Is aspirin clinically effective and safe for venous thromboembolism prophylaxis following total hip and knee replacement? A systematic review and meta-analysis of randomized controlled trials

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Key points

Question

What is the effectiveness and safety of aspirin for venous thromboembolism prophylaxis after hip and knee replacement?

Findings

In this meta-analysis of 13 trials (6,060 participants), the risk of venous thromboembolism after hip and knee replacement was not significantly different when using aspirin compared with other anticoagulants. Adverse events, including bleeding, wound hematoma and infection, were not significantly different in patients receiving aspirin compared with other anticoagulants.

Meaning

Aspirin has an efficacy and safety that was not significantly different to other anticoagulants used for venous thromboembolism prophylaxis after hip and knee replacement, and hence remains an option for use.

Abstract

Importance

Total hip and knee replacement (THR and TKR) patients receive venous thromboembolism (VTE) pharmacoprophylaxis. It is unclear which anticoagulant is preferable. Observational data suggests aspirin provides effective VTE prophylaxis.

Objective

We assessed the effectiveness and safety of aspirin for VTE prophylaxis after THR and TKR.

Data Sources

We performed a meta-analysis of randomized controlled trials (RCTs), with no language restrictions, until 19th September 2019 using MEDLINE, Embase, Web of Science, Cochrane Library, and bibliographic searches.

Study Selection

We included RCTs assessing the effectiveness and safety of aspirin for VTE prophylaxis compared with other anticoagulants in adults undergoing THR and TKR. We excluded RCTs with placebo groups. Two authors independently performed the searches and study selection.

Data Extraction and Synthesis

The review followed PRISMA recommendations, and used the Cochrane Collaboration's risk of bias tool. Data were screened and extracted independently by both reviewers. Study specific relative risks [RR] were aggregated using random-effects models. Quality of evidence was assessed by GRADE (PROSPERO: CRD42018118816).

Main Outcome(s) and Measure(s)

The primary outcome was any postoperative VTE (asymptomatic or symptomatic). Secondary outcomes were adverse effects of therapy, including bleeding.

Results

Of 437 identified articles, 13 trials were included (n=6,060). The RR of VTE following THR and TKR was 1.12 (95% CI=0.78-1.62) for aspirin compared to other anticoagulants. Comparable findings were observed for deep vein thrombosis (DVT) (RR=1.04, CI=0.72-1.51) and pulmonary embolism (PE) (RR=1.01, CI=0.68-1.48). The risk of adverse events, including major bleeding, wound hematoma and infection, were not significantly different in patients receiving aspirin versus other anticoagulants. When analyzing THRs and TKRs separately, there was no significant difference in the risk of VTE, DVT, and PE between aspirin and other anticoagulants. Aspirin had a VTE risk not significantly different to patients receiving low-molecular weight heparin (RR=0.76, CI=0.37-1.56) or rivaroxaban (RR=1.52, CI=0.56-4.12). The quality of the evidence ranged from low to high.

Conclusions and Relevance

In terms of clinical efficacy and safety profile, aspirin is not significantly different to other anticoagulants used for VTE prophylaxis following THR and TKR. Future trials should focus on non-inferiority analysis of aspirin in comparison to alternative anticoagulants and cost-effectiveness.

Introduction

Total hip and knee replacement (THR and TKR) are common and effective interventions for degenerative joint conditions, like osteoarthritis.[1] Venous thromboembolism (VTE), (deep vein thrombosis (DVT) and pulmonary embolism (PE)), is an important cause of long-term morbidity, a preventable cause of mortality, and has substantial healthcare costs.[2] All joint replacement patients are at risk of VTE due to the duration of surgery and reduced mobility perioperatively. To reduce VTE risk, nearly all patients receive up to 35-days of anticoagulation postoperatively.[3] Rates of VTE at 90-days following THR and TKR are variable (up to 5% for DVT and up to 2% for PE in anticoagulated patients).[4]

Anticoagulants for preventing VTE include simple oral (aspirin), injectable (low-molecular weight heparin (LMWH)) and newer oral agents (dabigatran and rivaroxaban). Aspirin is inexpensive, easily administered, requires no blood monitoring and is well tolerated with an excellent safety profile.[5] Currently aspirin is used off-label for VTE prevention in both the US and UK. However there are some concerns that the newer and more expensive oral agents may have higher bleeding risks, including major haemorrhage and wound problems.[5] Thus considerable debate remains about which agent(s) should be preferred given clinical efficacy must be balanced against bleeding risk and cost.

Major efforts have been made by many organizations to produce guidelines for preventing VTE, which all use a rigorous approach to evidence synthesis and producing recommendations. These organizations include the American Academy of Orthopedic Surgeons (AAOS), the American College of Chest Physicians (ACCP), and the UK National Institute for Health and Care Excellence (NICE).[6-8] The 2011 AAOS guideline recommended that patients undergoing THR or TKR should receive VTE prophylaxis (pharmacologic

and/or mechanical), which was based on moderate level of evidence.[6] However at that time, the AAOS was unable to recommend for or against any specific VTE prophylactic agents due to a lack of evidence.[6] In 2012, the ACCP endorsed aspirin for VTE prophylaxis following THR and TKR with a grade of 1B (moderate evidence) compared with administering no VTE prophylaxis, which is the same level of evidence assigned to both injectable and newer oral agents compared with no VTE prophylaxis.[7] In 2018 NICE recommended aspirin alone for VTE prophylaxis after TKR; however following THR, patients require ten-days of LMWH before receiving aspirin, or solely have the newer, more expensive oral agents.[8]

Although observational data provides some support for aspirin as VTE prophylaxis following THR and TKR, good quality randomized controlled trials (RCTs) supporting aspirin are limited.[4, 5] However, recently a large RCT (n=3,424), not included in the latest recommendations from ACCP, AAOS, or NICE, was published in which all patients received five-days of rivaroxaban following THR and TKR before being randomized to continue rivaroxaban or switch to aspirin.[6-9] Given this trial has not been considered in any previous meta-analysis it may change the interpretation of existing data.

We assessed the clinical effectiveness and safety of aspirin compared with other anticoagulants for VTE prophylaxis following THR and TKR by performing a systematic review and meta-analysis of RCTs.

Methods

Search strategy and selection criteria

We performed a systematic review and meta-analysis using a predefined protocol as per PRISMA recommendations.[10] Two authors (GSM and SKK) independently searched MEDLINE, Embase, Web of Science, and Cochrane Library databases for relevant articles (inception to 19th September 2019). The computer-based searches combined terms and combinations of key words related to the population (e.g., "hip replacement", "knee replacement", "hip arthroplasty", "knee arthroplasty"), drug intervention (e.g., "aspirin", "heparin", "clexane", "dabigatran", "rivaroxaban" "warfarin"), and outcome (e.g., "venous thromboembolism", "deep vein thrombosis", "pulmonary embolism", "bleeding") in humans without language restrictions. All trials included in the recent NICE VTE prevention guideline were also assessed for suitability.[8] The search strategy and specific terms used are detailed (eTable 1). Two reviewers (GSM and SKK) independently screened titles and abstracts of all initially identified studies according to the selection criteria. Full-text articles of studies meeting the selection criteria were retrieved. Reference lists of selected studies and relevant review articles were manually searched for relevant articles.

We included RCTs assessing the clinical effectiveness and safety of aspirin for VTE prophylaxis compared with other agents in patients (≥18 years) undergoing THR or TKR. Patients had to be randomised to aspirin or another anticoagulant for inclusion. Trials using hybrid VTE prophylaxis strategies where aspirin was one of two agents used (e.g. initial course of LMWH before a longer course of aspirin) were included to reflect current practice.[8, 9, 11] We excluded all other study types (non-randomized and observational stuides), as well as RCTs with a placebo control group. The primary outcome was any VTE event

(including DVT and/or PE) after surgery, regardless of whether the event was asymptomatic or symptomatic. Secondary outcomes, where reported, included mortality, major bleeding complications, (including gastrointestinal and cerebrovascular haemorrhage), other bleeding complications, and wound complications, like haematoma and infection. No limits were placed on study follow-up duration.

Data extraction and quality assessment

The data extraction was conducted by two independent reviewers (GSM and SKK). In cases of inconsistency consensus was reached by a third author (MRW). A standardised predesigned data extraction form was used to obtain the relevant data from each study including: design, baseline demographics, geographical location, numbers enrolled and randomised, allocation concealment, blinding, VTE prophylaxis regimens (including dosage and duration), outcomes of interest, and follow-up duration. In cases of multiple publications involving the same study, the most up-to date or comprehensive information was extracted.

Potential sources of bias in RCTs were assessed using the Cochrane Collaboration's risk of bias tool,[12] which assesses seven possible sources of bias: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. For each individual domain, studies were classified into low, unclear or high risk of bias.

Statistical analysis

Summary measures were presented as relative risks [RR] with 95% confidence intervals (CIs). We used reported RRs or calculated risk estimates for studies that reported raw counts. Heterogeneity was assessed using the Cochrane χ^2 statistic and the I^2 statistic. Random-

effects models, which take into account heterogeneity within and between studies, were used to combine RRs. Parallel analyses employed fixed effects models. The decision to use random or fixed effects models was based on I^2 quantification of heterogeneity as well as variability in the clinical and methodological aspects of the studies, number of studies available for pooling, and study sample sizes.[13, 14] Study-level characteristics including geographical location, RCT design, allocation concealment, type of surgery (THR vs. TKR), specific thromboprophylactic agent, VTE endpoint (deep vein thrombosis vs. pulmonary embolism), and number of reported VTE events, were pre-specified as characteristics for assessment of heterogeneity, which was conducted using stratified analysis and random effects meta-regression. Other characteristics explored post-hoc included publication year; type of VTE (symptomatic vs. asymptomatic); types and doses of anticoagulants reflecting modern practice; modern VTE diagnostic methods; use of mechanical VTE prophylaxis; and follow-up period. Potential for publication bias was assessed through formal tests (Begg's funnel plots and Egger's regression symmetry tests).[15] We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess the quality of the body of evidence, based on study limitations, inconsistency of effect, imprecision, indirectness and publication bias.[16] STATA (version 14.2) was used for all analyses. This study was PROSPERO registered (CRD42018118816).

Results

Study identification

The initial search identified 437 potentially relevant citations. After screening titles and abstracts, 15 articles remained for full-text assessment. Two were subsequently excluded. Thirteen studies met the meta-analysis inclusion criteria (Figure 1), with their characteristics summarized (Table 1 and 2).[9, 11, 17-27]

Study characteristics

The 13 RCTs included 6,060 participants (2,969=aspirin and 3,091=comparator). Eleven trials were open-label and two were double-blinded. Seven studies were from North America, four from Asia and two from Europe. Participants ranged from 21 to 86 years, and 42.8% were male. Seven studies reported on THR patients only, with three studies reporting on both THR and TKR patients, and three reporting on TKR patients only. The commonest comparators were LMWH (5 studies) or rivaroxaban (3 studies; 1 of which used an initial five-day LMWH course followed by 14-days of rivaroxaban). All studies reported VTE events. Twelve studies reported specifically on DVT, and 9 reported PE.

Risk of bias

Using the Cochrane Collaboration tool, eleven trials had a high risk of bias with each study having between one and four of the seven possible sources of bias (eFigure 1). This bias was most commonly in the blinding of participants and personnel domain, followed by the blinding of outcome assessments and allocation concealment domains. Two studies had a low risk of bias in all domains.

Primary VTE outcomes

In the whole cohort, the pooled risk of VTE following THR and TKR in patients receiving aspirin was not significantly different to those receiving comparators (RR=1.12, 95% CI=0.78-1.62) (Figure 2). There was evidence of heterogeneity between the included studies (I^2=63%, 95% CI=33-80%; p=0.001), which was not explained by any of the study-level characteristics evaluated (Figure 3). On exclusion of the largest trial contributing data to the analysis (based on a noninferiority study design),[9] the pooled RR remained the same (1.14 (CI=0.77-1.70)) with minimal change in heterogeneity (I^2=66%, CI=38-82%; p=0.001).

The pooled risks of DVT (12 studies) (RR=1.04, CI=0.72-1.51) and PE (9 studies) (RR=1.01, CI=0.68-1.48) following THR and TKR in patients receiving aspirin were also not significantly different compared with those receiving comparators.

Adverse events

There was variable reporting of adverse events between the studies. The commonest adverse event reported was wound hematoma (5 studies), followed by major bleeding, wound infection and other wound complications (each reported in 3 studies). In the pooled analysis, the risks of the following events were not significantly different in patients receiving aspirin versus the comparator: any bleeding, major bleeding, minor bleeding, gastrointestinal bleeding, wound hematoma, wound infection, other wound complications, myocardial infarction, and death (eFigure 2). Patients receiving aspirin had a significantly reduced pooled risk of bruising (RR=0.68, CI=0.54-0.84) and lower limb edema (RR=0.57, CI=0.37-0.88) compared with those receiving comparators.

Subgroup analysis

Due to limited data, subgroup analysis only assessed the primary outcome of interest (VTE). There was no evidence of effect modification by any of the clinically relevant study-level characteristics explored (Figure 3). Specifically, the type of surgery (THR vs. TKR) and thromboprophylactic agent did not effect the risk of VTE. In the five studies reporting on VTE in patients receiving LMWH, the risk of VTE was not significantly different in patients receiving aspirin versus LMWH (RR=0.76, CI=0.37-1.56). The risk of DVT (RR=0.83, CI=0.42-1.63) and PE (RR=0.71, CI=0.19-2.61) were also not significantly different. In the three studies reporting on VTE events in patients receiving aspirin compared to rivaroxaban (with/without an initial course of LMWH), the risks of VTE (RR=1.52, CI=0.56-4.12) and DVT (RR=1.67, CI=0.53-5.26) were also not significantly different. Further subgroup analyses by study-level characteristics such as year of publication, follow-up duration, modern VTE diagnostic methods, type of VTE, type and dose of anticoagulant reflecting modern practice, and equal distribution of mechanical VTE prophylaxis, did not demonstrate any evidence of effect modification.

Publication bias

For comparisons involving ten or more studies, visual inspection of funnel plots for studies of VTE and DVT were symmetrical (eFigure 3) and these were consistent with Egger's regression tests, showing no statistical evidence of publication bias.

GRADE

GRADE ratings for outcomes involving pooled analyses of five or more studies were assessed (eTable 2). GRADE ratings for VTE, DVT, PE, and wound hematoma ranged from low to high quality evidence.

Discussion

This systematic review and meta-analysis demonstrated that there was no significant difference in the risk of VTE (including DVT and PE) when comparing aspirin to other anticoagulants in THR and TKR patients. The findings for VTE remained consistent when THR and TKR patients were assessed separately, and also when comparing aspirin to other commonly used anticoagulants, including LMWH and rivaroxaban. There were no differences in the risk of adverse events such as bleeding, wound complications, myocardial infarction, and death when aspirin was compared with other anticoagulants; although patients receiving aspirin had a reduced risk of bruising and lower limb edema. Findings for adverse events were based on data reported by few studies and some of the estimates were imprecise, hence caution is needed when interpreting these findings. In addition, RCTs were heterogeneous in terms of populations studied (THR and/or TKR) and anticoagulants compared to aspirin (specific drug and dosage). However formal subgroup analyses confirmed that the main study findings were not modified by several study level characteristics. The quality of the evidence ranged from low to high quality for the primary outcomes of VTE and/or DVT and PE, and the most commonly reported complication of wound haematoma.

Our findings are consistent with large observational cohorts, which have reported that aspirin was effective for VTE prophylaxis, and that aspirin had a similar or slightly improved efficacy and safety profile to other commonly used anticoagulants.[4, 5, 28-31] We therefore believe current evidence supports the continued use of aspirin in VTE prophylaxis following THR and TKR.

The inclusion of a recent RCT in this meta-analysis was important given it was relatively large, represented one of only two studies appraised which had a low risk of bias,[9] and was one of only a few studies comparing the newer oral anticoagulants (rivaroxaban) to aspirin, albeit after an initial five-day course of rivaroxaban for all patients.. Furthermore, this RCT has not been considered in any previous evidence synthesis, and therefore could change the interpretation of existing data. The authors of this trial observed no difference in the risk of VTE or adverse events between aspirin and rivaroxaban.[9] This one trial comprised more than half the patients included in our review. However, analyses excluding this large trial also demonstrated that aspirin was not significantly different to LMWH, which is an alternative current method of VTE prophylaxis frequently used worldwide.

We consider the current evidence on VTE prophylaxis following THR and TKR to be more in line with the recommendations from the ACCP[7] rather than NICE,[8] with the latter still not recommending aspirin monotherapy following THR despite supportive evidence here and from others.[5, 29] However, given most current trials included were associated with a high risk of bias we still require robust data from large well-designed RCTs to explore the efficacy, safety, and cost-effectiveness of aspirin compared with other commonly used anticoagulants. One on-going RCT in North America will randomise 25,000 patients undergoing THR and TKR either to aspirin, warfarin, or rivaroxaban to determine the efficacy and safety of each drug for VTE prophylaxis;[32] however this study does not include commonly used agents such as dabigatran and LMWH. It is acknowledged that some VTE prophylaxis agents are becoming less popular in certain regions/countries due to potential drawbacks compared with aspirin and DOACs. For example, LMWH requires daily injections administered by either the patient or healthcare professionals, and warfarin requires regular blood testing to ensure

therapeutic levels of anticoagulation, with potentially life-threatening consequences if patients are excessively anticoagulated.

This study has several strengths compared with previous work. Our review is the first to include the largest RCT in this area, thus providing the most comprehensive update on the efficacy and safety of aspirin for VTE prophylaxis following THR and TKR. We have used a detailed and robust search strategy, which spanned multiple databases and which was without language restriction. This allowed us to include trials from all over the world, which improves the generalizability of our findings. Only RCTs were included, so by excluding observational studies we removed the inherent bias associated with this study design. A detailed assessment of methodological quality of the included studies was performed. We systematically explored for sources of heterogeneity using several study-level characteristics and tested for evidence of effect modification. Importantly we have stratified our analyses for THR and TKR patients, and compared aspirin to specific anticoagulants, which have been limitations of previous trials and reviews. Our results remained robust in several sensitivity analyses and formal testing demonstrated no evidence of publication bias.

There were several limitations, with the majority inherent to the meta-analysis. The analysis was limited by the few RCTs that have been published and relatively small sample sizes given the outcomes of interest. The low event rate in some trials led to wide confidence intervals around the relative risks, thus reducing the precision of the respective estimates. Most studies had a high risk of bias in at least one domain. Furthermore, there was variability in the populations assessed (THR, TKR, or both), aspirin dosing and duration, the comparator (drug, dosage, and duration), the reporting of outcomes (including routine VTE screening versus symptomatic VTE) and adverse events, use of mechanical VTE prophylaxis, and

follow-up duration. These factors potentially could have led to biased estimates despite being assessed in sensitivity analyses. There appeared to be selective reporting by some studies on adverse events, as data on some adverse events were not reported by some of the included studies, which could have led to loss of power to demonstrate if any associations existed. There was significant heterogeneity between contributing studies that could not be explained by several relevant study level characteristics, suggesting that other factors might be responsible. It is acknowledged that there is bias towards underreporting symptomatic DVT in the trials that routinely screened for asymptomatic DVT, given the latter is frequently treated when identified. Finally, one trial contributed over 50% of the overall sample size, however, exclusion of this study in sensitivity analysis did not change the overall estimate.

Conclusions

Available evidence from RCTs suggests that in terms of clinical efficacy and safety profile, aspirin is not significantly different to other anticoagulants used for VTE prophylaxis following THR and TKR. The body of evidence ranges from low to high quality. However, given that most current trial evidence is associated with a high risk of bias, we still require large well-designed RCTs to validate these findings. Furthermore, these trials must determine whether newer more expensive anticoagulants (including rivaroxaban and dabigatran) have any clinical benefit over aspirin for VTE prophylaxis after THR and TKR, and whether they are cost-effective.

References

1. Learmonth ID, Young C, Rorabeck C. The operation of the century: total hip replacement. *Lancet*. 2007;**370**(9597):1508-1519.

2. Select Committee on Health Written Evidence. Appendix 6.:https://publications.parliament.uk/pa/cm200405/cmselect/cmhealth/200499/200499we200407.htm.

3. Eikelboom JW, Quinlan DJ, Douketis JD. Extended-duration prophylaxis against venous thromboembolism after total hip or knee replacement: a meta-analysis of the randomised trials. *Lancet*. 2001;**358**(9275):9-15.

4. Bala A, Huddleston JI, 3rd, Goodman SB, Maloney WJ, Amanatullah DF. Venous Thromboembolism Prophylaxis After TKA: Aspirin, Warfarin, Enoxaparin, or Factor Xa Inhibitors? *Clin Orthop Relat Res*. 2017;**475**(9):2205-2213.

5. Parvizi J, Ceylan HH, Kucukdurmaz F, Merli G, Tuncay I, Beverland D. Venous Thromboembolism Following Hip and Knee Arthroplasty: The Role of Aspirin. *J Bone Joint Surg Am*. 2017;**99**(11):961-972.

6. American Acadmey of Orthopaedic Surgeons. Preventing venous thromboembolic disease in patients undergoing elective hip and knee arthroplasty. Evidence-Based Guideline and Evidence Report. September 2011. Available at: https://www.aaos.org/uploadedFiles/PreProduction/Quality/Guidelines_and_Reviews/VTE_full_guideline_10.31.16.pdf

7. Falck-Ytter Y, Francis CW, Johanson NA, Curley C, Dahl OE, Schulman S, Ortel TL, Pauker SG, Colwell CW, Jr. Prevention of VTE in orthopedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. *Chest*. 2012;**141**(2 Suppl):e278S-e325S.

8. National Institute for Health and Care Excellence (NICE). Venous thromboembolism in over 16s: reducing the risk of hospital-acquired deep vein thrombosis or pulmonary embolism. NICE guideline [NG89]. March 2018. Available at: https://www.nice.org.uk/guidance/ng89.

9. Anderson DR, Dunbar M, Murnaghan J, Kahn SR, Gross P, Forsythe M, Pelet S, Fisher W, Belzile E, Dolan S, Crowther M, Bohm E, MacDonald SJ, Gofton W, Kim P, Zukor D, Pleasance S, Andreou P, Doucette S, Theriault C, Abianui A, Carrier M, Kovacs MJ, Rodger MA, Coyle D, Wells PS, Vendittoli PA. Aspirin or Rivaroxaban for VTE Prophylaxis after Hip or Knee Arthroplasty. *N Engl J Med*. 2018;**378**(8):699-707.

10. Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. *J Clin Epidemiol*. 2009;**62**(10):1006-1012.

11. Anderson DR, Dunbar MJ, Bohm ER, Belzile E, Kahn SR, Zukor D, Fisher W, Gofton W, Gross P, Pelet S, Crowther M, MacDonald S, Kim P, Pleasance S, Davis N, Andreou P, Wells P, Kovacs M, Rodger MA, Ramsay T, Carrier M, Vendittoli PA. Aspirin versus low-molecular-weight heparin for extended venous thromboembolism prophylaxis after total hip arthroplasty: a randomized trial. *Ann Intern Med*. 2013;**158**(11):800-806.

12. Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, Savovic J, Schulz KF, Weeks L, Sterne JA, Cochrane Bias Methods G, Cochrane Statistical Methods G. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. *BMJ*. 2011;**343**:d5928.

13. Higgins JP, Thompson SG, Deeks JJ, Altman DG. Measuring inconsistency in meta-analyses. *BMJ*. 2003;**327**(7414):557-560.

14. Tufanaru C, Munn Z, Stephenson M, Aromataris E. Fixed or random effects meta-analysis? Common methodological issues in systematic reviews of effectiveness. *Int J Evid Based Healthc*. 2015;**13**(3):196-207.

15. Egger M, Davey Smith G, Schneider M, Minder C. Bias in meta-analysis detected by a simple, graphical test. *BMJ*. 1997;**315**(7109):629-634.

16. Guyatt G, Oxman AD, Akl EA, Kunz R, Vist G, Brozek J, Norris S, Falck-Ytter Y, Glasziou P, DeBeer H, Jaeschke R, Rind D, Meerpohl J, Dahm P, Schunemann HJ. GRADE guidelines: 1. Introduction-GRADE evidence profiles and summary of findings tables. *J Clin Epidemiol*. 2011;**64**(4):383-394.

17. Gelfer Y, Tavor H, Oron A, Peer A, Halperin N, Robinson D. Deep vein thrombosis prevention in joint arthroplasties: continuous enhanced circulation therapy vs low molecular weight heparin. *J Arthroplasty*. 2006;**21**(2):206-214.

18. Harris WH, Athanasoulis CA, Waltman AC, Salzman EW. Prophylaxis of deep-vein thrombosis after total hip replacement. Dextran and external pneumatic compression compared with 1.2 or 0.3 gram of aspirin daily. *J Bone Joint Surg Am*. 1985;**67**(1):57-62.

19. Jiang Y, Du H, Liu J, Zhou Y. Aspirin combined with mechanical measures to prevent venous thromboembolism after total knee arthroplasty: a randomized controlled trial. *Chin Med J (Engl)*. 2014;**127**(12):2201-2205.

20. Josefsson G, Dahlqvist A, Bodfors B. Prevention of thromboembolism in total hip replacement. Aspirin versus dihydroergotamine-heparin. *Acta Orthop Scand*. 1987;**58**(6):626-629.

21. Kim YH, Choi IY, Park MR, Park TS, Cho JL. Prophylaxis for deep vein thrombosis with aspirin or low molecular weight dextran in Korean patients undergoing total hip replacement. A randomized controlled trial. *Int Orthop*. 1998;**22**(1):6-10.

22. Lotke PA, Palevsky H, Keenan AM, Meranze S, Steinberg ME, Ecker ML, Kelley MA. Aspirin and warfarin for thromboembolic disease after total joint arthroplasty. *Clin Orthop Relat Res*. 1996(324):251-258.

23. Salzman EW, Harris WH, DeSanctis RW. Reduction in venous thromboembolism by agents affecting platelet function. *N Engl J Med*. 1971;**284**(23):1287-1292.

24. Westrich GH, Bottner F, Windsor RE, Laskin RS, Haas SB, Sculco TP. VenaFlow plus Lovenox vs VenaFlow plus aspirin for thromboembolic disease prophylaxis in total knee arthroplasty. *J Arthroplasty*. 2006;**21**(6 Suppl 2):139-143.

25. Woolson ST, Watt JM. Intermittent pneumatic compression to prevent proximal deep venous thrombosis during and after total hip replacement. A prospective, randomized study of compression alone, compression and aspirin, and compression and low-dose warfarin. *J Bone Joint Surg Am*. 1991;**73**(4):507-512.

26. Zou Y, Tian S, Wang Y, Sun K. Administering aspirin, rivaroxaban and low-molecular-weight heparin to prevent deep venous thrombosis after total knee arthroplasty. *Blood Coagul Fibrinolysis*. 2014;**25**(7):660-664.

27. Alfaro MJ, Paramo JA, Rocha E. Prophylaxis of thromboembolic disease and platelet-related changes following total hip replacement: a comparative study of aspirin and heparin-dihydroergotamine. *Thromb Haemost*. 1986;**56**(1):53-56.

28. Jameson SS, Baker PN, Charman SC, Deehan DJ, Reed MR, Gregg PJ, Van der Meulen JH. The effect of aspirin and low-molecular-weight heparin on venous thromboembolism after knee replacement: a non-randomised comparison using National Joint Registry Data. *J Bone Joint Surg Br*. 2012;**94**(7):914-918.

29. Jameson SS, Charman SC, Gregg PJ, Reed MR, van der Meulen JH. The effect of aspirin and low-molecular-weight heparin on venous thromboembolism after hip

replacement: a non-randomised comparison from information in the National Joint Registry. *J Bone Joint Surg Br*. 2011;**93**(11):1465-1470.

30. Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) trial. *Lancet*. 2000;**355**(9212):1295-1302.

31. Cusick LA, Beverland DE. The incidence of fatal pulmonary embolism after primary hip and knee replacement in a consecutive series of 4253 patients. *J Bone Joint Surg Br*. 2009;**91**(5):645-648.

32. Comparative Effectiveness of Pulmonary Embolism Prevention After Hip and Knee Replacement (PEPPER). 2016:https://clinicaltrials.gov/ct2/show/NCT02810704.

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Access to data and data analysis

GSM and SKK had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

Meeting presentation

Not applicable.

Originality of content

We verify that all information and materials in the manuscript are original, unless otherwise specified.

Authors' contributions

GSM, SKK, AJ, AWB, and MRW conceived and designed the study. GSM and SKK acquired data. GSM and SKK analyzed and interpreted the data. GSM drafted the manuscript. SKK, AJ, AWB, and MRW critically revised the manuscript for important intellectual content. MRW supervised the study.

Declaration of interests

We declare no competing interests for any author.

Ethics committee approval

Not required as systematic review of published literature.

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Figure legends

Figure 1 PRISMA flow diagram

Figure 2. Effect of aspirin compared with other anticoagulants on venous thromboembolism (including deep vein thrombosis and pulmonary embolism) in randomized controlled trials of patients undergoing total hip and knee replacement.

Outcomes included both symptomatic and asymptomatic venous thromboembolism events; the summary estimate presented was calculated using a random effects model; sizes of data markers are proportional to the inverse of the variance of the relative ratio; CI, confidence interval (bars); RR, relative risk

Figure 3. Effect of aspirin compared with other anticoagulants on venous thromboembolism in randomized controlled trials of patients undergoing total hip and knee replacement, grouped according to several study-level characteristics

Outcomes included both symptomatic and asymptomatic venous thromboembolism events; *p*-values are for meta-regression; CI, confidence interval (bars); DVT, deep vein thrombosis; LMWH, low molecular weight heparin; PE, pulmonary embolism; RR, relative risk; THR, total hip replacement; TKR, total knee replacement; VTE, venous thromboembolism

Table 1 Summary characteristics of the included trials

	Randomised controlled trials (n=13)
Number of participants	
Total	6,060
Aspirin	2,969
Comparator *	3,091
Mean age (range) in years	63.0 (21 to 86)
Mean percentage of males	42.8
Joint replacement population	
Both THR and TKR	3 studies (n=3,857)
THR only	7 studies (n=1,495)
TKR only	3 studies (n=708)
Study location	
North America	7 studies (n=5,223)
Asia	4 studies (n=665)
Europe	2 study (n=172)
Comparator *	
Rivaroxaban +/- LMWH	3 studies (n=1,879)
LMWH	5 studies (n=747)
Warfarin	3 studies (n=258)
LMW Dextran	4 studies (n=173)
Dipyridamole	1 study (n=34)
Outcome **	
Venous thromboembolism	13 studies (n=6,060)
Deep vein thrombosis	11 studies (n=5,835)
Pulmonary embolism	9 studies (n=5,426)
Follow-up period for outcome assessment	Range (when specified): 9 days to 6 months

* Studies could report on more than one comparator versus aspirin

** Studies could report on more than one outcome

THR = total hip replacement; TKR = total knee replacement; LMWH = low molecular weight heparin

557 **Table 2** Specific details of the treatment arms and outcomes for the included trials
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Study	Population (n)	Aspirin dose and duration	Comparator dose and duration	Mechanical VTE prophylaxis	Routine DVT screening or symptomatic DVT	DVT diagnostic methods	Follow-up duration
Anderson 2018	THR (1804) TKR (1620)	5 days rivaroxaban (10mg OD) then aspirin (81mg OD) for 30 days for THR, and 9 days for TKR	Rivaroxaban (10mg OD) for 35 days for THR, and 14 days for TKR	As per local policy (none, IPC, graduated stockings, or both) – equal distribution of these between treatment groups	Symptomatic	Venous ultrasonography	90 days
Jiang 2014	TKR (120)	14 days Aspirin (100mg OD)	5 days LMWH (5000 Units OD) then 14 days of rivaroxaban (10 mg OD)	IPC + graduated stockings in both groups	Routine screening (4^{th} and 5^{th} post-op day) + any symptomatic VTE during FU	Venous ultrasonography	6 weeks
Zou 2014	TKR (324)	14 days Aspirin (100mg OD)	14 days of Rivaroxaban (10mg OD) OR 14 days of LMWH (4000 Units OD)	NS	Routine screening (2^{nd} and 4^{th} post-op week) + any symptomatic VTE during FU	Venous ultrasonography	4 weeks
Anderson 2013	THR (778)	10 days of LWMH (Dalteparin: 5000 Units OD) then aspirin (81mg OD) for 28 days	38 days LWMH (Dalteparin: 5000 Units OD)	As per local policy (NS what used or how distributed between groups)	Symptomatic	Venous ultrasonography	90 days
Westrich	TKR (264)	28 days Aspirin (325	28 days LWMH	IPC in both	Routine	Venous	6 weeks

2006		mg OD)	(Enoxaparin: 40 mg OD)	groups	screening (3 to 5 days post-op, and at 4 to 6 weeks post-op) + any symptomatic VTE during FU	ultrasonography	
Gelfer 2006	THR and TKR (121)	Aspirin (100 mg OD; duration NS)	LWMH (Enoxaparin: 40 mg OD; duration NS)	IPC in aspirin group only	Routine screening (5 to 8 days post-op) + any symptomatic VTE during FU	Venogram for screening + venous ultrasonography for symptomatic events	3 months
Kim 1998	THR (100)	16 days Aspirin (1200 mg OD)	3 days LMW Dextran (500ml OD)	NS	Routine screening (7 to 10 days post-op)	Venogram	10 days
Woolson 1991	THR (141)	Aspirin (650 mg BD; duration NS)	Warfarin (7.5mg or 10mg initially then dose titrated based on prothrombin time; duration NS)	IPC + graduated stockings in both groups	Routine screening (4 to 13 days post-op) + any symptomatic VTE during FU	Venogram and/or venous ultrasonography	3 months
Josefsson 1987	THR (82)	9 days Aspirin (1500 mg BD)	9 days Dihydroergotamine-heparin (DHE 0.5 mg / Heparin 5000 Units BD)	Graduated stockings in both groups	Routine screening (9 days post-op)	Lung perfusion scan and fibrinogen uptake test (venogram done if uptake scan was positive)	9 days
Harris 1985	THR (135)	Aspirin (1200 mg OD; duration NS)	3 days LMW Dextran (OD, dose NS)	IPC in LMW Dextran group	Routine screening (see	Fibrinogen uptake test	14 days

		OR Aspirin (300 mg OD; duration NS)		only	right hand cell for timings) + any symptomatic VTE during FU	(daily), cuff impedance (4-5 days post-op then every 3rd day, and venography (done before 10th day if one of above was positive, otherwise done between 10th and 14th post-op day)	
Lotke 1996	THR (133) TKR (179)	42 days Aspirin (325 mg BD)	42 days Warfarin (10 mg initially then dose titrated based on prothrombin time)	NS	Routine screening (7 to 10 days post-op) + any symptomatic VTE during FU	Lung perfusion scan and venogram	6 months
Salzman 1971	THR (169)	21 to 35 days Aspirin (600 mg BD)	21 to 35 days of either: 1. Warfarin (dose titrated based on prothrombin time) 2. Dipyridamole (400 mg OD) 3. Dextran (500ml / 10% solution OD)	NS	Symptomatic	Lung perfusion scan and pulmonary angiography (no venogram or fibrinogen uptake test used for DVT detection)	NS
Alfaro 1986	THR (120)	7 days Aspirin (125 mg BD) OR	7 days Dihydroergotamine-heparin (DHE 0.5 mg	NS	Routine screening (minimum of 7	Fibrinogen uptake test (venogram done	NS

		7 days Aspirin (500 mg BD)	/ Heparin 5000 Units BD)		days post-op)	if uptake scan was positive)	

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560 DVT = deep vein thrombosis; OD = once daily; BD = twice daily; NS = not specified; IPC = intermittent pneumatic compression; FU = follow-
561 up; LMWH = low molecular weight heparin; THR = total hip replacement; TKR = total knee replacement; VTE = venous thromboembolism
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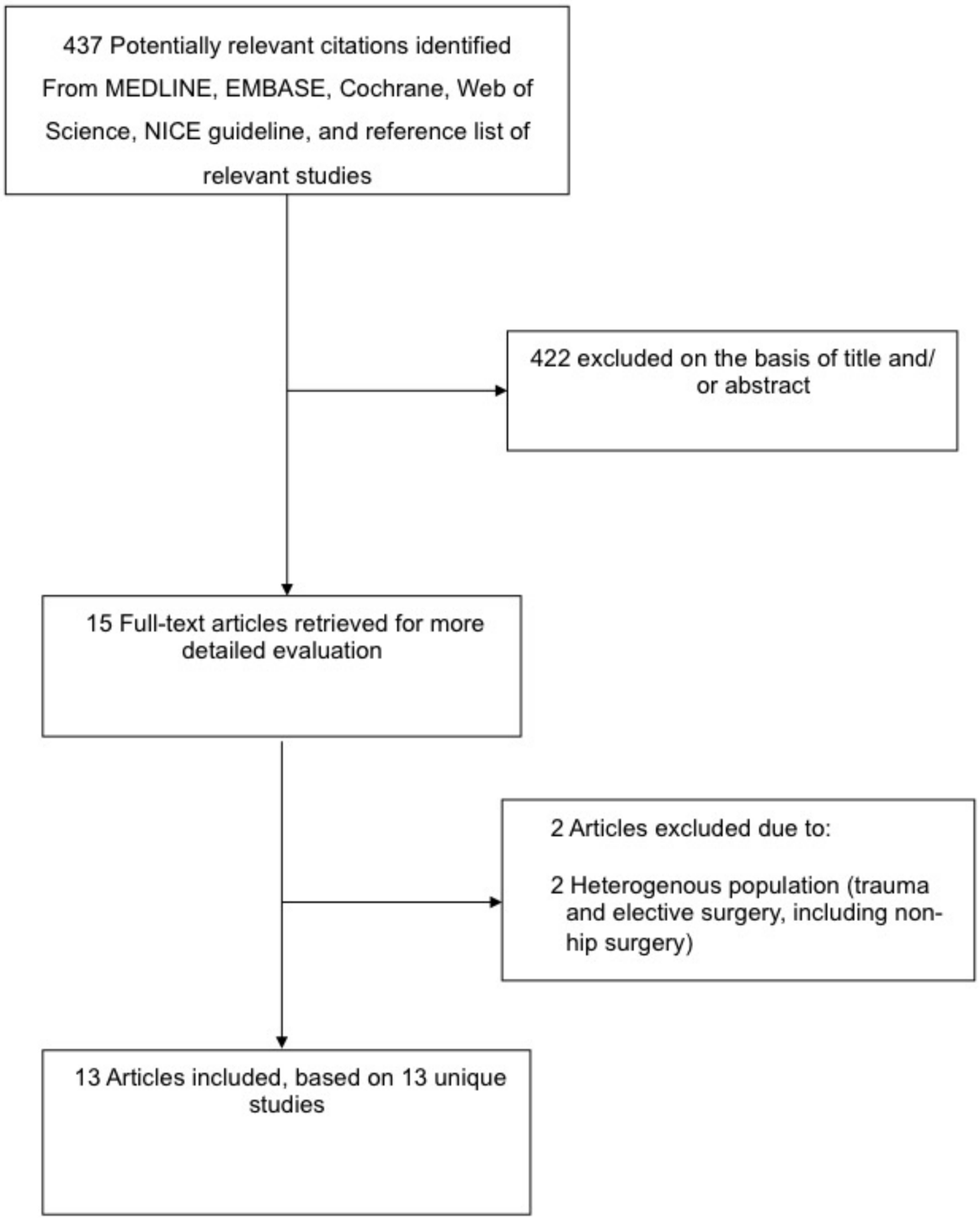
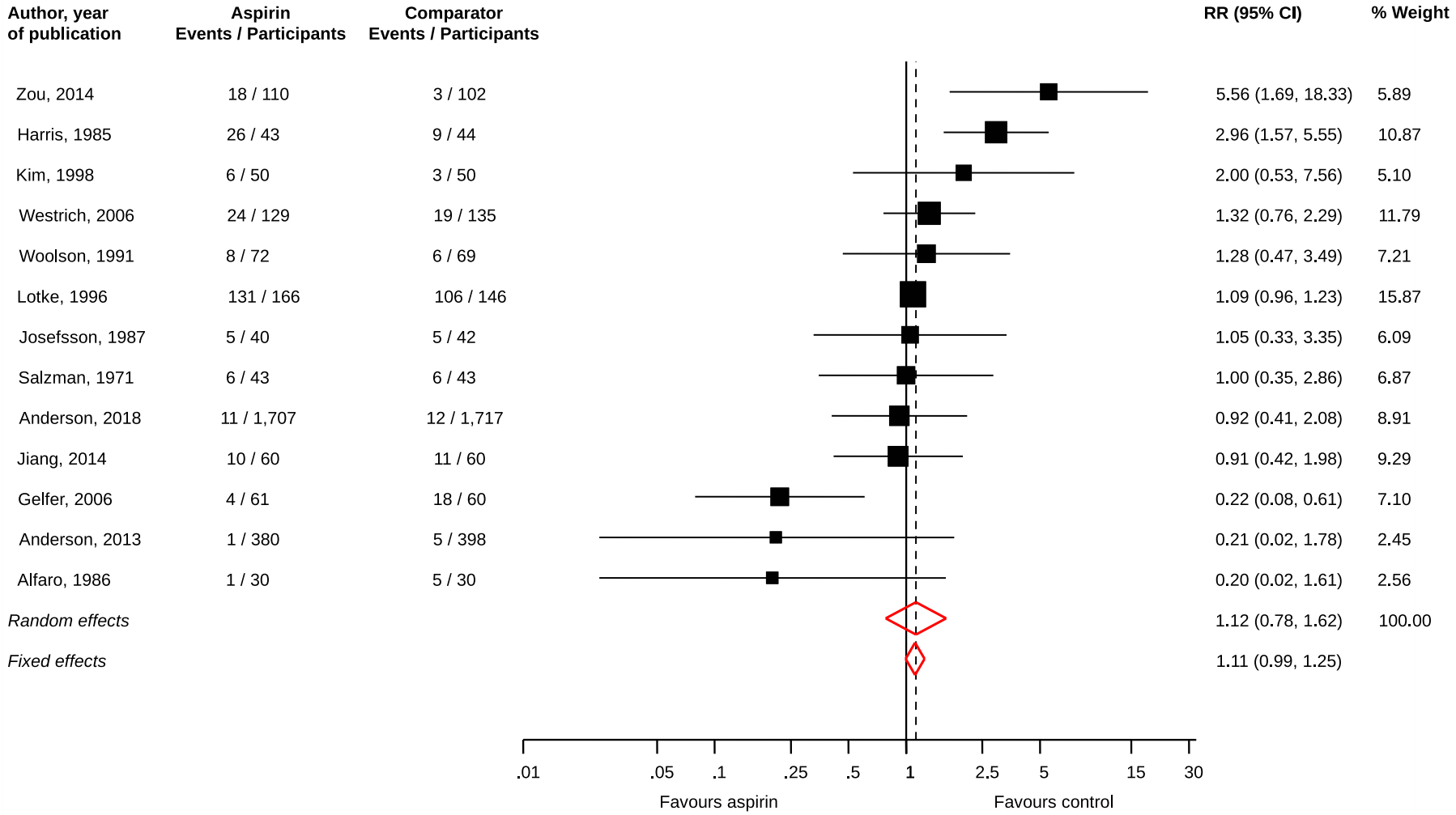
Identification

Screening

Eligibility

Included




Author, year of publication
Aspirin Events / Participants
Comparator Events / Participants
RR (95% CI)
% Weight
Zou, 2014 18 / 110 3 / 102 5.56 (1.69, 18.33) 5.89
Harris, 1985 26 / 43 9 / 44 2.96 (1.57, 5.55) 10.87
Kim, 1998 6 / 50 3 / 50 2.00 (0.53, 7.56) 5.10
Westrich, 2006 24 / 129 19 / 135 1.32 (0.76, 2.29) 11.79
Woolson, 1991 8 / 72 6 / 69 1.28 (0.47, 3.49) 7.21
Lotke, 1996 131 / 166 106 / 146 1.09 (0.96, 1.23) 15.87
Josefsson, 1987 5 / 40 5 / 42 1.05 (0.33, 3.35) 6.09
Salzman, 1971 6 / 43 6 / 43 1.00 (0.35, 2.86) 6.87
Anderson, 2018 11 / 1,707 12 / 1,717 0.92 (0.41, 2.08) 8.91
Jiang, 2014 10 / 60 11 / 60 0.91 (0.42, 1.98) 9.29
Gelfer, 2006 4 / 61 18 / 60 0.22 (0.08, 0.61) 7.10
Anderson, 2013 1 / 380 5 / 398 0.21 (0.02, 1.78) 2.45
Alfaro, 1986 1 / 30 5 / 30 0.20 (0.02, 1.61) 2.56
Random effects 1.12 (0.78, 1.62) 100.00
Fixed effects 1.11 (0.99, 1.25)
.01
.05
.1
.25
.5
1
2.5
5
15
30
Favours aspirin
Favours control

Subgroup	No. of studies	Aspirin Events / Participants	Comparator Events / Participants	RR (95% CI)	*P*-value
Location					
North America	7	207 / 2,540	163 / 2,552	1.26 (0.88, 1.79)	.64
Asia	4	38 / 281	35 / 272	1.17 (0.33, 4.20)	
Europe	2	6 / 0	10 / 72	0.58 (0.12, 2.75)	
Year of publication					
After 2000	6	68 / 2,447	68 / 2,472	0.91 (0.43, 1.93)	.44
Before 2000	7	183 / 444	140 / 424	1.32 (0.84, 2.06)	
RCT design					
Double blind	2	12 / 2,087	17 / 2,115	0.62 (0.17, 2.25)	.32
Open label	11	239 / 804	191 / 781	1.20 (0.81, 1.78)	
Allocation concealment					
Adequate	4	24 / 2,220	41 / 2,244	0.56 (0.23, 1.39)	.08
Unclear	2	28 / 170	14 / 162	2.12 (0.36, 12.47)	
Inadequate	7	199 / 501	153 / 490	1.33 (0.89, 1.97)	
Joint type					
THR	9	75 / 1,622	70 / 1,649	1.08 (0.65, 1.79)	.64
TKR	5	135 / 1,208	92 / 1,187	1.25 (0.84, 1.85)	
Follow-duration					
≥14 days	9	233 / 2,728	189 / 2,731	1.16 (0.75, 1.79)	.90
<14 days	3	17 / 133	14 / 135	1.21 (0.62, 2.38)	
Modern VTE diagnosis					
Yes	10	239 / 2,778	192 / 2,781	1.20 (0.79, 1.81)	.77
No	3	12 / 113	16 / 115	0.83 (0.39, 1.75)	
VTE endpoint					
DVT	12	181 / 2,848	155 / 2,852	1.04 (0.72, 1.51)	.92
PE	9	46 / 2,641	43 / 2,654	1.01 (0.68, 1.48)	
Type of VTE					
Symptomatic VTE	3	18 / 2,130	23 / 2,158	0.84 (0.45, 1.55)	.36
Asymptomatic VTE	10	233 / 761	185 / 738	1.22 (0.79, 1.87)	
Regimen comparison					
Aspirin vs Rivaroxaban	3	39 / 1,877	26 / 1,978	1.52 (0.56, 4.12)	.25
Aspirin vs LMWH	5	52 / 720	61 / 747	0.76 (0.37, 1.56)	
Mechanical VTE prophylaxis					
Distributed equally between groups	5	58 / 2,008	53 / 2,023	1.12 (0.79, 1.59)	.94
None	8	193 / 883	155 / 873	1.07 (0.56, 2.07)	
Type/doses of anticoagulants					
Reflecting modern practice	6	68 / 2,447	68 / 2,472	0.91 (0.43, 1.93)	.44
Others	7	183 / 444	140 / 424	1.32 (0.84, 2.06)	
No. of VTE events					
≥20	7	224 / 2,276	178 / 2,264	1.22 (0.76, 1.98)	.49
<20	6	27 / 615	30 / 632	0.97 (0.55, 1.70)