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# Aspirin as Thromboprophylaxis in Orthopedic Surgery: A Matter of Perspective

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Venous thromboembolism (VTE) is a frequently occurring complication after elective total hip arthroplasty (THA) or total knee arthroplasty (TKA), for which thromboprophylaxis is unanimously recommended in the clinical guidelines. However, there is inconsistency in the choice of drug to use for thromboprophylaxis. Over the last decade, orthopedic surgeons were more and more in favor of prescribing aspirin as primary thromboprophylaxis.[1]

The use of aspirin in patients undergoing TKA or THA was studied by the randomized Extended Venous Thromboembolism Prophylaxis Comparing Rivaroxaban to Aspirin Following Total Hip and Knee Arthroplasty II (EPCAT II) trial in 2018, where all patients (n = 3424) received once-daily oral rivaroxaban (10 mg) until postoperative day 5 and then were randomly assigned to continue rivaroxaban or switch to aspirin (81 mg daily) for an additional 9 days after TKA or for 30 days after THA.[2] VTE occurred in 0.64% in the aspirin group and 0.70% in the rivaroxaban group, meeting the criteria for noninferiority, with no differences in bleeding complications. However, it should be emphasized that in this trial, the use of aspirin was studied as extended prophylaxis as all patients received rivaroxaban in the first 5 days. The subsequent 2019 American Society of Hematology (ASH) guidelines suggest aspirin or anticoagulants for patients undergoing total THA or TKA, a weak recommendation based on very low certainty.[3] A systematic review from 2021 on this topic identified a lack of high-quality randomized controlled trials to support the use of aspirin as VTE prophylaxis in these patients.[4]

The CRISTAL trial (2022) was a cluster-randomized, crossover, trial across 31 hospitals in Australia.[5] Hospitals were randomized to administer aspirin (100 mg/d) or enoxaparin (40 mg/d) for 35 days after THA and for 14 days after TKA and crossover occurred after the patient enrollment target had been met for the first group. The trial was prematurely stopped after inclusion of 9711 patients of the prespecified 15,562. The symptomatic VTE rate in the aspirin group was 3.5% versus 1.8% in the enoxaparin group (estimated difference, 1.97% [95% CI, 0.54%-3.41%]). This failed to meet the criterion for noninferiority for aspirin and showed superiority for enoxaparin ($P$ = 0.007). In a prespecified secondary analysis of the CRISTAL trial, the 90-days mortality was compared.[6] Mortality occurred as often in the aspirin group as in the enoxaparin group: 1.7% versus 1.5%, respectively, indicating no benefit from one over the other.

Earlier this year, the PREVENTion of Clot in Orthopaedic Trauma (PREVENT CLOT) trial from the Major Extremity Trauma Research Consortium published their results of the randomized trial in 12,211 patients who had a fracture of an extremity that had been treated operatively or who had any pelvic or acetabular fracture.[7] Patients were randomly assigned to aspirin (81 mg twice daily) or enoxaparin (30 mg twice daily) while they were in the hospital. The primary outcome was death from any cause at 90 days; death occurred in 0.78% in the aspirin group and in 0.73% in the enoxaparin group, indicating noninferiority for aspirin (which was 0.75% points). From the findings of this trial, it was suggested by others to reconsider current guidelines for the prevention of VTE in hospitalized patients, including the option to use aspirin in patients with extremity fractures, especially in those with ischemic heart disease and/or a history of coronary revascularization who are already on treatment with single or dual antiplatelet therapy at the time of traumatic injury.[8]

Whether the use of mortality as primary end point is the most sensitive marker for antithrombotic efficacy should be questioned. None of the major thromboprophylaxis trials showed a difference in mortality rates, both for extended-duration and standard-duration antithrombotic prophylaxis.[3] In a network meta-analysis on antithrombotic therapy for secondary prevention of unprovoked VTE, the all-cause death rates were not different between aspirin versus placebo, aspirin versus warfarin, or warfarin versus placebo.[9] Yet, guidelines unanimously recommend antithrombotic therapy in VTE as they all show significant lower risk of recurrent VTE as compared with placebo.

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*HemaSphere (2023) 7:8(e933). http://dx.doi.org/10.1097/HS9.0000000000000933.*

The PREVENT CLOT trial also documented the occurrence of VTE. Deep venous thrombosis (DVT) rates were 2.5% for aspirin versus 1.5% for enoxaparin, although this difference was not statistically significant. For distal DVT, there was a statistically significant difference of 0.58% in favor of enoxaparin. For nonfatal pulmonary embolism, rates were 1.49% in both groups. This trial also led to discussions on generalizability, as 23% of patients were not at high risk for VTE and would therefore not receive thromboprophylaxis at all in general practice according to the Caprini score.[10]

An important consideration to use thromboprophylaxis is safety, that is, bleeding. In the CRISTAL trial, major bleeding rates were similarly low in the aspirin and enoxaparin group (0.31% and 0.40%, respectively). This was also the case for the PREVENT CLOT trial (13.7% and 14.7%, respectively). The difference in bleeding rates between the 2 trials is explained by the definition of a bleeding; when using the CRISTAL criteria, these bleedings occurred in <1% in the PREVENT CLOT trial.[11] The notion that aspirin is the safer drug as compared with other antithrombotics was also refuted by a meta-analysis showing equal bleeding rates as compared with full dose factor Xa or IIa inhibition.[12]

In the light of the above, what should we do as clinicians? The evidence for aspirin versus low molecular weight heparin or rivaroxaban in orthopedic surgery is driven by the primary end point that is used. When looking at prevention of VTE, the evidence for aspirin is either poor, equally effective or inferior. There is not a trial that shows superiority of aspirin in this aspect, but one can argue that a cheap widely available drug does not have to show superiority. The EPCAT II trial showed equal effectiveness of aspirin compared with rivaroxaban, but all patients received rivaroxaban in the first week, while it is known that most of the VTEs occur in the first 14 days postoperatively. When looking at mortality as primary end point, aspirin was noninferior to enoxaparin, but as argued above, this particular end point was not reached in many other large trials. When taking major bleeding as end point, aspirin is equally safe (or harmful) as anticoagulant prophylaxis.

In patients undergoing THA or TKA, the 2019 ASH guideline panel judged the balance of effects to probably favor the use of direct factor Xa or IIa inhibitors over low molecular weight heparin (LMWH) based on the moderate certainty in the evidence of effects.[3] To date, there are no high-quality randomized trials that compare primary thromboprophylaxis using aspirin with a direct factor Xa or IIa inhibitor in orthopedic surgery. Therefore, the current primary pharmacological thromboprophylaxis in orthopedic surgery should be a direct factor Xa or IIa inhibitor over LMWH and over aspirin, in patients that qualify for VTE prophylaxis. At best, extended prophylaxis might be switched to aspirin.

## AUTHOR CONTRIBUTIONS

Both authors designed and wrote the article.

## DISCLOSURES

REGS is a Scientific Editor at HemaSphere.

SM has received honoraria from Astra Zeneca, Norgine, Alveron, Bayer, Abbvie, Hemab, Viatris, and Sanofi. All fees are directly paid to the hospital.

## SOURCES OF FUNDING

The authors declare no sources of funding.

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