



Oral Aspirin for Venous Thromboembolism Prophylaxis After Orthopedic Surgery: An Evidence-Based Review

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Abstract

Background: Venous thromboembolism (VTE) remains a major complication after total hip arthroplasty (THA), total knee arthroplasty (TKA), and fracture surgery. While anticoagulants such as low-molecular-weight heparin (LMWH) and direct oral anticoagulants (DOACs) are standard, aspirin (ASA) is increasingly considered due to its convenience, safety profile, and low cost.

Methods: We systematically reviewed randomized controlled trials (RCTs) and international guidelines on ASA for orthopedic VTE prophylaxis. Nine RCTs and four guidelines were included. Outcomes assessed were deep vein thrombosis (DVT), pulmonary embolism (PE), major bleeding, and mortality.

Results: In arthroplasty, EPCAT II demonstrated that short-course rivaroxaban followed by ASA was noninferior to extended rivaroxaban, whereas CRISTAL showed higher symptomatic VTE rates with ASA compared to enoxaparin when used from day 0. PREVENT CLOT established ASA as noninferior to LMWH for mortality after fracture surgery, with similar PE and bleeding rates but slightly more distal DVTs. Smaller RCTs from Asia and South America found no major differences between ASA and rivaroxaban, warfarin, or sequential regimens. Guidelines remain heterogeneous: ASH (2019) provides conditional recommendations, NICE (2018/2022) and AAOS (2022) endorse ASA in specific settings, and the 2024 European guideline emphasizes individualized prophylaxis.

Conclusions: ASA is most reliably used as extended prophylaxis after initial anticoagulation in arthroplasty and as a pragmatic alternative to LMWH in trauma surgery. Anticoagulants remain superior when initiated immediately after arthroplasty. ASA's favorable safety, low cost, and oral administration make it attractive in selected patient groups, though high-risk patients still benefit most from anticoagulants.

Keywords: Aspirin; Venous Thromboembolism Prophylaxis; Total Joint Arthroplasty; Orthopedic Trauma; Randomized Controlled Trials

Abbreviations

AAOS – American Academy of Orthopaedic Surgeons, ASA – Acetylsalicylic acid (aspirin), ASH – American Society of Hematology, CADTH – Canadian Agency for Drugs and Technologies in Health, CI – Confidence interval, CRISTAL – Comparison of Risk of Symptomatic Thromboembolism After Knee or Hip, Arthroplasty Using Aspirin or Low-molecular-weight heparin Trial, DVT – Deep vein thrombosis, DOAC – Direct oral anticoagulant, ERAS – Enhanced recovery after surgery, EPCAT II – Extended Prophylaxis Comparing Aspirin and Rivaroxaban II Trial, GI – Gastrointestinal, LMWH – Low-molecular-weight heparin, NICE – National Institute for Health and Care Excellence, PE – Pulmonary embolism, PRISMA – Preferred Reporting Items for Systematic Reviews and Meta-Analyses, RCT – Randomized controlled trial, THA – Total hip arthroplasty, TKA – Total knee arthroplasty, VTE – Venous thromboembolism

Introduction

Venous thromboembolism (VTE), which includes deep vein thrombosis (DVT) and pulmonary embolism (PE), remains one of the most serious complications following major orthopedic surgery such as total hip arthroplasty (THA), total knee arthroplasty (TKA), and fracture fixation [10, 14]. Without prophylaxis, reported rates of asymptomatic DVT can reach 40–60% after arthroplasty, and symptomatic events remain clinically significant despite enhanced recovery protocols [17–19]. VTE contributes to morbidity, mortality, and substantial healthcare costs, underscoring the need for effective prevention strategies [10, 14].

Enhanced recovery after surgery (ERAS) programs, emphasizing multimodal analgesia, early mobilization, and standardized perioperative care, have contributed to reductions in VTE risk [20, 21]. Nevertheless, pharmacologic prophylaxis remains a cornerstone of prevention [20, 21]. Current prophylactic strategies rely predominantly on low-molecular-weight heparins (LMWH), vitamin K antagonists, and direct oral anticoagulants (DOACs). While effective, these agents are associated with drawbacks such as bleeding risk, injection-related inconvenience, need for laboratory monitoring, and higher direct costs [17-19].

Aspirin (acetylsalicylic acid, ASA) represents a low-cost, orally administered alternative with favorable safety characteristics [15, 16]. Its mechanism of action, through irreversible inhibition of platelet cyclooxygenase and suppression of thromboxane A₂, primarily targets arterial thrombosis. Nonetheless, platelet activation also contributes to venous thrombus formation, particularly in the setting of tissue injury and inflammation [15, 16,]. These pathophysiological insights provide the rationale for the use of ASA in VTE prophylaxis.

Several observational studies and systematic reviews have suggested that ASA may be comparable to anticoagulants in efficacy, while potentially conferring a lower risk of bleeding complications [14,15]. For instance, Matharu et al. (2020) demonstrated in a large meta-analysis that ASA is noninferior to anticoagulants in preventing symptomatic VTE after arthroplasty [16]. Zheng et al. (2023) confirmed similar findings across randomized and observational data [23].

Despite these encouraging signals, evidence remains heterogeneous, and guideline recommendations differ markedly. The American Society of Hematology (ASH) 2019 guidelines permit ASA as one option but only conditionally [12], while the UK National Institute for Health and Care Excellence (NICE) explicitly allows ASA after TKR and sequentially after LMWH in THR [11]. The American Academy of Orthopaedic Surgeons (AAOS) endorses ASA in typical-risk patients [AAOS], and the 2024 European update emphasizes risk-stratified prophylaxis [13]. These discrepancies highlight ongoing uncertainty and the need for a critical synthesis of contemporary RCTs and guidelines.

The aim of this review is therefore to summarize and contextualize the current evidence from randomized controlled trials and international guidelines on the role of ASA in orthopedic VTE prophylaxis. This review also integrates the risk–benefit profile of ASA, its place relative to anticoagulants, and implications for clinical practice (see Figure 1 for the evidence hierarchy and Figure 2 for the study selection process).

Methods

We conducted a structured review according to PRISMA guidelines [22]. PubMed, Embase, Web of Science, and Cochrane Library were searched through September 2025 with terms including 'aspirin', 'acetylsalicylic acid', 'venous thromboembolism', 'thromboprophylaxis', 'arthroplasty', and 'fracture'. Inclusion criteria were RCTs comparing ASA with anticoagulants in adults undergoing THA, TKA, or fracture fixation, and major guidelines addressing ASA use. Exclusion criteria were observational studies, case reports, pediatric populations, or studies with <10 days prophylaxis. Data extraction focused on trial design, ASA regimen, comparator, follow-up, and outcomes.

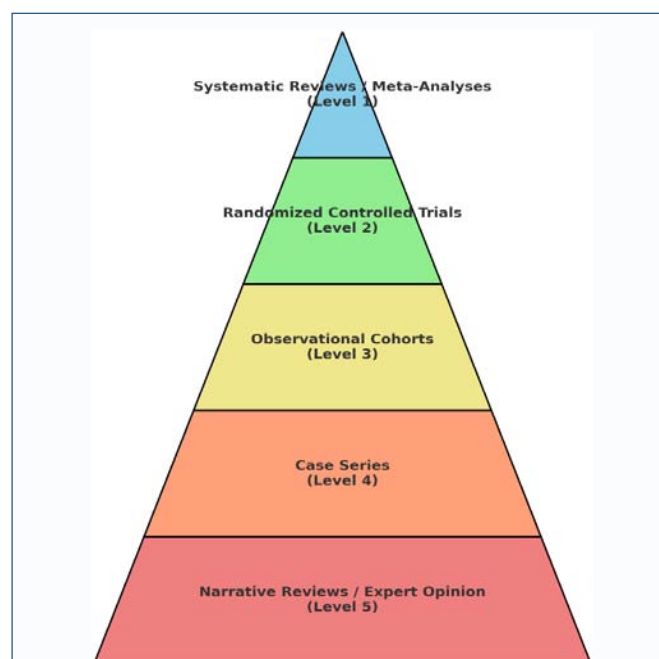


Figure 1: Evidence pyramid of included studies.

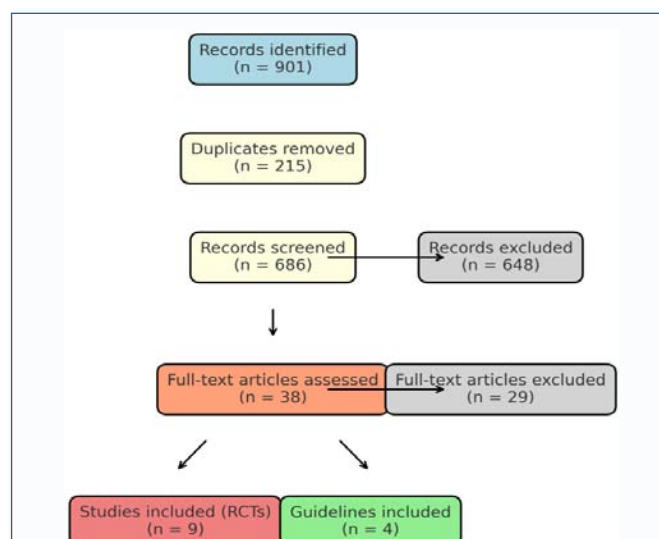


Figure 2: PRISMA flow diagram.

Results

Across the nine included randomized controlled trials (RCTs), outcomes demonstrated that aspirin (ASA) provided comparable venous thromboembolism (VTE) prophylaxis to standard anticoagulants in several orthopedic settings, though important differences emerged depending on the timing and comparator. In arthroplasty, the large EPCAT II trial found that switching from rivaroxaban to ASA after 5 days was noninferior to continued rivaroxaban, with nearly identical VTE rates (0.64% vs 0.70%) and no increase in bleeding [1]. By contrast, the CRISTAL trial reported a significantly higher incidence of symptomatic VTE when ASA 100 mg daily was used as sole prophylaxis from day 0 after surgery compared with enoxaparin (3.5% vs 1.8%), although bleeding outcomes were similar [2].

Table 1: Characteristics of included randomized controlled trials.

Study (year)	Country	Population	ASA regimen	Comparator	Duration	Outcomes
EPCAT II (Anderson 2018)	Canada	3,424 THA/TKA	Rivaroxaban 5d → ASA 81 mg OD	Rivaroxaban full course	90d	VTE, bleeding, mortality
CRISTAL (Sidhu 2022)	Australia	9,711 THA/TKA	ASA 100 mg OD	Enoxaparin 40 mg OD	90d	Symptomatic VTE, bleeding
PREVENT CLOT (O'Toole 2023)	US/Canada	12,211 fractures	ASA 81 mg BID	Enoxaparin 30 mg BID	90d	Mortality, VTE, bleeding
Zhou 2023	China	120 TKA	ASA 100 mg OD	Rivaroxaban 10 mg OD	90d	VTE, bleeding
Hongnaparak 2022	Thailand	40 TKA	ASA 300 mg OD	Rivaroxaban 10 mg OD	14d	DVT, PE, bleeding
Colleoni 2018	Brazil	27 TKA	ASA 150 mg BID	Rivaroxaban 10 mg OD	4w	VTE, wound complications
Jiang 2014	China	120 TKA	ASA 100 mg OD + mechanical	LMWH 5d → Rivaroxaban 9d	6w	VTE, bleeding, cost
Zou 2014	China	212 TKA	ASA 100 mg OD	Rivaroxaban 10 mg OD	4w	VTE, bleeding
Lotke 1996	USA	192 THA/TKA	ASA 325 mg BID	Warfarin	6m	VTE, PE, bleeding

Smaller RCTs from Asia and South America, including those by Zhou, Hongnaparak, Colleoni, Jiang, Zou, and Lotke, consistently reported no statistically significant differences between ASA and rivaroxaban, warfarin, or sequential LMWH regimens in preventing DVT, PE, or major bleeding [4-9]. These trials, although limited by sample size, reinforce the general observation that ASA achieves comparable efficacy when dosed between 81–325 mg daily or twice daily for 2–6 weeks.

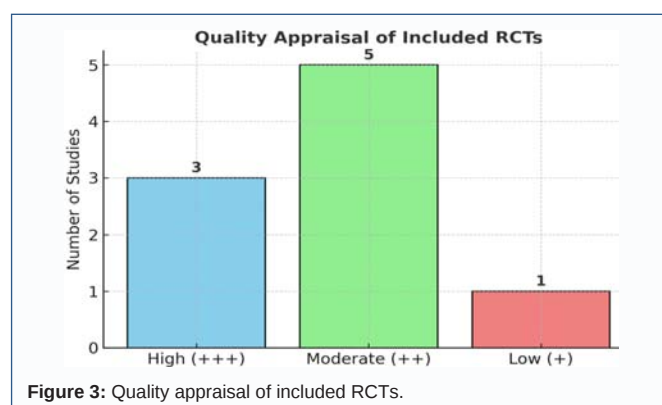
In the trauma population, the large pragmatic PREVENT CLOT trial evaluated 12,211 patients with operatively treated fractures or pelvic/acetabular trauma. It demonstrated that ASA 81 mg twice daily was noninferior to LMWH for the primary endpoint of 90-day mortality. The rates of pulmonary embolism and major bleeding were similar, although ASA was associated with a modest increase in distal DVT events [3].

Taken together, the RCT evidence indicates that ASA is most reliable when used as extended prophylaxis following a short course of a DOAC or LMWH in arthroplasty, and as a pragmatic, noninferior option to LMWH in trauma surgery. However, when initiated immediately after arthroplasty as the sole agent, anticoagulants appear more effective in reducing symptomatic VTE.

Nine RCTs and four guidelines were included

Key findings by trial:

- EPCAT II (Anderson 2018): In 3,424 THA/TKA patients, rivaroxaban 5 days then ASA 81 mg daily was noninferior to extended rivaroxaban for VTE (0.64% vs 0.70%) [Anderson 2018] [1].
- CRISTAL (Sidhu 2022): In 9,711 patients, ASA 100 mg daily started from day 0 led to higher VTE (3.5% vs 1.8%) compared to enoxaparin [Sidhu 2022] [21]. - PREVENT CLOT (O'Toole 2023): In 12,211 fracture patients, ASA 81 mg BID was noninferior to LMWH for 90-day mortality; distal DVT was slightly higher with ASA [O'Toole 2023] [2].
- Zhou 2023 [Zhou 2023]: In 120 TKA patients, ASA 100 mg OD vs rivaroxaban showed no significant differences [4].
- Hongnaparak 2022 [Hongnaparak 2022]: In 40 TKA patients, ASA 300 mg OD vs rivaroxaban showed comparable outcomes [5].
- Colleoni 2018 [Colleoni 2018]: In 27 TKA patients, ASA 150 mg BID vs rivaroxaban showed no difference [6].

**Figure 3:** Quality appraisal of included RCTs.

- Jiang 2014 [Jiang 2014]: In 120 TKA patients, ASA 100 mg OD + mechanical vs LMWH→rivaroxaban showed similar outcomes [7].
- Zou 2014 [Zou 2014]: In 212 TKA patients, ASA 100 mg OD vs rivaroxaban showed no difference [8].
- Lotke 1996 [Lotke 1996]: In 192 THA/TKA patients, ASA 325 mg BID vs warfarin showed similar efficacy [9].

Guidelines

- ASH 2019: Suggest ASA or anticoagulants for THA/TKA (conditional, low certainty [10]).
- NICE 2018/2022: ASA permitted after TKR or following LMWH after THR [11].
- AAOS 2022 [AAOS 2022]: Recommends ASA 81–325 mg BID for 4–6 weeks in typical-risk patients [12].
- European 2024 [European 2024]: Emphasizes individualized prophylaxis; ASA allowed in selected cases [13].

Discussion

The present review synthesizes evidence from nine randomized controlled trials and four international guidelines to delineate the role of aspirin (ASA) in venous thromboembolism (VTE) prophylaxis following orthopedic surgery. Overall, the accumulated data confirm that ASA is a viable prophylactic option; however, its effectiveness and appropriateness depend strongly on patient risk profile, surgical context, and the timing of initiation.

Comparison with anticoagulants in arthroplasty

The evidence is most robust in total hip and knee arthroplasty.

The EPCAT II trial demonstrated that switching to ASA after a brief course of rivaroxaban yielded outcomes indistinguishable from extended rivaroxaban, establishing ASA as an effective continuation strategy [1]. By contrast, CRISTAL highlighted a clear inferiority of ASA when used as sole prophylaxis from the immediate postoperative period, with nearly double the rate of symptomatic VTE compared to enoxaparin, despite similar bleeding risks [2]. These findings underscore a key clinical nuance: ASA is reliable when used as extended prophylaxis, but anticoagulants remain indispensable during the early high-risk window after surgery (see Table 1. for trial details).

Evidence in trauma populations

The PREVENT CLOT trial provided compelling evidence for trauma patients, showing ASA to be noninferior to low-molecular-weight heparin (LMWH) with respect to all-cause mortality in over 12,000 patients [3]. Importantly, bleeding and pulmonary embolism rates were similar, but a modest increase in distal DVT was observed with ASA. This trial establishes ASA as a pragmatic and scalable strategy, particularly in healthcare systems where the cost, logistics, and adherence challenges of LMWH are prohibitive (summarized in Table 1.).

Smaller RCTs and heterogeneity

Smaller trials conducted in Asia and South America (Zhou, Hongnarak, Colleoni, Jiang, Zou, Lotke) consistently demonstrated noninferiority of ASA compared to rivaroxaban, warfarin, or sequential LMWH regimens [4–9]. While individually underpowered and methodologically heterogeneous, their convergence strengthens the overall signal of comparable efficacy. Importantly, these trials applied diverse ASA doses (81–325 mg, once or twice daily), prophylaxis durations (2–6 weeks), and adjunctive measures (mechanical prophylaxis in some), reflecting real-world variability and enhancing external validity. These findings are reflected in Table 1 and the overall methodological quality is illustrated in Figure 3.

Safety considerations

Across all included trials, ASA did not increase major bleeding, wound complications, or mortality compared with anticoagulants. Observational studies have further suggested a lower bleeding risk with ASA compared to DOACs [14]. This favorable safety profile is critical in surgical patients where wound healing and reoperation risk are paramount (see Figure 1 for evidence hierarchy).

Guideline interpretation

Guidelines remain heterogeneous in their endorsement of ASA. The ASH 2019 guideline issues only a conditional recommendation, citing very low certainty of evidence [10]. In contrast, NICE (2018/2022) explicitly permits ASA monotherapy after total knee replacement and sequential use after LMWH in total hip replacement [11]. The AAOS perioperative toolkit recommends ASA (81–325 mg twice daily for 4–6 weeks) for “typical-risk” patients [12], while the 2024 European guidelines emphasize individualized prophylaxis, listing ASA as an option within tailored regimens [13]. These discrepancies reflect varying prioritization of efficacy, safety, patient convenience, and cost across guideline panels. The inclusion pathway of these guidelines and trials is illustrated in the PRISMA flow diagram (Figure 2).

Strengths and limitations of the evidence

The strengths of the evidence base include several large, pragmatic

RCTs (EPCAT II, CRISTAL, PREVENT CLOT), inclusion of diverse geographic settings, and consistency of findings across multiple smaller trials. Limitations include heterogeneity in comparator agents and regimens, limited blinding in some RCTs, small sample sizes in early studies, and variability in outcome definitions (routine ultrasound vs symptomatic events). Furthermore, most trials excluded very high-risk groups (e.g., prior VTE, active cancer, morbid obesity), limiting generalizability.

Implications for clinical practice

The synthesis suggests that ASA is best employed in risk-stratified protocols:

- As extended prophylaxis following an initial short course of anticoagulation in arthroplasty.
- As a pragmatic alternative to LMWH in fracture patients, particularly when resource constraints or adherence challenges exist.
- Avoided as sole agent from day 0 in arthroplasty, where anticoagulants are superior for symptomatic VTE prevention.

Future directions

Further research should refine patient selection criteria, clarify optimal dosing (81 vs 325 mg; once vs twice daily), and determine ideal duration of prophylaxis across surgical subgroups. Pragmatic cost-effectiveness studies comparing ASA and DOACs in different health systems are warranted. Moreover, trials including higher-risk populations are needed to establish whether ASA can safely substitute anticoagulants in those settings. Taken together, the overall synthesis of trial data, guidelines, and evidence grading (Table 1, Figures 1–3) provides a comprehensive framework for contextualizing the role of ASA in modern VTE prophylaxis.

Conclusions

This review of nine randomized controlled trials and four international guidelines highlights the nuanced role of aspirin (ASA) in venous thromboembolism (VTE) prophylaxis following orthopedic surgery. The evidence consistently shows that ASA can be considered an effective and pragmatic alternative to anticoagulants, but its utility depends heavily on clinical context and timing of administration.

In arthroplasty, the large EPCAT II trial demonstrated that ASA is highly effective when introduced after a short lead-in with a direct oral anticoagulant (DOAC), producing noninferior outcomes compared to extended rivaroxaban [1]. Conversely, the CRISTAL trial revealed that when ASA is used as the sole prophylactic agent from the immediate postoperative period, it is associated with higher rates of symptomatic VTE compared to enoxaparin, despite comparable bleeding outcomes [2]. This suggests that while ASA is suitable as extended prophylaxis, anticoagulants remain superior during the highest-risk early postoperative phase.

The PREVENT CLOT trial further expands the role of ASA by showing noninferiority to LMWH in over 12,000 patients with operatively treated fractures [3]. With similar pulmonary embolism and bleeding rates, ASA provided a mortality benefit equivalent to LMWH, though distal DVTs were slightly more frequent. These findings support ASA as a practical, safe, and cost-effective strategy in trauma surgery, especially in settings where adherence, cost, or injection burden limit the use of LMWH.

Smaller RCTs from China, Brazil, Thailand, and the USA consistently reinforce the overall comparability of ASA with

rivaroxaban, warfarin, or sequential LMWH regimens [4–9]. Although individually underpowered, their convergence lends credence to the robustness of the findings. Importantly, these studies spanned different geographic regions and health systems, enhancing generalizability.

Observational data such as Simon et al. (2023) further suggest that ASA may carry a lower bleeding risk than DOACs [14]. Meta-analyses including Matharu (2020) and Zheng (2023) confirm that ASA provides similar efficacy with potentially improved safety compared to oral anticoagulants [16, 23].

Guidelines reflect this heterogeneous evidence. The ASH 2019 guideline provides only conditional recommendations for ASA use [10], while NICE explicitly permits ASA as monotherapy after total knee replacement or sequentially after LMWH in total hip replacement [11]. The AAOS toolkit endorses ASA for typical-risk arthroplasty patients [12], and the 2024 European update emphasizes individualized prophylaxis, listing ASA as an option in selected populations [13]. These differences illustrate how guideline committees weigh efficacy, safety, convenience, and cost differently.

Overall, the evidence indicates that ASA is most appropriately used as extended prophylaxis in arthroplasty following a short course of anticoagulation, and as a noninferior substitute for LMWH in patients undergoing surgery for trauma. Its low cost, ease of administration, and acceptable safety profile make it particularly attractive in resource-limited or outpatient settings. However, for immediate prophylaxis from day 0 after arthroplasty, anticoagulants such as LMWH or DOACs remain the superior choice for reducing symptomatic VTE.

Future research should focus on refining risk stratification to better define which patients benefit most from ASA and on optimizing dose and duration strategies.

Declarations

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