were review articles, case reports, or abstracts

**Outcomes**
**All outcomes reported:** transfusion rate, blood loss, change of haemoglobin level, postoperative drainage, incidence of thromboembolic events (DVT, PE, MI, CVA), mortality

**Review primary outcome:** total transfusion rate and total blood loss

(Continued)

**Outcomes relevant to this overview:** number of people with blood transfusion, adverse events (thromboembolic events), mortality (time point not clearly specified)

**Data analysis methods:** random-effects model was used when significant heterogeneity was presented ( $P < 0.1$  or  $I^2 > 50\%$ ), or fixed-effect model in the absence of statistical heterogeneity

## Luo 2020

### Review information

**Comparison:** IV and topical TXA vs control

**Aim:** to evaluate the efficacy and safety of TXA in elderly people with intertrochanteric fractures treated by intramedullary fixation surgery

**Protocol/trial registration:** PROSPERO CRD42019121457

**Sources of funding:** none

**Declarations of interest:** review authors declared no conflicts of interest

### Search methods

**Date of search:** December 2018

**Databases:** 3 databases: Cochrane Library<sup>a</sup>, MEDLINE, Embase

**Additional searches:** review authors also read and retrieved references "from the literature"

**Any restrictions or limitations on searches:** not specified

**Methods to select studies and extract data:** 2 review authors extracted data from the included studies using a pre-designed data extraction form. One review author extracted the data, and the other checked the extracted data, with disagreements resolved through discussion.

**Methods to assess risk of bias:** Cochrane risk of bias tool<sup>b</sup>

**Methods to judge certainty of evidence:** not specified. We assumed certainty was not assessed

### Inclusion criteria

**Types of study designs:** RCTs

**Inclusion criteria:** elderly people with intertrochanteric fractures treated with intramedullary fixation surgery

**Exclusion criteria:** RCTs were excluded if they were low-quality RCTs, included people  $< 60$  years of age, had incomplete reporting of primary outcomes, or lost more than 20% participants prior to follow-up, were repeated publication articles, or were published in a language other than English

### Outcomes

**All outcomes reported:** total blood loss, transfusion rate, and transfusion volume, intraoperative visible blood loss, hidden blood loss, postoperative Hb values, the occurrence of thrombotic events including DVT, PE, cerebral infarction, and mortality within 3 months

**Review primary outcome:** total blood loss, transfusion rate, and transfusion volume

**Outcomes relevant to this overview:** number of people with blood transfusion, volume of blood transfusion, adverse events (DVT, PE, cerebral infarction), mortality (3 months)

**Data analysis methods:** when  $P > 0.1$ , the summary effect size was analysed with the fixed-effect model, but when  $P < 0.1$  and  $I^2 > 50\%$ , the random-effects model was used. Subgroup analysis was undertaken to explore the sources of heterogeneity

## Masouros 2022

### Review information

**Comparison:** IV TXA vs placebo

**Aim:** to assess the efficacy and safety of TXA in hip fracture surgery, focusing on the effect of TXA dosage and administration timing

(Continued)

**Protocol/trial registration:** review authors state that they had a pre-defined protocol that adhered to PRISMA, however there is no reference for the protocol, and it is not clear if the review was registered

**Sources of funding:** not specified

**Declarations of interest:** not specified

## Search methods

**Date of search:** February 2021

**Databases:** 3 databases: Cochrane Library, PubMed, Embase

**Additional searches:** reference lists of all relevant systematic reviews

**Any restrictions or limitations on searches:** no language or data limitations

**Methods to select studies and extract data:** conducted by 2 independent review authors, disagreements resolved through discussion

**Methods to assess risk of bias:** Cochrane risk of bias tool<sup>b</sup>

**Methods to judge certainty of evidence:** not specified. We assumed certainty was not assessed

## Inclusion criteria

**Types of study designs:** RCTs

**Inclusion criteria:** geriatric people (mean age > 70 years) undergoing surgery for either intra- or extracapsular hip fracture

**Exclusion criteria:** low sample size (< 50 participants), local administration of TXA, comparison to other antifibrinolytics other than placebo, total blood loss based on blood drain measurements, poor methodological quality as implied by Jadad score < 3

## Outcomes

**All outcomes reported:** perioperative total blood loss, transfusion rate (percentage of participants requiring at least 1 unit of RBC), mean count of transfused RBCs per participant, rate of thromboembolic events (DVT, PE, MI, CVA)

**Review primary outcome:** perioperative total blood loss

**Outcomes relevant to this overview:** number of people with blood transfusion, volume of blood transfusion, adverse events (DVT, PE, MI, CVA)

**Data analysis methods:** included sensitivity analyses (leave-one-out technique; intracapsular/extracapsular fractures; other factors where relevant)

## Perel 2013

### Review information

**Comparison:** IV TXA vs placebo or no TXA

**Aim:** to assess the effects of tranexamic acid on mortality, blood transfusion, and thromboembolic events in adults undergoing emergency or urgent surgery

**Protocol/trial registration:** Cochrane Database of Systematic Reviews (Perel P, Ker K, Morales Uribe CH, Roberts I. Tranexamic acid for reducing mortality in emergency and urgent surgery. Cochrane Database of Systematic Reviews 2012, Issue 11. Art. No.: CD010245. DOI: 10.1002/14651858.CD010245)

**Sources of funding:** NIHR Incentive Scheme

**Declarations of interest:** 1 review author received funding (to his institution) from pharmaceutical companies to pay for TXA and placebo in RCTs of TXA

**Note:** review included a mixed population in 5 studies: 2 studies with hip fracture, 2 with femur fracture, 1 with CABG. Data available separately for hip fractures



(Continued)

<b>Search methods</b>	<p><b>Date of search:</b> August 2012</p> <p><b>Databases:</b> 5 databases: CENTRAL, MEDLINE, Embase, ISI Web of Science CPCI-S, Web of Science - SCI-Expanded</p> <p><b>Additional searches:</b> Injuries Group Specialised Register, Pfizer website, reference lists of published reviews, and relevant studies, and clinical trials register (WHO Clinical Trials Registry Portal)</p> <p><b>Any restrictions or limitations on searches:</b> not limited by date, language, or publication status</p> <p><b>Methods to select studies and extract data:</b> 2 review authors examined titles, abstracts and keywords, and obtained the full text of all potentially relevant records. Because the definition of emergency surgery was challenging, a third author independently (and blinded from the trial results) assessed whether the selected studies included emergency surgeries. Data extraction was completed by 2 review authors</p> <p><b>Methods to assess risk of bias:</b> Cochrane RoB 1 (<a href="#">Higgins 2011</a>)</p> <p><b>Methods to judge certainty of evidence:</b> not specified. We assumed certainty was not assessed</p>
<b>Inclusion criteria</b>	<p><b>Types of study designs:</b> RCTs</p> <p><b>Inclusion criteria:</b> adults (&gt; 18 years of age) undergoing emergency or urgent surgery (surgery within 48 hours of hospital admission, or implicit from injury that emergency surgery is required)</p> <p><b>Exclusion criteria:</b> not specified</p>
<b>Outcomes</b>	<p><b>All outcomes reported:</b> all-cause mortality at end of follow-up, MI, CVA, DVT, PE, seizure, renal failure, re-operation, blood transfusion, units of blood transfused</p> <p><b>Review primary outcome:</b> mortality</p> <p><b>Outcomes relevant to this overview:</b> number of people with blood transfusion, adverse events (DVT, PE, MI, CVA), mortality</p> <p><b>Data analysis methods:</b> included a sensitivity analysis for the pooled analysis of transfusion (random/fixed-effects model, only studies at low risk of bias)</p>

## Qi 2019

<b>Review information</b>	<p><b>Comparison:</b> IV TXA vs placebo</p> <p><b>Aim:</b> to compare the efficacy and safety of intravenous application of TXA with placebo in people with hip fracture undergoing hip surgeries</p> <p><b>Protocol/trial registration:</b> not specified</p> <p><b>Sources of funding:</b> supported by the National Natural Science Foundation of China, National Natural Science Foundation of China for Young Scholars, Natural Science Foundation of Jiangsu Province for Young Scholars, Summit of the Six Top Talents Program of Jiangsu Province, Wuxi City Science and Technology Development, Medical and Public Health Technology Research and Development Project Funding, Key Medical Talent's Project in Science and Education of Jiangsu Province, and Soft Science Research Projects of Nanjing Science and Technology Commission</p> <p><b>Declarations of interest:</b> review authors declared no conflicts of interest</p>
<b>Search methods</b>	<p><b>Date of search:</b> March 2018</p> <p><b>Databases:</b> 3 databases: Cochrane Library<sup>a</sup>, PubMed, Embase</p> <p><b>Additional searches:</b> reference lists of all eligible studies and relevant reviews</p> <p><b>Any restrictions or limitations on searches:</b> language of publications was limited to English</p>

(Continued)

**Methods to select studies and extract data:** searched by 2 review authors; 2 review authors independently scanned the titles and abstracts of potentially included studies, then full texts of articles were reviewed. Data extraction independently conducted by 2 review authors. Disagreements resolved through discussion or consulting another review author

**Methods to assess risk of bias:** Cochrane RoB 1 ([Higgins 2011](#))

**Methods to judge certainty of evidence:** not specified. We assumed certainty was not assessed

## Inclusion criteria

**Types of study designs:** RCTs

**Inclusion criteria:** people undergoing hip surgery after hip fracture

**Exclusion criteria:** other fractures, multiple fractures, or undergoing elective total hip replacement or hemiarthroplasty; oral or topical use of TXA; not comparing TXA with placebo; not including transfusion rate nor total blood loss; not RCTs, or whose exact description could not be extracted, or letters and comments

## Outcomes

**All outcomes reported:** transfusion rate, total blood loss (both intraoperative and postoperative blood loss), intraoperative blood loss, postoperative blood loss and postoperative Hb; postoperative thromboembolic complications (DVT, PE, CVA)

**Review primary outcome:** transfusion rate and total blood loss

**Outcomes relevant to this overview:** number of people with blood transfusion, adverse events (thromboembolic events)

**Data analysis methods:** significant heterogeneity indicated when  $I^2 > 50\%$  or  $P < 0.1$ , and a random-effects model was applied for the meta-analysis. Otherwise, a fixed-effect model was used. Included sensitivity analysis to investigate significant heterogeneity

## Wang 2017a

## Review information

**Comparison:** IV and topical TXA vs placebo

**Aim:** to assess the efficacy and safety of TXA in reducing blood loss and transfusion requirements in people with intertrochanteric fractures

**Protocol/trial registration:** not specified

**Sources of funding:** none

**Declarations of interest:** review authors declared no conflicts of interest

## Search methods

**Date of search:** September 2017

**Databases:** 5 databases: Cochrane Library<sup>a</sup>, MEDLINE, PubMed, Embase, ScienceDirect

**Additional searches:** references in the included studies

**Any restrictions or limitations on searches:** no restrictions on the publication language

**Methods to select studies and extract data:** 2 review authors independently assessed titles and abstracts, then full texts to make a final decision. Disagreements were resolved by consulting a third review author; 2 review authors independently extracted using a standard data extraction form

**Methods to assess risk of bias:** Cochrane RoB 1 ([Higgins 2011](#))

**Methods to judge certainty of evidence:** GRADE

## Inclusion criteria

**Types of study designs:** RCTs

**Inclusion criteria:** adults with intertrochanteric fractures who were prepared for internal fixation

(Continued)

	<b>Exclusion criteria:</b> insufficient clinical outcome data in articles, and reviews, case reports, letters, or conference articles
<b>Outcomes</b>	<p><b>All outcomes reported:</b> total blood loss, Hb decline, and transfusion rates, length of stay and post-operative complications (infection, DVT and PE)</p> <p><b>Review primary outcome:</b> total blood loss, Hb decline, and transfusion rates</p> <p><b>Outcomes relevant to this overview:</b> number of people with blood transfusion, adverse events (DVT, PE, infection)</p> <p><b>Data analysis methods:</b> when there was no statistical evidence of heterogeneity (<math>I^2 &lt; 50\%</math>, <math>P &gt; 0.05</math>), a fixed-effect model was adopted; otherwise, a random-effects model was used. No sensitivity analysis conducted</p>
<b>Xiao 2019</b>	
<b>Review information</b>	<p><b>Comparison:</b> IV TXA vs control (placebo, saline, or no treatment)</p> <p><b>Aim:</b> to assess the efficacy of IV TXA administration during hip fracture surgery for reducing the transfusion requirement and blood loss; as well as its safety, regarding the risk of thrombolysis</p> <p><b>Protocol/trial registration:</b> not specified</p> <p><b>Sources of funding:</b> none</p> <p><b>Declarations of interest:</b> reviewer authors declared "None of the authors has financial or personal relationships with other people or organizations that could inappropriately influence this work"</p>
<b>Search methods</b>	<p><b>Date of search:</b> May 2018</p> <p><b>Databases:</b> 4 databases: CENTRAL, PubMed, Embase, Web of Science</p> <p><b>Additional searches:</b> reference lists of eligible studies</p> <p><b>Any restrictions or limitations on searches:</b> no limitations on language or publication type</p> <p><b>Methods to select studies and extract data:</b> 2 review authors screened titles and abstracts and then full texts. Disagreements were resolved with discussion</p> <p><b>Methods to assess risk of bias:</b> Cochrane risk of bias tool and Jadad scores<sup>a</sup></p> <p><b>Methods to judge certainty of evidence:</b> not specified. We assumed certainty was not assessed</p>
<b>Inclusion criteria</b>	<p><b>Types of study designs:</b> RCTs</p> <p><b>Inclusion criteria:</b> people with hip fractures</p> <p><b>Exclusion criteria:</b> studies were excluded if their quality was too low, studies with other types of fracture were included, or the outcome information was insufficient, even after contacting the study authors</p>
<b>Outcomes</b>	<p><b>All outcomes reported:</b> proportion of people transfused with allogenic blood, total blood loss, DVT, and total thromboembolic events</p> <p><b>Review primary outcome:</b> proportion of people transfused with allogenic blood</p> <p><b>Outcomes relevant to this overview:</b> number of people with blood transfusion, adverse events (DVT, total thromboembolic events)</p> <p><b>Data analysis methods:</b> If <math>P &gt; 0.10</math> but <math>I^2 &lt; 50\%</math>, heterogeneity was considered absent, and a fixed-effect model was used; otherwise a random-effects model was used. No sensitivity or subgroup analyses were conducted</p>

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## Xing 2020

<b>Review information</b>	<p><b>Comparison:</b> IV and topical TXA vs control (placebo, saline or no treatment)</p> <p><b>Aim:</b> to focus on whether TXA reduces perioperative blood loss in geriatric trauma patients undergoing proximal femoral intramedullary nail surgery; and whether TXA increases the rate of perioperative complications</p> <p><b>Protocol/trial registration:</b> not specified</p> <p><b>Sources of funding:</b> financially supported by Natural Science Foundations of China and Foundation of Sino-German Center for Research Promotion</p> <p><b>Declarations of interest:</b> review authors declared no competing interests</p>
<b>Search methods</b>	<p><b>Date of search:</b> April 2019</p> <p><b>Databases:</b> 4 databases: CENTRAL, MEDLINE, PubMed, Embase</p> <p><b>Additional searches:</b> not specified</p> <p><b>Any restrictions or limitations on searches:</b> no specific database filters were applied</p> <p><b>Methods to select studies and extract data:</b> 2 independent review authors searched for studies and extracted study data. Disagreements were resolved through discussion</p> <p><b>Methods to assess risk of bias:</b> Cochrane RoB 1 (<a href="#">Higgins 2011</a>)</p> <p><b>Methods to judge certainty of evidence:</b> not specified. We assumed certainty was not assessed</p>
<b>Inclusion criteria</b>	<p><b>Types of study designs:</b> RCTs</p> <p><b>Inclusion criteria:</b> geriatric people (aged <math>\geq 60</math> years) with intertrochanteric fractures, undergoing proximal femoral intramedullary nail surgery</p> <p><b>Exclusion criteria:</b> people with multiple fractures, retrospective studies, outcome information was insufficient, duplicate publications, case reports or letters, cohort studies</p>
<b>Outcomes</b>	<p><b>All outcomes reported:</b> perioperative blood transfusion rate, surgical time, total perioperative blood loss, perioperative hidden blood loss, intraoperative blood loss, postoperative drainage, postoperative Hb, length of hospital stay, mortality (12 months), DVT, PE, and other complications</p> <p><b>Review primary outcome:</b> not specified; however, first outcome reported is blood loss</p> <p><b>Outcomes relevant to this overview:</b> number of people with blood transfusion, adverse events (DVT, PE, wound haematoma, wound infection, respiratory infection, renal failure, CVA, mortality)</p> <p><b>Data analysis methods:</b> random-effects model used when <math>I^2 &gt; 50\%</math>. Sensitivity analysis conducted (leave-one-out technique)</p>

## Yu 2020

<b>Review information</b>	<p><b>Comparison:</b> IV and topical TXA vs control (placebo, saline, or no treatment)</p> <p><b>Aim:</b> to explore the efficacy and safety of TXA in intertrochanteric fracture surgery, by comparing their clinical results</p> <p><b>Protocol/trial registration:</b> not specified</p> <p><b>Sources of funding:</b> none</p> <p><b>Declarations of interest:</b> review authors declared no conflicts of interest</p>
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<b>Search methods</b>	<p><b>Date of search:</b> October 2019</p> <p><b>Databases:</b> 3 databases: Cochrane Library, PubMed, Embase</p> <p><b>Additional searches:</b> reference lists of previously published randomised trials, review articles, and meta-analyses</p> <p><b>Any restrictions or limitations on searches:</b> only English studies</p> <p><b>Methods to select studies and extract data:</b> 2 independent review authors screened titles, abstracts, and then full texts. 2 independent review authors extracted data which was checked by a third review author for consistency. Disagreements resolved through discussion. Contact with study authors for missing information</p> <p><b>Methods to assess risk of bias:</b> Cochrane RoB 1 (<a href="#">Higgins 2011</a>)</p> <p><b>Methods to judge certainty of evidence:</b> not specified. We assumed certainty was not assessed</p>
<b>Inclusion criteria</b>	<p><b>Types of study designs:</b> RCTs</p> <p><b>Inclusion criteria:</b> skeletally mature people (&gt; 18 years of age) with intertrochanteric fractures</p> <p><b>Exclusion criteria:</b> non-RCTs, abstracts, case reports, letters, editorials, conference articles; re-peated studies and data</p>
<b>Outcomes</b>	<p><b>All outcomes reported:</b> intraoperative blood loss, hidden blood loss, postoperative drainage, and total blood loss, postoperative Hb, length of stay, transfusion rate, mortality rate, thromboembolic events (DVT, PE, CVA, MI), and wound complications (infection and haematoma)</p> <p><b>Review primary outcome:</b> not specified; however, first reported outcome is blood loss</p> <p><b>Outcomes relevant to this overview:</b> number of people with blood transfusion, adverse events (DVT, PE, CVA, MI, wound complications), mortality</p> <p><b>Data analysis methods:</b> random-effects model used when heterogeneity was detected, or the statistical heterogeneity was high (<math>P &lt; 0.05</math> or <math>I^2 &gt; 50\%</math>), and then further subgroup analysis and meta-regression analysis were performed to detect the origin of heterogeneity. Otherwise, a fixed-effect model was used (<math>P \geq 0.05</math> or <math>I^2 \leq 50\%</math>)</p>
<b>Zhang 2017</b>	
<b>Review information</b>	<p><b>Comparison:</b> IV TXA vs control (placebo or saline)</p> <p><b>Aim:</b> to investigate the efficacy and safety of IV TXA in people with hip fractures</p> <p><b>Protocol/trial registration:</b> not specified</p> <p><b>Sources of funding:</b> not specified</p> <p><b>Declarations of interest:</b> review authors declared no conflicts of interest</p> <p><b>Note:</b> although the methods of this review are very similar to <a href="#">Zhang 2018</a>, we determined that these were different reviews because of the difference in search dates</p>
<b>Search methods</b>	<p><b>Date of search:</b> December 2016</p> <p><b>Databases:</b> 6 databases: Cochrane Library<sup>a</sup>, PubMed, Embase, Web of Science, Chinese Biomedical Literature, China National Knowledge Infrastructure</p> <p><b>Additional searches:</b> references of included studies</p> <p><b>Any restrictions or limitations on searches:</b> no language restrictions</p>

(Continued)

**Methods to select studies and extract data:** 2 independent review authors completed database searches, 2 review authors independently extracted data using a predefined data extraction form. Disagreement resolved through discussion

**Methods to assess risk of bias:** 12-item scale ([Furlan 2009](#))

**Methods to judge certainty of evidence:** GRADE

<b>Inclusion criteria</b>	<p><b>Types of study designs:</b> RCTs</p> <p><b>Inclusion criteria:</b> people with hip fractures</p> <p><b>Exclusion criteria:</b> not RCTs; studies with other types of fractures included; studies with incomplete information; and duplicate publication</p>
<b>Outcomes</b>	<p><b>All outcomes reported:</b> total blood loss, hidden blood loss, postoperative Hb decline, transfusion rates, thrombotic events, and operative time</p> <p><b>Review primary outcome:</b> not specified; however, first reported outcome is total blood loss</p> <p><b>Outcomes relevant to this overview:</b> blood transfusion, adverse events (thromboembolic events)</p> <p><b>Data analysis methods:</b> subgroup analyses were conducted (mean age, hip fracture type, and surgical management); studies which did not meet the requirements of subgroup analysis were excluded. If necessary, sensitivity analysis was conducted to identify the origins of significant heterogeneity</p>
<b>Zhang 2018</b>	
<b>Review information</b>	<p><b>Comparison:</b> TXA (topical and IV) vs control (placebo or saline)</p> <p><b>Aim:</b> to investigate the efficacy and safety of TXA usage following surgery for femoral fractures</p> <p><b>Protocol/trial registration:</b> not specified</p> <p><b>Sources of funding:</b> not specified</p> <p><b>Declarations of interest:</b> review authors declared no conflicts of interest</p>
<b>Search methods</b>	<p><b>Date of search:</b> January 2018</p> <p><b>Databases:</b> 4 databases: Cochrane Library<sup>a</sup>, MEDLINE, Embase, Web of Science</p> <p><b>Additional searches:</b> reference lists of included studies</p> <p><b>Any restrictions or limitations on searches:</b> only English studies were included</p> <p><b>Methods to select studies and extract data:</b> searches and data extraction completed independently by 2 review authors. Disagreements resolved through discussion</p> <p><b>Methods to assess risk of bias:</b> 12-item scale (<a href="#">Furlan 2009</a>)</p> <p><b>Methods to judge certainty of evidence:</b> not specified. We assumed certainty was not assessed</p>
<b>Inclusion criteria</b>	<p><b>Types of study designs:</b> RCTs and NRS</p> <p><b>Inclusion criteria:</b> people undergoing femoral fracture surgery</p> <p><b>Exclusion criteria:</b> case reports and publications only included an abstract; studies included other types of fractures; not published in English; duplicate publications</p>
<b>Outcomes</b>	<p><b>All outcomes reported:</b> total blood loss, postoperative haemoglobin decline, transfusion rate, thromboembolic events, 90-day mortality and operative time</p>



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**Review primary outcome:** not specified; however, first reported outcome is total blood loss

**Outcomes relevant to this overview:** blood transfusion, adverse events (DVT), mortality (3 months)

**Data analysis methods:** data reported separately for topical and IV TXA. If  $P$  was  $> 0.1$  and  $I^2$  was  $< 50\%$ , the fixed-effect model was used; otherwise, a random-effects model was used

## Zhou 2019a

### Review information

**Comparison:** IV and topical TXA vs control (placebo, saline, or no treatment)

**Aim:** to investigate and help determine the efficacy and safety of TXA administration in reducing bleeding and transfusion in elderly people with intertrochanteric fractures

**Protocol/trial registration:** not specified

**Sources of funding:** supported (in part) by National Natural Science Foundation of China, and Major Scientific and Technological Project of Changzhou Municipal Commission of Health and Family Planning.

**Declarations of interest:** review authors declared no conflicts of interest

### Search methods

**Date of search:** October 2018

**Databases:** 2 databases: MEDLINE, PubMed

**Additional searches:** not specified

**Any restrictions or limitations on searches:** published in English, no other limits

**Methods to select studies and extract data:** 2 review authors independently screened titles and abstracts and then full texts, contacting study authors for further information, if required. Data extracted independently by 2 review authors. Disagreements resolved through discussion

**Methods to assess risk of bias:** Cochrane RoB 1 ([Higgins 2011](#))

**Methods to judge certainty of evidence:** GRADE

### Inclusion criteria

**Types of study designs:** RCTs

**Inclusion criteria:** adults who had undergone intertrochanteric fracture fixation, regardless of the type or size of internal fixation material, anaesthesia, postoperative care, or different methods or doses of TXA administration

**Exclusion criteria:** other types of surgery, including arthroscopy and hemiarthroplasty; articles in which the diagnosis was not intertrochanteric fracture, only abstracts or protocols

### Outcomes

**All outcomes reported:** blood loss; postoperative Hb and haematocrit changes; transfusion-related information; any complication.

**Review primary outcome:** blood loss, transfusion, and complications

**Outcomes relevant to this overview:** blood transfusion, adverse events (DVT)

**Data analysis methods:** fixed-effect method if no methodological heterogeneity, otherwise a random-effects model was used. Sensitivity and subgroup analyses conducted

## Zhu 2018

### Review information

**Comparison:** IV and topical TXA vs control (placebo, saline, or no treatment)

**Aim:** to evaluate the efficacy and safety of TXA in reducing transfusion requirements and blood loss for intertrochanteric fracture surgery

(Continued)

	<b>Protocol/trial registration:</b> not specified <b>Sources of funding:</b> none <b>Declarations of interest:</b> review authors declared no conflicts of interest
<b>Search methods</b>	<b>Date of search:</b> February 2018 <b>Databases:</b> 3 databases: Cochrane <sup>a</sup> , PubMed, Embase <b>Additional searches:</b> handsearched reference lists from original articles and identified reviews <b>Any restrictions or limitations on searches:</b> not specified <b>Methods to select studies and extract data:</b> 2 review authors independently screened all articles. Disagreement resolved through discussion <b>Methods to assess risk of bias:</b> Cochrane risk of bias tool <sup>b</sup> <b>Methods to judge certainty of evidence:</b> GRADE
<b>Inclusion criteria</b>	<b>Types of study designs:</b> RCTs <b>Inclusion criteria:</b> adults with intertrochanteric fractures for internal fixation <b>Exclusion criteria:</b> in vitro or animal studies, case reports, reviews, meta-analyses, and letters to editors; inclusion of adults with femoral neck fractures; not RCTs
<b>Outcomes</b>	<b>All outcomes reported:</b> transfusion rate, surgical blood loss, total blood loss, postoperative drainage, postoperative Hb, postoperative haematocrit, and thromboembolic events (DVT and PE) <b>Review primary outcome:</b> not specified; however, first reported outcome was transfusion rate <b>Outcomes relevant to this overview:</b> number of people with blood transfusion, adverse events (DVT, PE) <b>Data analysis methods:</b> when there was no statistical heterogeneity (as judged by Chi <sup>2</sup> test $P > 0.1$ or $I^2 < 50\%$ ), a fixed-effect model was used; otherwise, a random-effects model was used. Reliability of pooled results was tested by sensitivity analyses

<sup>a</sup>The review reported no additional details about the database source and we have reported the resource as described in the review

<sup>b</sup>The review did not report a citation for the version of the Cochrane risk of bias tool, and we could not be certain which version of the tool was used in the review

ABT: allogenic blood transfusion; AO: Arbeitsgemeinschaft für Osteosynthesefragen (fracture classification system); CABG: coronary artery bypass graft; CVA: cerebrovascular accident; DVT: deep vein thrombosis; Hb: haemoglobin; IV: intravenous(ly); MI: myocardial infarction; MMAT: mixed methods and assessment tool; NRS: non-randomised studies; PE: pulmonary embolism; RBC: red blood counts; RCTs: randomised controlled trials; THA: total hip arthroplasty; TXA: tranexamic acid; VTE: venous thromboembolic event

## Appendix 7. Characteristics of included systematic reviews evaluating iron or iron with erythropoietin (EPO)

<b>Chen 2021</b>	
<b>Review information</b>	<b>Comparison:</b> oral or IV iron supplementation (iron alone or iron with EPO) vs placebo or control <b>Aim:</b> to investigate the association between iron supplementation and blood transfusion risks, hospital length of stay, postoperative infection, and mortality in geriatric people undergoing hip fracture surgeries

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**Protocol/trial registration:** PROSPERO CRD42019133717

**Sources of funding:** supported by Sichuan Science and Technology Program and National Nature Science Foundation of China

**Declarations of interest:** review authors declared no conflicts

<b>Search methods</b>	<p><b>Date of search:</b> 2 April 2019</p> <p><b>Databases:</b> 3 databases: Cochrane Library, PubMed, Embase</p> <p><b>Additional searches:</b> not specified</p> <p><b>Any restrictions or limitations on searches:</b> no restrictions on language, publication year, or study design</p> <p><b>Methods to select studies and extract data:</b> for screening, 2 review authors independently screened titles and abstracts. For data extraction, disagreement was resolved through discussion</p> <p><b>Methods to assess risk of bias:</b> Jadad<sup>a</sup></p> <p><b>Methods to judge certainty of evidence:</b> not specified. We assumed certainty was not assessed</p>
<b>Review criteria</b>	<p><b>Types of study designs:</b> RCTs and NRS</p> <p><b>Inclusion criteria:</b> older people (age &gt; 64 years) undergoing hip fracture surgery, including those with femoral neck fractures, trochanteric fractures, intertrochanteric fractures, or subtrochanteric fractures</p> <p><b>Exclusion criteria:</b> case series, case reports, and reviews</p>
<b>Outcomes</b>	<p><b>All outcomes reported in review:</b> blood transfusion rate, blood transfusion volume, length of stay, postoperative infection (superficial/deep surgical wound infections), respiratory infections, urinary infections, or other infections occurring during the perioperative period), and mortality</p> <p><b>Review primary outcome(s):</b> blood transfusion rate</p> <p><b>Outcomes relevant to this overview:</b> blood transfusion rate, blood transfusion volume, adverse events (postoperative infection (superficial/deep surgical wound infections), respiratory infections, urinary infections, or other infections occurring during the perioperative period), and mortality</p> <p><b>Data analysis methods:</b> ORs, MDs and 95% CIs, pooled by fixed- or random-effects models according to statistical heterogeneity. Random-effects model used if <math>I^2 &gt; 50\%</math>. Sensitivity analysis when <math>I^2 &gt; 40\%</math>.</p> <p><b>Subgroup analyses:</b> route of administration (oral or IV), time of administration (pre- or postoperative), and doses</p>

## Gomez-Ramirez 2019

<b>Review information</b>	<p><b>Comparison:</b> short-term perioperative administration of IV iron (<math>\leq 7</math> days before and/or after surgery) with or without EPO, or postoperative administration of oral iron vs control (standard care or placebo)</p> <p><b>Aim:</b> to ascertain the efficacy and safety of short-term perioperative administration of oral or IV iron, with or without recombinant human EPO, for anaemia management in people undergoing major orthopaedic surgery</p> <p><b>Protocol/trial registration:</b> not specified</p> <p><b>Sources of funding:</b> none</p> <p><b>Declarations of interest:</b> one review author received honoraria for lectures and/or consultancies from Vifor Pharma (Spain &amp; Switzerland), Wellspect HealthCare (Sweden), Pharmacosmos (Den-</p>
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mark), Ferrer Pharma (Spain), CSL Bering (Germany), PharmaNutra (Italy) and Zambon (Spain). Remaining review authors had nothing to declare

<b>Search methods</b>	<p><b>Date of search:</b> 2018</p> <p><b>Databases:</b> 1 database: MEDLINE (via PubMed)</p> <p><b>Additional searches:</b> not specified</p> <p><b>Any restrictions or limitations on searches:</b> only articles written in Spanish or English</p> <p><b>Methods to select studies and extract data:</b> 2 review authors independently assessed for inclusion, disagreement resolved through discussion</p> <p><b>Methods to assess risk of bias:</b> not specified</p> <p><b>Methods to judge certainty of evidence:</b> not specified; we assumed certainty was not assessed</p>
<b>Review criteria</b>	<p><b>Types of study designs:</b> RCTs and NRS</p> <p><b>Inclusion criteria:</b> adults undergoing major orthopaedic surgery (studies included: orthopaedic surgery, hip fracture, lower limb arthroplasty)</p> <p><b>Exclusion criteria:</b> not specified</p>
<b>Outcomes</b>	<p><b>All outcomes reported in review:</b> Hb increase, reduction in transfusion requirements, medication side effects during the perioperative period, length of hospital stay, rate of postoperative infection, mortality</p> <p><b>Review primary outcome(s):</b> Hb increase, reduction in transfusion requirements, medication side effects during the perioperative period</p> <p><b>Outcomes relevant to this overview:</b> blood transfusion rate, adverse events (gastrointestinal symptoms; hypotension; headache; general discomfort; skin rash; flushing and tingling in the lips; infection rate), mortality</p> <p><b>Data analysis methods:</b> meta-analysis not performed for outcomes in which there was too much heterogeneity</p>
<b>Lin 2013</b>	
<b>Review information</b>	<p><b>Comparison:</b> iron and EPO vs control (autologous blood donation, oral iron, or placebo)</p> <p><b>Aim:</b> to evaluate the use of ESA as a transfusion avoidance strategy in perioperative blood management</p> <p><b>Protocol/trial registration:</b> PROSPERO CRD42012002599</p> <p><b>Sources of funding:</b> no external funding</p> <p><b>Declarations of interest:</b> not specified other than that there was no external funding</p>
<b>Search methods</b>	<p><b>Date of search:</b> July 2012</p> <p><b>Databases:</b> 3 databases: Cochrane Library, MEDLINE (via PubMed), CINAHL</p> <p><b>Additional searches:</b> backward citation searching of included studies</p> <p><b>Any restrictions or limitations on searches:</b> limited to English, published between 1997 and 2012</p> <p><b>Methods to select studies and extract data:</b> 2 review authors worked independently and checked for accuracy together</p>

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**Methods to assess risk of bias:** review authors report that Cochrane tool was used. We are uncertain which version is used as there is no citation and domains include conflict of interest

**Methods to judge certainty of evidence:** not specified, we assumed certainty was not assessed

## Review criteria

**Types of study designs:** RCTs and NRS

**Inclusion criteria:** adults with anaemia scheduled for surgery (included people having orthopaedic, gynaecologic, oncologic, cardiothoracic surgery)

**Exclusion criteria:** pregnancy and use of IV hematinic to augment autologous blood donation

## Outcomes

**All outcomes reported in review:** ABT, haematologic parameters, thromboembolic events, other adverse events related to intervention

**Review primary outcome(s):** perioperative transfusion rate

**Outcomes relevant to this overview:** blood transfusion rate, volume of transfused blood, adverse events (infection, thromboembolic events), mortality

**Data analysis methods:** meta-analysis not performed

## Schack 2019

### Review information

**Comparison:** oral or IV iron with or without adjuncts (given between indication for surgery and 24 hours after surgery) vs control (no intervention, active comparator, or another iron treatment)

**Aim:** to investigate whether iron treatment, initiated perioperatively, improves clinical outcomes in terms of need for ABT, changes in Hb, length of stay, postoperative infections and mortality in people undergoing acute major non-cardiac surgery

**Protocol/trial registration:** PROSPERO CRD42018087385

**Sources of funding:** not specified

**Declarations of interest:** not specified

### Search methods

**Date of search:** 11 November 2017

**Databases:** 3 databases: PubMed, EMBASE, Scopus

**Additional searches:** manual screening of reference lists of identified studies and systematic reviews

**Any restrictions or limitations on searches:** review authors state that "searches were run without filters, limits, and publication date or language restrictions". However, they also report that they included studies written in Danish, English, French, or Spanish

**Methods to select studies and extract data:** for screening, 2 review authors individually screened studies and in duplicate, with disagreements resolved through discussion and involvement of a third review author

**Methods to assess risk of bias:** Cochrane RoB 1 ([Higgins 2011](#))

**Methods to judge certainty of evidence:** not specified. We assumed certainty was not assessed

### Review criteria

**Types of study designs:** RCTs and NRS

**Inclusion criteria:** people undergoing major, acute, non-cardiac surgery (included orthopaedic, abdominal, gynaecological, and mixed surgery)

**Exclusion criteria:** elective surgery, cardiac surgery (due to extracorporeal circulation), surgery performed on children (< 18 years of age), studies with < 10 participants, or without a control

(Continued)

group, experimental studies (involving animals or conducted in a laboratory), abstracts, conference publications or proceedings, letters, and duplicate publications

## Outcomes

**All outcomes reported in review:** peri- and postoperative blood transfusion, changes in Hb levels, mortality, length of stay, adverse reactions including infection

**Review primary outcome(s):** peri- and postoperative blood transfusion, changes in Hb level

**Outcomes relevant to this overview:** blood transfusion, mild adverse events (abdominal discomfort, serious adverse events, infection, mortality (30 days, and 1 year)

**Data analysis methods:** meta-analysis if > 3 studies, using RevMan 5.1. Generic inverse variance, random-effects model. Results of meta-analysis not reported when heterogeneity was considerable ( $I^2 > 75\%$ ) or if data on the outcome were deemed insufficient (size and number of trials). In outcome variables with heterogeneity ( $I^2 > 0\%$ ), both random- and fixed-effect models were tested to identify a potential small-study effect. In case of a suspected small-study effect, a random-effects model was chosen.

## Shah 2018

### Review information

**Comparison:** IV iron (given at any time during perioperative period) vs control (type not specified)

**Aim:** to investigate the safety and efficacy of IV iron specifically in people undergoing non-elective surgery

**Protocol/trial registration:** PROSPERO CRD42018096288

**Sources of funding:** no external funding

**Declarations of interest:** 1 review author supported by the NIHR Doctoral Support Fellowship. Remaining review authors declared no conflicts of interest

### Search methods

**Date of search:** June 2018

**Databases:** 7 databases: CENTRAL, MEDLINE, Embase, CINAHL, PubMed, Transfusion Evidence Library, Web of Science ISI Conference Proceedings

**Additional searches:** 2 clinical trials registers (clinicaltrials.gov and ICTRP)

**Any restrictions or limitations on searches:** not specified (search strategies appear to have no limitations)

**Methods to select studies and extract data:** 2 review authors independently screened citations, extracted data, and assessed risk of bias

**Methods to assess risk of bias:** Cochrane RoB 1 ([Higgins 2011](#))

**Methods to judge certainty of evidence:** not specified. We assumed certainty was not assessed

### Review criteria

**Types of study designs:** RCTs

**Inclusion criteria:** undergoing non-elective surgery, defined by NCEPOD as a decision to operate within days (expedited), hours (urgent), or minutes (immediate). Review included studies on hip fracture surgery and kidney transplantation

**Exclusion criteria:** not specified

### Outcomes

**All outcomes reported in review:** all-cause infection; mean difference in Hb concentration (short-term:  $\leq 7$  days; medium-term: 8 to 21 days; long-term:  $> 21$  days); transfusion requirements; iron deficiency diagnosis (perioperatively); hospital length of stay; HRQoL; mortality ( $\leq 30$  days;  $> 30$  days); in hospital adverse events (anaphylaxis, medical and surgical complications, e.g. stroke, MI, PE, re-operation)



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**Review primary outcome(s):** all-cause infection, Hb concentrations

**Outcomes relevant to this overview:** number of people with blood transfusion, volume of transfused blood, postoperative delirium, adverse events (nausea, constipation, hypotension, diarrhoea, low-grade fever, cholestasis, epigastralgia, peripheral phlebitis, acute coronary disease, stroke, heart failure, VTE, COPD exacerbation, renal function deterioration, skin pressure ulcer, skin rash, general discomfort), HRQoL (SF-36), mortality (60 days)

**Data analysis methods:** meta-analysis using a random-effects model when enough data were available. MD and RR with 95% CIs. Heterogeneity assessed using  $I^2$  statistic. Post hoc trial sequential analysis to calculate the sample size required to obtain the required statistical power to detect an effect of IV iron on red blood cell transfusion in people with hip fracture

## Shin 2019

### Review information

**Comparison:** iron (given perioperatively) vs control (not specified)

**Aim:** to evaluate the efficacy of IV iron therapy, with respect to details of transfusion and recovery profiles, such as length of hospital stay, rate of postoperative infection, and mortality, among people undergoing orthopaedic surgery

**Protocol/trial registration:** PROSPERO CRD42018081647

**Sources of funding:** none

**Declarations of interest:** review authors declared no conflicts of interest

### Search methods

**Date of search:** September 2018

**Databases:** 5 databases: CENTRAL, PubMed, Embase, KoreaMed, Google Scholar

**Additional searches:** not specified

**Any restrictions or limitations on searches:** no language restrictions

**Methods to select studies and extract data:** 2 independent review authors completed screening; discussion to resolve disagreements; 2 independent review authors completed data extraction using a standardised form

**Methods to assess risk of bias:** Cochrane RoB 1 ([Higgins 2011](#))

**Methods to judge certainty of evidence:** not specified. We assumed certainty was not assessed

### Review criteria

**Types of study designs:** RCTs and NRS

**Inclusion criteria:** adults (> 19 years of age) undergoing orthopaedic surgery (included hip fracture, orthopaedic, cardiac, lower-limb arthroplasty, total hip or knee arthroplasty)

**Exclusion criteria:** review articles, case reports, letters to the editor, commentaries, proceedings, laboratory studies, and other non-relevant studies

### Outcomes

**All outcomes reported in review:** proportion of participants who received transfusion, units of red blood cells transfused during the perioperative period, length of stay, postoperative infection, and mortality

**Review primary outcome:** number of people with blood transfusion, volume of transfused blood

**Outcomes relevant to this overview:** number of people with blood transfusion, volume of transfused blood, adverse events (infection), mortality

**Data analysis methods:** using RevMan 5.3., MD and RR with 95% CI. Heterogeneity considered significant at  $I^2 \geq 50\%$ . Random-effects model used because of small number of trials, and clinical heterogeneity. One study-at-a-time sensitivity analysis. Subgroup analyses on iron dose (low dose  $\leq$

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300 mg or high dose &gt; 400 mg), period of iron therapy (preoperative, postoperative, perioperative), and study design (RCTs vs CCS)

## Sinclair 2022

### Review information

**Comparison:** IV iron (any preparation) in the perioperative period vs control

**Aim:** to assess the evidence and effect of IV iron preparations on duration of acute hospitalisation, mortality, blood transfusion, quality of life, and discharge haemoglobin in people presenting to surgery with hip fracture

**Protocol/trial registration:** PROSPERO CRD42020171197

**Sources of funding:** none

**Declarations of interest:** 1 review author (RCFS) received honorarium from Pharmacosmos UK. Another review author (IKM) is Deputy Director of the Health Services Research Centre. IKM is the co-lead of the Perioperative Specialist Interest Group of the Fragility Fracture Network and a member of the Quality Standards Group for NICE. IKM has received research funding for studies into the perioperative management of hip fracture and his department has received consultancy funding from Astra Zeneca for work unrelated to hip fracture, blood transfusion, or intravenous iron. IKM did not perform data extraction on the study for which he is an author. Another author (MG) is a Chief Scientist's Office Scotland NHS Research Scheme Clinician. One author (MB) has no competing interests.

**Note:** we sourced details about this unpublished review via personal communication with the review author ([Sinclair 2022 \[pers comm\]](#))

### Search methods

**Date of search:** 14 January 2021

**Databases:** 4 databases: CENTRAL, MEDLINE, Embase, DARE

**Additional searches:** 2 clinical trials registers (clinicaltrials.gov and ISRCTN), manual searching (not further defined), and backward citation searching of selected full text articles

**Any restrictions or limitations on searches:** studies published in any language were considered

**Methods to select studies and extract data:** for screening, two independent review authors; disagreements resolved through discussion. For data extraction and RoB: not reported

**Methods to assess risk of bias:** Cochrane RoB 1 ([Higgins 2011](#))

**Methods to judge certainty of evidence:** GRADE

### Review criteria

**Types of study designs:** RCTs and NRS

**Inclusion criteria:** adults (> 18 years) undergoing emergency or urgent surgery for hip fracture

**Exclusion criteria:** studies in which none of the outcomes of interest were reported, people undergoing elective hip surgery were studied, and there was no comparison group (who did not receive the intervention) reported

### Outcomes

**All outcomes reported in review:** length of stay; mortality (at 30 days, discharge, and 90 days following surgery); quality of life after emergency hip surgery; postoperative red cell transfusion; Hb concentration at acute hospital discharge

**Review primary outcome:** length of hospital stay

**Outcomes relevant to this overview:** number of people with blood transfusion, HRQoL, mortality, activities of daily living

**Data analysis methods:** heterogeneity assessed using Chi<sup>2</sup> and I<sup>2</sup> tests - cutoffs to determine level of heterogeneity. Random-effects models used throughout because of heterogeneity. OR for di-

(Continued)

chotomous data and MD for continuous data, with 95% CIs. RCTs and non-RCTs analysed separately

## Smith 2020

### Review information

**Comparison:** IV iron (with and without EPO) in preoperative setting vs control (not specified)

**Aim:** to evaluate the current evidence supporting IV iron administration as a preoperative treatment for anaemia in people undergoing major orthopedic surgery.

**Protocol/trial registration:** PROSPERO CRD42020160872

**Sources of funding:** none

**Declarations of interest:** review authors declared no conflicts of interest

### Search methods

**Date of search:** 20 September 2019

**Databases:** 5 databases: Cochrane Library, PubMed, Embase, CINAHL, Web of Science

**Additional searches:** not specified

**Any restrictions or limitations on searches:** not specified

**Methods to select studies and extract data:** for screening, 1 review author completed each stage and a third person assessed reasons for exclusion. For data extraction, 1 review author extracted data, which was checked by a second reviewer

**Methods to assess risk of bias:** Cochrane RoB 1 ([Higgins 2011](#))

**Methods to judge certainty of evidence:** not specified. We assumed certainty was not assessed

### Review criteria

**Types of study designs:** RCTs and NRS

**Inclusion criteria:** > 18 years of age, undergoing major orthopedic surgery (included total hip replacements, total knee replacements, and hip fracture repairs)

**Exclusion criteria:** review articles, published abstracts, letters to the editor, study protocols, and case reports

### Outcomes

**All outcomes reported in review:** ABT, serum Hb, morbidity, mortality, length of stay, cost effectiveness

**Review primary outcome(s):** ABT

**Outcomes relevant to this overview:** number of people with blood transfusion, volume of transfused blood, serious adverse events, major complications, infection, HRQoL, mortality

**Data analysis methods:** meta-analysis not conducted because of the limited number of studies

## Yang 2011

### Review information

**Comparison:** oral or IV iron vs control (placebo or no iron supplementation)

**Aim:** to identify and summarise the evidence from RCTs on the therapeutic effects of iron supplementation for elderly people undergoing hip or knee surgery

**Protocol/trial registration:** not specified

**Sources of funding:** not specified

**Declarations of interest:** not specified

### Search methods

**Date of search:** May 2011

(Continued)

**Databases:** 3 databases: Cochrane Library, PubMed, Embase

**Additional searches:** backward citation search of eligible studies

**Any restrictions or limitations on searches:** all the results were limited by RCTs and comparative studies, and studies written in English

**Methods to select studies and extract data:** 2 review authors conducted each stage independently, disagreements resolved by discussion

**Methods to assess risk of bias:** Cochrane risk of bias tool ([van Tulder 2003](#))

**Methods to judge certainty of evidence:** not specified. We assumed certainty was not assessed

<b>Review criteria</b>	<b>Types of study designs:</b> RCTs  <b>Inclusion criteria:</b> elderly people undergoing hip or knee surgery (included hip arthroplasty, total hip or knee arthroplasty, hip fracture repair)  <b>Exclusion criteria:</b> studies not written in English
<b>Outcomes</b>	<b>All outcomes reported in review:</b> Hb level, length of hospital stay, mortality (1 month), transfusion rate and volume of blood transfusion, infection rate, morbidity, adverse events (gastrointestinal, general discomfort, skin rash)  <b>Review primary outcome:</b> not specified, but Hb level is first reported outcome  <b>Outcomes relevant to this overview:</b> number of people with blood transfusion, volume of transfused blood, adverse events (infection, gastrointestinal disturbance, skin rash, general discomfort), mortality  <b>Data analysis methods:</b> RevMan 5.0 for analysis. WMD and 95% CIs using inverse variance method, or RR by Mantel-Haenszel method. $I^2$ values > 40% was suggestive of statistical heterogeneity and then random-effects model was used, otherwise a fixed-effect model was used

<sup>a</sup>Review authors did not provide a citation for this tool and we could not be certain of which version was used in the review

ABT: allogenic blood transfusion; CCS: controlled clinical study; CI: confidence interval; COPD: chronic obstructive pulmonary disease; EPO: erythropoietin; ESA: erythropoietin-stimulating agents; IV: intravenous(ly); Hb: haemoglobin; HRQoL: health-related quality of life; MD: mean difference; MI: myocardial infarction; NCEPOD: National Confidential Enquiry into Patient Outcome and Death; NIHR: National Institute for Health Research; NRS: non-randomised trial(s); PE: pulmonary embolism; RCT: randomised controlled trial(s); RR: risk ratio; SF-36: short-form 36; VTE: venous thrombo-embolism; WMD: weighted mean difference (now mean difference is used)

## Appendix 8. AMSTAR 2 summary of judgements for reviews of tranexamic acid

### Summary of results for each of 16 domains in the AMSTAR 2 critical appraisal tool

1. All reviews adequately reported the research question and details of the inclusion criteria.
2. Four reviews were registered with a review registry ([Agius 2022](#); [Farrow 2016](#); [Jiang 2019](#); [Luo 2020](#)). However, we judged that [Luo 2020](#) did not meet the requirements for the relevant AMSTAR 2 domain to score 'yes' because the review registry did not include sufficient information, which was supplied by the other three reviews. Although [Masouros 2022](#) had a protocol, we judged this review to have only partially met this AMSTAR 2 requirement because there was no reference for this protocol and we could not verify its contents.
3. No reviews explained their reasons for including only RCTs, or both RCTs and non-randomised studies, and each scored 'no' for this domain.
4. No reviews completed sufficiently comprehensive searches according to the AMSTAR 2 guidelines, and each scored a 'partial yes' for this domain. Often this was because reviews did not justify publication restrictions (e.g. languages), or did not consult experts in the field, or search grey literature; all reviews provided key search words or search strategies with 24 months of completion of the review.

5. Only five reviews failed to report that they conducted study selection in duplicate (Haj-Younes 2020; Luo 2020; Xiao 2019; Zhang 2017; Zhou 2019a). The remaining reviews used two independent reviewers, and in most cases, described that consensus was reached through discussion or involvement with a third reviewer; where consensus was not described, we inferred this from other methodological approaches in the review.

6. Again, most reviews described that data extraction was completed in duplicate, and consensus reached through discussion. We scored seven reviews as 'no' (Agius 2022; Farrow 2016; Haj-Younes 2020; Luo 2020; Masouros 2022; Xiao 2019; Zhu 2018). Although it did not meet AMSTAR 2 requirements, we noted that Farrow 2016 used one review author to complete data extraction and another to check for accuracy; no comparable methods were described in the other reviews.

7. Four reviews presented a list of excluded studies with references (Masouros 2022; Xiao 2019; Zhang 2018; Zhang 2017). Nine reviews presented flow charts, and reported the number of excluded studies with a reason for exclusion; although they did not meet AMSTAR 2 requirements, we judged these trials with non-critical flaws for this domain (Farrow 2016; Haj-Younes 2020; Liu 2022; Qi 2019; Wang 2017a; Xing 2020; Yu 2020; Zhou 2019a; Zhu 2018). Jiang 2019 did not exclude any studies at full-text review.

8. Reviews reported varying degrees of detail when describing characteristics of included studies. As well as detail regarding the intervention and control, types of study characteristics included information such as: number of participants, age, gender, body mass index, status according to the American Society of Anesthesiologists (ASA), fracture type, fixation method, anaesthesia, DVT prophylaxis and screening, and transfusion thresholds. When judging whether reviews described the included studies in adequate detail, we scored reviews with a 'Yes' vote if they had, as a minimum, reported the number of participants and their age or gender alongside at least two other characteristics from the above list. Therefore, we judged 14 reviews to have adequately reported this study level detail and scored these with a 'Yes' vote; we judged that the remaining three reviews had only partially met this AMSTAR 2 criteria (Agius 2022; Baskaran 2018; Haj-Younes 2020). Only five reviews reported the country in which the studies were conducted (Liu 2022; Xiao 2019; Xing 2020; Yu 2020; Zhou 2019a), and nine reviews reported a time for study follow-up (Jiang 2019; Wang 2017a; Xiao 2019; Xing 2020; Zhang 2017; Zhang 2018; Zhou 2019a; Zhu 2018). We did not use information about study setting and follow-up as a reason to down-vote a review for this domain if we judged that other study characteristics were well-reported.

9. All reviews used a method to assess risk of bias of the included studies. Most reviews used the Cochrane risk of bias tool; although not always cited, we assumed that this tool was from Higgins 2011. One review used the Cochrane ROB2 tool (Agius 2022), and two reviews used an earlier version of the Cochrane risk of bias tool (Zhang 2017; Zhang 2018). Although not a domain within AMSTAR 2, we note there that six reviews used GRADE to assess the certainty of the evidence (Agius 2022; Farrow 2016; Wang 2017a; Zhang 2017; Zhou 2019a; Zhu 2018). The remaining reviews did not describe a method to assess certainty and we assumed that no approach was used.

10. No reviews reported the sources of funding for the included studies.

11. Three reviews reported insufficient detail about their methods for meta-analysis including methods to explore heterogeneity or a comment when this was not feasible (Baskaran 2018; Haj-Younes 2020; Xiao 2019). Jiang 2019 did not clearly state a rationale for choosing to combine studies in their protocol; however, we judged the studies to be sufficiently similar. The remaining reviews reported this information adequately.

12. We judged that four reviews had adequately considered the impact of risk of bias decisions on the results of meta-analysis (Baskaran 2018; Farrow 2016; Liu 2022; Xiao 2019). These reviews noted that all included studies were at low risk of bias, or they conducted a sensitivity analysis with only studies at low risk of bias.

13. Most reviews accounted for risk of bias when interpreting or discussing the results of their review, although often this was only to note that all studies were at low risk of bias. Seven reviews did not account for risk of bias in interpretation of their findings (Agius 2022; Haj-Younes 2020; Qi 2019; Wang 2017a; Xing 2020; Zhang 2017; Zhang 2018).

14. Effect estimates for the meta-analyses in most reviews included low  $I^2$  values, indicating no important levels of heterogeneity. In addition, some reviews explored high levels of heterogeneity. We scored four reviews with 'No' for this domain (Haj-Younes 2020; Jiang 2019; Wang 2017a; Zhang 2018); these reviews did not report  $I^2$  values, or explore or comment on high levels of heterogeneity which were apparent in their analyses.

15. Seven reviews conducted formal tests to explore publication bias and we scored these reviews with 'Yes' for this domain (Agius 2022; Liu 2022; Luo 2020; Qi 2019; Xiao 2019; Yu 2020; Wang 2017a). Whilst we scored the remaining reviews with 'No' for this domain, we noted that six reviews commented on publication bias within their reports (Baskaran 2018; Farrow 2016; Jiang 2019; Zhang 2017; Zhang 2018; Zhou 2019a). Baskaran 2018 and Zhou 2019a did not conduct formal tests, both reviews noted that publication bias may be present in their findings. Farrow 2016 presented a funnel plot, but with no narrative interpretation. Jiang 2019 stated in the Methods section that this was addressed, however they reported no additional information alongside their results. Zhang 2017 and Zhang 2018 noted that they were unable to assess publication bias because of insufficient studies; however, we also noted in Zhang 2017 that review authors stated that "publication bias exists" in their review. In total, we noted that seven reviews included fewer than 10 studies which could limit the reliability of any formal tests for publication bias had they been conducted (Baskaran 2018; Farrow 2016; Jiang 2019; Xing 2020; Zhang 2017; Zhou 2019a; Zhu 2018).

16. Most reviews adequately reported sources of funding and declared conflicts of interest; only one review did not specify this information (Masouros 2022).

## Appendix 9. AMSTAR 2 summary of judgements for reviews of iron

### Summary of results for each of 16 domains in the AMSTAR 2 critical appraisal tool

1. All reviews adequately reported the research question and details of the inclusion criteria.
2. Seven of the nine reviews were registered with PROSPERO and had described in this register an adequate plan for their review (Chen 2021; Lin 2013; Schack 2019; Shah 2018; Sinclair 2020; Smith 2020). The remaining reviews did not report registration or specify whether a protocol was published for their review.
3. No reviews explained their reasons for including only RCTs, or both RCTs and non-randomised studies, and each scored 'No' for this domain.
4. No reviews completed sufficiently comprehensive searches according to the AMSTAR 2 guidelines and most scored a 'partial yes' for this domain. Often this was because reviews did not justify publication restrictions (e.g. languages), did not consult experts in the field, or search grey literature; reviews provided key search words or search strategies with 24 months of completion of the review. One review only searched one database, and we scored the domain 'no' (Gomez-Ramirez 2019).
5. Smith 2020 did not perform study selection in duplicate, although we note that reasons for excluding studies were evaluated by a third review author; therefore, we scored the domain 'no'. The remaining reviews all adequately described methods to select studies in duplicate, using two independent review authors for this task.
6. Again, most reviews described that data extraction was completed in duplicate, and consensus reached through discussion. We scored only three reviews as 'no'; these reviews either did not specify their methods for data extraction or used only one review author for this stage (Gomez-Ramirez 2019; Schack 2019; Smith 2020). Although not a domain in AMSTAR 2, we note here that only Sinclair 2020 reported the use of GRADE to assess the certainty of their findings.
7. Three reviews presented references for the excluded studies, so we scored them as 'yes' for this domain (Gomez-Ramirez 2019; Sinclair 2020; Yang 2011). Although they did not give references for excluded studies, the remaining six reviews enumerated reasons for exclusion in a flowchart, thus, we did not rate these reviews as having a critical flaw in this domain (Chen 2021; Lin 2013; Schack 2019; Shah 2018; Shin 2019; Smith 2020).
8. All reviews for this comparison group reported limited detail for study characteristics. Whilst all reported intervention details in sufficient detail, population details and other information was limited, and included, at most, the number of participants and their age, broad surgical types (e.g. hip fracture repair surgery), blood transfusion thresholds, and baseline haemoglobin levels. Most of the reviews included no more than two of these characteristics. Therefore, we scored all reviews as a 'partial yes' for this domain. We noted that the country in which studies were conducted was reported in five reviews (Chen 2021; Shah 2018; Shin 2019; Sinclair 2020; Smith 2020); and time to follow-up was reported in three reviews (Chen 2021; Sinclair 2020; Yang 2011). However, because all reviews reported inadequate detail for other characteristics, we did not consider the reporting of setting and follow-up information to significantly improve the rating of these reviews.
9. Only one review did not specify a method to assess risk of bias (Gomez-Ramirez 2019). The remaining reviews used the Cochrane risk of bias tool (with most reviews citing the version in Higgins 2011); one review used Jadad scores to assess risk of bias (Chen 2021); we scored these reviews as a 'yes' for this domain.
10. Only one review reported the funding sources from each included study (Lin 2013).
11. Three reviews did not pool data with a meta-analysis (Gomez-Ramirez 2019; Lin 2013; Smith 2020). We judged all the remaining reviews to have used an appropriate weighted technique in meta-analysis, and described methods to manage heterogeneity in their findings.
12. Of the six reviews in which meta-analysis was performed, we scored only one review as a 'no' vote for this domain (Yang 2011); we judged that this review did not adequately consider the impact of risk of bias judgements in their evidence synthesis. The remaining reviews included studies judged to be at low risk of bias in all or most domains, or they conducted subgroup or sensitivity analyses, which accounted for differences in risk of bias judgements between included studies.
13. One review did not account for risk of bias in the included studies when discussing their findings (Shah 2018). We judged that risk of bias was adequately considered in the discussion of findings in the remaining reviews.
14. We judged all reviews to have adequately considered heterogeneity, and its possible causes, when discussing their findings.
15. Of the six reviews in which meta-analysis was performed, three reviews reported an assessment of publication bias alongside their results (Shin 2019; Schack 2019; Sinclair 2020). Three reviews did not conduct a formal analysis of publication bias, but we noted that they included fewer than 10 studies (Chen 2021; Shah 2018; Yang 2011); the remaining reviews did not report specific methods to assess this risk.



16. Most reviews adequately reported sources of funding and declared conflicts of interest; only two reviews did not specify this information (Schack 2019; Yang 2011).

## Appendix 10. Sensitivity analysis for tranexamic acid: comparing the effect estimates from Liu 2022 and Masouros 2022 with effect estimates from other reviews

Review	Blood transfusion	Volume of transfused blood	Deep vein thrombosis	Pulmonary embolism	Myocardial infarction	Cerebrovascular accident	Mortality
<a href="#">Liu 2022</a> (Primary review)	RR 0.56, 95% CI 0.46 to 0.68; $I^2 = 60.1\%$ ; 21 studies, 2148 participants <sup>a</sup>	-	RR 1.16, 95% CI 0.74 to 1.81; $I^2 = 0\%$ ; 22 studies	RR 1.01, 95% CI 0.36 to 2.86; $I^2 = 0\%$ ; 9 studies	RR 1.00, 95% CI 0.23 to 4.33; $I^2 = 0\%$ ; 8 studies	RR 1.45, 95% CI 0.56 to 3.70; $I^2 = 0\%$ ; 8 studies	<i>At 30 days:</i> RR 1.01, 95% CI 0.70 to 1.46; $I^2 = 0\%$ ; 10 studies
<a href="#">Masouros 2022</a> (Primary review)	RR 0.60, 95% CI 0.47 to 0.78; $I^2 = 73\%$ ; 10 studies, 1150 participants	MD -0.53 units per person, 95% CI -0.27 to -0.80; $I^2 = 78\%$ ; 7 studies, 813 participants	-	-	-	-	-
<a href="#">Agius 2022</a>	RR 0.50, 95% CI 0.30 to 0.84; $I^2 = 96\%$ ; 13 studies, 1194 participants	-	-	-	-	-	-
<a href="#">Baskaran 2018</a>	OR 0.37, 95% CI 0.26 to 0.53; $I^2 = 0\%$ ; 8 studies, 786 participants <sup>b</sup>	-	-	-	-	-	-
<a href="#">Farrow 2016</a>	RR 0.60, 95% CI 0.39 to 0.92; $I^2 = 76\%$ ; 6 studies, 479 participants	-	RD 0.01, 95% CI -0.03 to 0.04; $I^2 = 43\%$ ; 5 studies, 412 participants	RD 0.00, 95% CI -0.02 to 0.02; $I^2 = 0\%$ ; 5 studies, 412 participants <sup>c</sup>	-	-	<i>At 30 days:</i> RR 1.33, 95% CI 0.53 to 3.34; $I^2 = 0\%$ ; 4 studies, 520 participants
<a href="#">Haj-Younes 2020</a>	RR 0.72, 95% CI 0.59 to 0.88; 10 studies, 842 participants	-	RR 1.14, 95% CI 0.43 to 3.06; 5 studies, 487 participants	RR 0.53, 95% CI 0.09 to 3.02; 5 studies, 457 participants	-	RR 0.78, 95% CI 0.16 to 3.68; 6 studies, 547 participants	<i>At any time point:</i> RR 1.17, 95% CI 0.65 to 2.10; 6 studies, 554 participants
<a href="#">Jiang 2019</a>	RR 0.55, 95% CI 0.41 to 0.74; $I^2 = 11.2\%$ ; 4 studies	-	RR 0.81, 95% CI 0.24 to 2.75; $I^2 = 0\%$ ; 4 studies	RR 0.64, 0.25 to 1.62; $I^2 = 0\%$ ; 4 studies	-	-	-

(Continued)

Luo 2020	RR 0.71, 95% CI 0.52 to 0.97; $I^2 = 63\%$ ; 5 studies, 540 participants	MD -0.43 units per person; 95% CI - 0.63 to -0.23; $I^2 = 54\%$ ; 5 studies, 540 participants	-	-	-	-	-	At 90 days:  RR 1.69, 95% CI 0.20 to 14.2; $I^2 = 44\%$ ; 3 studies, 239 participants
Qi 2019	RR 0.66, 95% CI 0.56 to 0.78; $I^2 = 60\%$ ; 8 studies, 707 participants	-	-	-	-	-	-	-
Wang 2017a	RD -1.11, 95% CI -0.19 to -0.04; $I^2 = 43.3\%$ ; 4 studies	-	RD 0.004, 95% CI -0.02 to 0.03; $I^2 = 0\%$ ; 4 studies	RD 0.00, 95% CI -0.03 to -0.03; $I^2 = 0\%$ ; 4 studies	-	-	-	-
Xiao 2019	RR 0.60, 95% CI 0.38 to 0.93; $I^2 = 94\%$ ; 11 studies, 892 participants	-	RD 0.02, 95% CI -0.01 to 0.04; $I^2 = 0\%$ ; 10 studies, 854 participants	-	-	-	-	-
Xing 2020	RD -0.16, 95% CI -0.24 to -0.08; $I^2 = 21\%$ ; 4 studies, 467 participants	-	RD 0.01, 95% CI -0.02 to 0.04; $I^2 = 0\%$ ; 4 studies, 467 participants	RD -0.01, 95% CI -0.04 to 0.03; $I^2 = 0\%$ ; 2 studies, 277 participants	-	-	-	At 12 months:  RD 0.01, 95% CI -0.04 to 0.07; $I^2 = 44\%$ ; 4 studies, 439 participants
Yu 2020	RR 0.559, 95% CI 0.469 to 0.667; $I^2 = 40.1\%$ ; 9 studies	-	RR 1.057, 95% CI 0.594 to 1.882; $I^2 = 0\%$ ; 8 studies	RR 0.857, 95% CI 0.279 to 2.636; $I^2 = 0\%$ ; 4 studies	RR 1.703, 95% CI 0.500 to 5.299; $I^2 = 0\%$ ; 3 studies	RR 0.779, 95% CI 0.344 to 1.765; $I^2 = 0\%$ ; 6 studies	-	At 12 months:  RR 1.270, 95% CI 0.779 to 2.069; $I^2 = 0\%$ ; 5 studies
Zhang 2017	RD -0.19, 95% CI -0.27 to -0.11; $I^2 = 0\%$ ; 6 studies, 445 participants	-	-	-	-	-	-	-
Zhang 2018	RD -0.172, 95% CI -0.224 to -0.121; $I^2 = 3.8\%$ ; 10 studies, 1006 participants <sup>b</sup>	-	-	-	-	-	-	At 90 days:  RD 0.009, 95% CI -0.040 to 0.058; $I^2 = 17\%$ ; 5 studies, 625 participants
Zhou 2019a	OR 0.50, 95% CI 0.36 to 0.69; $I^2 = 0\%$ ; 8 studies, 836 participants	-	OR 1.34, 95% CI 0.49 to 3.69; $I^2 =$	-	-	-	-	-

0%; 5 studies, 539  
participants

(Continued)

<a href="#">Zhu 2018</a>	RR 0.75, 95% CI 0.50 to 1.11; $I^2 = 92\%$ ; 7 studies, 736 participants	-	-	-	-	-	-
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Note: there are some missing  $I^2$  values and numbers of participants in this table, because these data were not reported in the review reports

<sup>a</sup>Number of participants not reported in [Liu 2022](#); we calculated this total using information we sourced from the primary studies

<sup>b</sup>Effect estimate provides indirect evidence, because it includes RCTs and NRS; unpooled data available in review for RCTs

<sup>c</sup>Risk difference calculated with zero events in each group

**CI:** confidence interval; **NRS:** non-randomised trial; **OR:** odds ratio; **RCT:** randomised controlled trial; **RD:** risk difference; **RR:** risk ratio

# Appendix 11. Outcomes reported in reviews other than Liu 2022 and Masouros 2022: adverse events (thromboembolic events, acute coronary syndrome, wound complications, infection, haematoma, respiratory infection, renal failure)

Review	Thomboembolic events	Acute coronary syndrome	Wound complications	Infection	Haematoma	Respiratory infection	Renal failure
<a href="#">Agius 2022</a>	RD 0.01, 95% CI -0.02 to 0.04; $I^2 = 23\%$ ; 12 studies, 1148 participants						
<a href="#">Baskaran 2018</a>	OR 1.59, 95% CI 0.67 to 3.75; $I^2 = 35\%$ ; 7 studies, 760 participants <sup>a</sup>	-	-	-	-	-	-
<a href="#">Farrow 2016</a>	RD 0.01, 95% CI -0.03 to 0.05; $I^2 = 68\%$ ; 6 studies, 683 participants <sup>a</sup>	-	-	-	-	-	-
<a href="#">Haj-Younes 2020</a>	-	RR 1.52, 95% CI 0.18 to 12.98; 4 studies, 385 participants	RR 1.61, 95% CI 0.51 to 5.13; 3 studies, 325 participants	-	-	-	-
<a href="#">Jiang 2019</a>	-	-	-	RR 0.22, 95% CI 0.05 to 1.00; $I^2 = 0\%$ ; 3 studies	RR 0.34, 95% CI 0.15 to 0.78; $I^2 = 0\%$ ; 4 studies	-	-
<a href="#">Luo 2020</a>	RR 0.84, 95% CI 0.46 to 1.54; $I^2 = 0\%$ ; 5 studies, 540 participants	-	-	-	-	-	-
<a href="#">Masouros 2022</a>	RR 1.08, 95% CI 0.68 to 1.69; $I^2 = 3\%$ ; 9 studies, 1150 participants	-	-	-	-	-	-
<a href="#">Qi 2019</a>	RR 1.38, 95% CI 0.74 to 2.55; $I^2 = 0\%$ ; 6 studies, 537 participants	-	-	-	-	-	-
<a href="#">Wang 2017a</a>	-	-	-	RD -0.01, 95% CI -0.04 to 0.02; $I^2 = 29.5\%$ ; 4 studies	-	-	-
<a href="#">Xiao 2019</a>	RD 0.02, 95% CI -0.01 to 0.05; $I^2 = 32\%$	-	-	-	-	-	-



(Continued)

Xing 2020	-	-	-	RD -0.04, 95% CI -0.07 to 0.00; $I^2 = 0\%$ ; 2 stud- ies, 277 partici- pants	RD -0.05, 95% CI -0.09 to -0.00; $I^2 = 0\%$ ; 2 studies, 277 participants	RD -0.00, 95% CI -0.07 to 0.06; $I^2 = 0\%$ ; 2 studies, 277 participants	RD -0.01, 95% CI -0.03 to 0.02; $I^2 = 0\%$ ; 2 studies, 277 participants
Yu 2020	-	-	RR 0.370, 95% CI 0.183 to 0.750; $I^2 = 0\%$ ; 4 studies	-	-	-	-
Zhang 2017	RD 0.02, 95% CI -0.01 to 0.05; $I^2 = 33.6\%$ ; 7 stud- ies, 531 participants	-	-	-	-	-	-
Zhang 2018	RD 0.008, 95% CI -0.017 to 0.034; $I^2 = 9\%$ ; 9 stud- ies, 958 participants <sup>a</sup>	-	-	-	-	-	-

Note: there are some missing  $I^2$  values and numbers of participants in this table, because these data were not reported in the review reports

<sup>a</sup>Effect estimate includes RCTs and NRS; unpooled data available in review for RCTs.

**CI:** confidence interval; **NRS:** non-randomised trial; **OR:** odds ratio; **RCT:** randomised controlled trial; **RD:** risk difference; **RR:** risk ratio

## Appendix 12. Subgroup information in reviews of tranexamic acid

Review	Time of administration	Age of participants	Baseline co-morbidities	People at high risk of bleeding	IV or topical administration	Subgroup analyses conducted within the review
<a href="#">Liu 2022</a> (Primary review)	SC: includes preoperative, intraoperative, and postoperative administration	NR	NR	NR	SC: IV and topical	Subgroup analyses (only using RCTs) for: geographical area (China vs non-China), type of fracture (intracapsular vs extracapsular), route of administration, frequency of dose (single vs two doses), blood transfusion threshold, time of follow-up (for mortality only)
<a href="#">Agius 2022</a>	SC: includes preoperative, intraoperative, and postoperative administration	NR	NR	NR	SC: IV only	Subgroup analysis according to transfusion thresholds (Hb < 8 g/dL or Hb < 10 g/dL)
<a href="#">Baskaran 2018</a>	SC: includes preoperative, intraoperative, and postoperative administration	NR	NR	NR	SC: IV only	None
<a href="#">Farrow 2016</a>	SC: includes preoperative, intraoperative, and postoperative administration	NR	NR	NR	SC: IV and topical	Subgroup analyses for: those aged ≥ 76 yrs, BMI ≥ 40, extracapsular hip fractures
<a href="#">Haj-Younes 2020</a>	IC: perioperative	NR	NR	NR	IC: IV only	None
<a href="#">Jiang 2019</a>	NR	NR	NR	NR	SC: IV and topical	Subgroup analyses for IV vs topical
<a href="#">Luo 2020</a>	SC: includes preoperative, intraoperative, and postoperative administration	IC: all > 60 years	NR	NR	SC: IV and topical	Subgroup by IV administration
<a href="#">Masouros 2022</a>	SC: includes preoperative, intraoperative, and postoperative administration	IC: all > 70yrs	NR	NR	IC: all IV	Subgroup analysis conducted for single and multiple dose
<a href="#">Qi 2019</a>	IC: preoperative or postoperative	NR	NR	NR	IC: IV only	None
<a href="#">Wang 2017a</a>	NR	NR	NR	NR	SC: IV and topical	None

(Continued)

<a href="#">Xiao 2019</a>	SC: includes pre-op, intra-operative, and postoperative administration	NR	NR	NR	IC: IV only	None
<a href="#">Xing 2020</a>	SC: includes preoperative, intraoperative, and postoperative administration	IC: $\geq 60$ years	NR	NR	SC: IV and topical	Subgroup analysis conducted for single dose vs two doses
<a href="#">Yu 2020</a>	SC: includes preoperative, intraoperative, and postoperative administration	NR	NR	NR	SC: IV and topical	None
<a href="#">Zhang 2017</a>	SC: includes preoperative, intraoperative, and postoperative administration	NR	NR	NR	SC: IV	Subgroup analysis on mean age, fracture type, and surgical management
<a href="#">Zhang 2018</a>	SC: includes preoperative, intraoperative, and postoperative administration	NR	NR	NR	SC: IV and topical	Subgroup analysis on mean age (< or > 65 years of age)
<a href="#">Zhou 2019a</a>	IC: includes preoperative and postoperative administration	NR	NR	NR	SC: IV and topical	None
<a href="#">Zhu 2018</a>	SC: includes preoperative, intraoperative, and postoperative administration	NR	NR	NR	SC: IV and topical	Subgroup analysis for type of administration, dosage, and timing (based on haemoglobin threshold for transfusion)

BMI: body mass index; Hb: haemoglobin; IC: review inclusion criteria; IV: intravenous(ly); NR: not reported; RCT: randomised controlled trial(s); SC: study characteristics reported in the review

### Appendix 13. Sensitivity analysis for iron: comparing the effect estimates of Shah 2018 with the effect estimates of other reviews

Review	Blood transfusion (number of people)	Blood transfusion (volume)	Postoperative delirium	Adverse events	ADL	HRQoL	Mortality (1 month)	Mortality (4 months)
<a href="#">Shah 2018</a> (primary review)	RR 0.90; 95% CI 0.73 to 1.11; $I^2 = 0\%$ ; 2 studies, 403 participants	MD -0.07, 95% CI -0.31 to 0.17; $I^2 = 0\%$ ; 2 studies, 403 participants	No effect estimate or ; 1 study, 303 participants <sup>a</sup>	<i>Infection</i> : RR 0.99, 95% CI 0.55 to 1.80; $I^2 = 9\%$ ; 2 studies, 403 participants  <i>Adverse events</i> : no effect estimate; 2 studies, 403 participants <sup>a</sup>	NR	No effect estimate or ; 1 study, 303 participants	<i>At 30 days</i> : RR 1.06; 95% CI 0.53 to 2.13; $I^2 = 0\%$ ; 2 studies, 403 participants	<i>At 60 days</i> : no effect estimate; 1 study, 203 participants <sup>a</sup>
<a href="#">Chen 2021</a>	OR 0.92, 95% CI 0.60 to 1.41; $I^2 = 61\%$ ; 6 studies, 1201 participants <sup>b</sup>	MD -0.28, 95% CI -0.91 to -0.11; $I^2 = 52\%$ ; 3 studies, 437 participants <sup>b</sup>	NR	<i>Infection</i> : OR 0.58, 95% CI 0.38 to 0.90; $I^2 = 32\%$ ; 4 studies, 701 participants <sup>b</sup>	NR	NR	<i>At 30 days</i> : OR 0.94, 95% CI 0.65 to 1.36; $I^2 = 28\%$ ; 5 studies, 937 participants <sup>b</sup>	
<a href="#">Gomez-Ramirez 2019</a>	No effect estimate; 3 studies, 582 participants <sup>a</sup>	No effect estimate; 3 studies, 582 participants <sup>a</sup>	NR	<i>Infection</i> : no effect estimate; 2 studies, 503 participants <sup>a</sup>  <i>Adverse events</i> : 13 gastrointestinal symptoms; 5 hypotension; 2 headache; 2 general discomfort; 1 skin rash; 1 tingling of the lips; 1 anaphylaxis; no effect estimate; 3 studies, 582 participants <sup>a</sup>	NR	NR	<i>At 30 days</i> : no effect estimate; 2 studies, 503 participants <sup>a</sup>	NR
<a href="#">Lin 2013</a>	No effect estimate; 1 study, 396 participants <sup>a</sup>	NR	NR	<i>Infection</i> : no effect estimate; 1 study, 396 participants <sup>a</sup>  <i>Adverse events</i> : none observed; 1 study, 158 participants	NR	NR	<i>At 30 days</i> : no effect estimate; 1 study, 396 participants <sup>a</sup>	NR
<a href="#">Schack 2019</a>	OR 0.69, 95% CI 0.39 to 1.22; 2 studies, 207 participants <sup>c</sup>	NR	NR	<i>Adverse events</i> : no effect estimate; 3 studies, 485 participants	NR	NR	<i>At 30 days</i> : no effect estimate; 1 study, 243 participants <sup>a</sup>	NR

(Continued)

Shin 2019	RR 0.84, 95% CI 0.65 to 1.09; $I^2 = 15\%$ ; 4 studies, 616 participants <sup>c</sup>	MD -0.11, 95% CI -0.33 to 0.10; $I^2 = 0\%$ ; 3 studies, 415 participants <sup>c</sup>	NR	Infection: RR 0.61, 95% CI 0.23 to 1.58; $I^2 = 71\%$ ; 3 studies, 595 participants <sup>c</sup>	NR	NR	At 30 days:  RR 0.34, 95% CI 0.03 to 3.81; $I^2 = 91\%$ ; 2 studies, 394 participants	NR
Sinclair 2020	OR 0.85, 95% CI 0.63 to 1.14; 4 studies, 732 participants	NR	NR	NR	BI (at hospital discharge): no effect estimate or ; 1 study, 253 participants	SF-36 at 90 days: no effect estimate or ; 1 study, 203 participants	At 30 days:  OR 1.14, 95% CI 0.62 to 2.10; $I^2 = 0\%$ ; 4 studies, 732 participants	NR
Smith 2020	No effect estimate; 3 studies, 579 participants <sup>a</sup>	No effect estimate; 1 study, 303 participants <sup>a</sup>	NR	Adverse events: no effect estimate or ; 1 study, 303 participants <sup>a</sup>  Cardiovascular complications: no effect estimate; 1 study, 80 participants <sup>a</sup>  Infections: no effect estimate; 2 studies, 276 participants <sup>a</sup>  Serious adverse events: no effect estimate or ; 1 study, 196 participants		At 60 days: no effect estimate or ; 1 study, 303 participants	At 30 days: no effect estimate; 2 studies, 276 participants <sup>a</sup>	At 60 days: no effect estimate or ; 1 study, 303 participants
Yang 2011	RR 0.46, 95% CI 0.16 to 1.27; 1 study, 196 participants	MD - 0.11, 95% CI -0.43 to 0.21; 1 study, 196 participants	NR	Infection: RR 1.25, 95% CI 0.56 to 2.57; 1 study, 196 participants  Adverse events: 41 gastrointestinal symptoms; 2 general discomfort; 1 skin rash; 3 no specific details	NR	NR	At 30 days:  RR 1.63, 95% CI 0.72 to 3.69; $I^2 = 0\%$ ; 2 studies, 596 participants	NR

<sup>a</sup>No pooled analyses: available for intervention and control groups for each study

<sup>b</sup>Effect estimate provides indirect evidence for this overview because it includes RCTs and NRS; unpooled available in the review for RCTs

<sup>c</sup>Effect estimate provides indirect evidence for this overview because it includes different types of surgery as well as hip fracture surgery; unpooled available in the review for hip fracture surgery

## Appendix 14. Subgroup information in reviews of iron

Review	Time of administration	Age of participants	Baseline co-morbidities	People at high risk of bleeding	IV or oral administration	Subgroup analyses conducted within the review
<a href="#">Chen 2021</a>	SC: includes preoperative and postoperative administration	NR	NR	NR	IC and SC: oral and IV	Subgroup analyses: time of administration; route of administration; and dose (200 mg to 300 mg, 600 mg, and > 600 mg)
<a href="#">Gomez-Ramirez 2019</a>	IC: perioperative ( $\leq 7$ days before and/or after surgery)	NR	NR	NR	IC and SC: IV only	Subgroup data for one study: fracture type; Hb on admission
<a href="#">Lin 2013</a>	SC: includes preoperative and postoperative administration	NR	NR	NR	IC: IV only	None
<a href="#">Schack 2019</a>	IC: between indication of surgery until 24 hours after surgery	NR	NR	NR	IC and SC: oral and IV	None
<a href="#">Shah 2018</a>	SC: includes preoperative and postoperative administration	SC: > 65 years	NR	NR	SC: IV and subcutaneous	Subgroup analyses not completed because of lack of data; subgroups not specified in Methods section
<a href="#">Shin 2019</a>	SC: includes preoperative and postoperative administration	IC: > 19 years	NR	NR	IC: IV only	Subgroup analyses: dose ( $\leq 300$ mg or > 400 mg); time of administration (preoperative, postoperative, and perioperative); study design (RCTs vs CCS)
<a href="#">Sinclair 2020</a>	IC: perioperative admin	IC: > 18 years	NR	NR	IC: IV only	None
<a href="#">Smith 2020</a>	IC: preoperative SC: 1 study includes doses given daily for 3 days	IC: > 18 years	NR	NR	IC: IV only	None (some subgroup analysis for individual studies, but not for studies eligible in this overview)
<a href="#">Yang 2011</a>	SC: includes preoperative and postoperative administration	IC: 'elderly'	NR	NR	IC and SC: oral and IV	None

CCS: case control studies; Hb: haemoglobin; IC: inclusion criteria; IV: intravenous(ly); NR: not reported; RCT: randomised controlled trials; SC: study characteristics



## HISTORY

Protocol first published: Issue 9, 2020

## CONTRIBUTIONS OF AUTHORS

SL (systematic reviewer): sifted and identified included reviews, extracted review data, interpreted the findings, and drafted the overview  
MP (systematic reviewer): sifted and identified included reviews, extracted review data, interpreted the findings, and drafted the overview  
LE (content expert, blood management): reviewed and approved the final draft  
SS (content expert, blood management): reviewed and approved the final draft  
XG (guarantor and content expert, Trauma and Orthopaedics): decision-making during initial sifting of references, interpreted the findings, reviewed and approved the final overview, and is the guarantor of the content

## DECLARATIONS OF INTEREST

SL (Deputy Co-ordinating Editor of the Cochrane Bone, Joint and Muscle Trauma group) has no known conflicts of interest. SL had no editorial role in this review.

MP has no known conflicts of interest.

XG (Co-ordinating Editor of the Cochrane Bone, Joint and Muscle Trauma group) is funded by a National Institute for Health Research Clinician Scientist Grant. Further funding from industry and charitable grants are, and have been made available to his institution. He has ongoing expert consultancy with several companies; none involve the development of any implant or alternative to allogeneic blood transfusion for use in hip fracture care. All decisions relating to the design, conduct, analysis, write-up, and publication of research are independent of these funders. XG had no editorial role in this review.

LE (Co-ordinating Editor of the Cochrane Haematology group) has no known conflicts of interest. LE had no editorial role in this review.

SS (Editor for the Cochrane Injuries group) has no known conflicts of interest. SS had no editorial role in this review.

## SOURCES OF SUPPORT

### Internal sources

- Bone and Joint Health, Blizzard Institute, Queen Mary University of London, London, UK

### External sources

- NIHR Systematic Review Programme Grant 16/114/15: a programme of high priority reviews for the management of patients with hip fracture: a collaboration which can inform future healthcare policy guidance, UK

## DIFFERENCES BETWEEN PROTOCOL AND REVIEW

Author team: Michael Pritchard joined the author team. Carolyn Doree left the author team.

Types of outcome measures: we planned to include systematic reviews that did not measure or report these outcomes. However, we found that it was challenging to determine review eligibility against the following criteria in the protocol: "We will include systematic reviews of studies that evaluated the effects of pharmacological or non-pharmacological interventions for preventing or minimising blood loss, for treating the effects of anaemia by improving the oxygen-carrying potential of the blood, and for reducing the need for allogeneic blood transfusion". To assist with the decision-making, we decided that an eligible review against this criteria should report data for blood loss or blood transfusion. Therefore, we excluded systematic reviews that did not measure our primary outcomes.

Search methods for identification of reviews: we did not conduct forward-citation searches.

Data extraction and management: in addition to the information listed in the protocol, we also collected data on the primary aim or objectives of the review, and if available, the primary objectives of the included studies within the review. This was in line with decisions made during the eligibility process (see above).

Assessment of methodological quality of the included reviews: we provided a judgment (Yes, No, Partial Yes) for each item in the AMSTAR 2 assessment tool in a table. We did not provide a separate judgement comment for each item in this table, as well. However, we provided a summary of our judgements in the appendix, including additional information that we considered when making our AMSTAR 2 judgments.

Data synthesis:

- we originally planned not to use data from systematic reviews that included studies of variable study designs (RCTs and non-randomised studies) if the data were not available, or reported separately. However, for completeness, we decided that it was appropriate to report

these data. We only included these data in sensitivity analysis, and we described them as indirect evidence in both the tables and the main text of the overview.

- in the protocol, we stated a hierarchical order to use when prioritising which review to select when the degree of overlap was high. When conducting the overview, we used a pragmatic approach to this decision making, choosing the review which we believed provided the most relevant data set.

Subgroup analysis: we expanded the methods section to more clearly describe the approach we used to identify subgroup information within the reviews, making the distinction between overall systematic review characteristics and any subgroup analysis conducted within each systematic review. We added an additional subgroup category (route of administration), because we judged that this subgroup was clinically important; it was also distinctly reported in many of the included systematic reviews.

Sensitivity analysis: we expanded the methods section to more clearly describe the approach we used to conduct sensitivity analysis.

Summary of findings tables and GRADE:

- we explained the approach we used when we found evidence from more than one type of adverse event.
- we stated in the protocol that we would consider risk of bias at the review level rather than the study level. Instead we judged the certainty of the evidence for risk of bias at the study level in each review, as guided by the *Cochrane Handbook for Systematic Reviews of Interventions*. We used our review-level judgements of quality (from AMSTAR 2) to contextualise the evidence base in the Discussion section of this overview.
- we explained our approach to manage overlapping studies for the summary of findings tables; we selected more than one priority review in order to capture data for as many outcomes as possible. Because selected priority reviews did not include a summary of findings table, we explained how we assessed certainty of the evidence in these reviews.
- we made a posthoc decision to present separate summary of findings tables for each group of interventions. We believed this approach provided the clearest presentation, and avoided the risk of end-users making indirect comparisons from the data.

## INDEX TERMS

### Medical Subject Headings (MeSH)

\*Anemia [therapy]; \*Emergence Delirium; Erythrocyte Transfusion; Hemorrhage; \*Hip Fractures [surgery]; Iron; Systematic Reviews as Topic; \*Tranexamic Acid [therapeutic use]

### MeSH check words

Aged; Humans