ASA for postoperative venous thromboembolism prevention in patients with extremity or hip fractures: A critical appraisal of the PREVENT CLOT trial

The PREVENT CLOT trial demonstrated that ASA is noninferior to low-molecular-weight heparin in reducing all-cause mortality for extremity fractures. However, caution is necessary due to the limited representation of the patient population and the increased risk of symptomatic thrombotic events with ASA, underscoring the need for personalized thromboprophylaxis based on patient risk factors and preferences.

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ABSTRACT: The open-label PREVENT CLOT trial compared ASA with low-molecular-weight heparin (LMWH) for thromboprophylaxis in extremity fractures. ASA was noninferior to LMWH in reducing all-cause mortality but was associated with more frequent symptomatic thrombotic events. The study findings should be cautiously interpreted due to the clinical relevance of the outcomes and the restricted population studied. The PREVENT CLOT trial consisted primarily of healthy young patients with nonmajor trauma. These patients have inherently lower risk of venous thromboembolism than other patient cohorts of interest, such as frail, elderly, and polytrauma patients, limiting the generalizability of the results. Further, a more fulsome analysis of another higher-risk group, such as patients with proximal lower limb trauma, was lacking. No significant difference in bleeding was found between the ASA and LMWH arms, supporting LMWH use in patients with higher risk of thromboembolism. Ultimately, thromboprophylaxis choice for extremity fractures should be individualized based on patient risk factors and preferences.

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Background

The baseline risk of symptomatic venous thromboembolism (VTE) in the first 35 days after major orthopaedic surgery has been estimated at 4.3%.[1] This burden of VTE, along with a much higher incidence of asymptomatic cases and potential complications, is the basis for the numerous clinical trials that have investigated pharmaceutical options for thromboprophylaxis in this patient population, including antiplatelet agents such as ASA and anticoagulants such as vitamin K antagonists, direct-acting anticoagulants, and low-molecular-weight heparin (LMWH). With these interventions, rates of VTE are reduced to 0.4% to 1.8% in patients with lower extremity surgeries; fatal VTE is very uncommon.[1,2] Therefore, thromboprophylaxis after major orthopaedic procedures that are associated with a higher risk of VTE is recommended as the standard of care by evidence-based clinical practice guidelines.

Although the total body of evidence supports a greater reduction of VTE with anticoagulants than with ASA, it is common practice for patients with orthopaedic fractures undergoing arthroplasties or fixations (e.g., nail insertions) to receive ASA for postoperative VTE prophylaxis, likely because of its lower cost and ease of administration compared with injections.[3-6] Enthusiasm for ASA use has been further amplified by favorable results in recent large trials.[7,8] In the EPCAT II trial, a multicentre double-blinded randomized controlled trial conducted in Canada,

extended prophylaxis with low-dose ASA was noninferior to low-dose rivaroxaban in patients undergoing elective total hip or knee arthroplasties; both treatment arms had similar rates of symptomatic deep vein thrombosis, pulmonary embolism, and bleeding events.[7] In the PREVENT CLOT trial, a large open-label randomized controlled trial at 21 trauma centres in Canada and the United States, ASA was noninferior to LMWH (enoxaparin) in preventing postoperative all-cause mortality in patients with upper or lower extremity fractures.[8] While both trials have the potential to significantly influence clinical practice and guidelines, careful and selective application of the study findings to patients undergoing major orthopaedic surgery is warranted given the study designs and patient populations studied.[9] Here, we outline our concerns about extrapolating the findings of the PREVENT CLOT trial and applying them to unselected patients with orthopaedic fractures, particularly those who are considered at higher risk for VTE.

Study summary

The PREVENT CLOT trial included 12 211 adult patients with limb fractures surgically treated in trauma centres across North America, including those with pelvic or acetabular fractures who did not undergo surgery. Patients were randomized to receive ASA 81 mg orally twice daily or LMWH (enoxaparin) 30 mg twice daily by subcutaneous injection, with dose adjustment for weight and kidney function consistent with standards of care. During the 90-day follow-up period, the primary outcome of all-cause mortality occurred in 0.78% of the ASA arm and 0.73% of the LMWH arm. The authors concluded that ASA was noninferior to LMWH in preventing all-cause mortality when given as thromboprophylaxis for extremity fractures.

Patient inclusion

Patients enrolled in the PREVENT CLOT trial were young (mean age: 44.6 ± 17.8 years), and most of them sustained nonmajor trauma (85.6% had an Injury Severity Score of less than 15 out of 75). Cancer (2.5%), diabetes (8.3%), and a previous history of VTE (0.7%) were reported as comorbidities; the orthopaedic trauma event was the only known risk factor for thrombosis in 27.3% of patients. These characteristics suggest that patients in the PREVENT CLOT trial had a decreased baseline risk of thrombosis and were less likely to require (and therefore benefit from) pharmacologic thromboprophylaxis. In comparison, previous studies in patients with hip fracture surgeries have typically been composed of patients older than 70 years of age, with up to 63% of patients having a history of cardiovascular disease.[10-16] Patients enrolled in the PREVENT CLOT trial also had lower injury severity compared with cohorts in other trauma studies.[17,18] Given that advanced age, a history of cardiovascular disease, and higher injury severity are well-established risk factors for VTE, a large number of patients in the PREVENT CLOT trial likely had a lower risk of VTE than the typical trauma cohort with hip fracture or major injuries.[19]

Thromboprophylaxis after major orthopaedic procedures that are associated with a higher risk of VTE is recommended as the standard of care by evidence-based clinical practice guidelines.

The PREVENT CLOT trial also included only patients with upper extremity fractures, which made up 12% of patients in each of the treatment arms. As thromboprophylaxis is not the standard of care for these patients, we question the rationale for including them. The inclusion of such a low-risk group may also reduce the ability to detect a difference in outcomes between ASA and LMWH.[20]

Outcomes

The investigators of the PREVENT CLOT trial selected all-cause mortality as the primary outcome. While mortality rate is a significant outcome and a robust hard endpoint, it is neither a sensitive outcome for assessing the efficacy and safety of pharmacologic thromboprophylaxis nor a typical primary outcome in trauma-related thromboprophylaxis studies.[3,21,22] Furthermore, given the low-risk patient population, it is not surprising that 90-day mortality was low and was similar between the ASA and LMWH arms.

The secondary efficacy outcomes were more informative: cause-specific mortality, nonfatal pulmonary embolism, and deep vein thrombosis. Bleeding, wound complications, and surgical site infection were secondary safety outcomes. These outcomes are essential for assessing the efficacy and safety of thromboprophylaxis and are important determinants of quality of life and cost-effectiveness.[23] Consistent with previous orthopaedic trials with arthroplasties and lower limb fractures, a significantly lower incidence of symptomatic deep vein thrombosis was observed in the LMWH arm (1.71%) compared with the ASA arm (2.51%) in the PREVENT CLOT trial. Around 50% of these were proximal, which is a significant risk factor for pulmonary embolism.[24] Notably, the decreased rate of deep vein thrombosis in the LMWH arm was not accompanied by a statistically significant increased incidence of bleeding. The absence of a trade-off from a safety perspective adds reassurance of the value of LMWH as a safe choice of thromboprophylaxis compared with ASA in patients with a higher risk for VTE.

Additional concerns

Another factor that limits our confidence in generalizing the trial results is the lack of detail about the collective group of lower extremity fractures. Although the number of patients in this group is well balanced between the two treatment arms, the distribution of fractures was not reported. Considering that the risk of VTE after a

lower extremity fracture is higher with more proximal locations than with more distal locations (e.g., hip versus ankle), an imbalance in the distribution of these fracture locations between treatment arms may impact the findings.[25,26] Furthermore, it would be highly informative to know the proportion of fractures at different locations, because the recommended indication and duration of postoperative VTE prophylaxis differ depending on the location and type. A more detailed breakdown of outcomes according to different sites of fracture (e.g., upper extremity vs pelvis, proximal femur vs distal lower limb) would also be welcome and hypothesis generating.

The types of procedures and surgeries performed were also not available in the PREVENT CLOT publication. This is useful information for interpreting the results, because the type of surgery can have a significant influence on VTE risk, with arthroplasties being associated with lower risk compared with fracture surgeries such as nail insertions and cephalomedullary nailing.[27]

Finally, fewer patients were discharged on enoxaparin (88.8%) than ASA (93.6%). Both arms were prescribed thromboprophylaxis for a median of 21 days. However, the authors did not elaborate on compliance to these regimens at home. The uncertainty around medication adherence makes it challenging to determine what effect this had on the reported outcomes.

Other published commentaries

Our appraisal of the PREVENT CLOT trial aligns with other critical reviews, editorials, and letters to the editor.[28-30] Importantly, the underrepresentation of a higher-risk population limits the generalizability of the PREVENT CLOT trial to those patients at higher risk of VTE, such as elderly patients and those with hip fractures.

Conclusions

The PREVENT CLOT trial provided evidence that in patients with lower risk of VTE after extremity fractures, there appears to be little difference between twice-daily regimens of ASA or LMWH for primary thromboprophylaxis. However, given the patient population and the primary outcome that were studied, we caution against generalizing and extrapolating the results to higher-risk populations who were underrepresented, such as elderly patients, patients with moderate or severe injuries, and those with comorbidities that increase risk for VTE (e.g., cardiovascular disease, cancer, history of VTE, obesity). It remains paramount for clinicians to assess VTE risk in individual patients with orthopaedic fractures to determine the appropriateness of ASA versus LMWH for pharmacological thromboprophylaxis. ■

Patients in the PREVENT CLOT trial had a decreased baseline risk of thrombosis and were less likely to require (and therefore benefit from) pharmacologic thromboprophylaxis.

Competing interests

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