Aspirin or low-molecular weight heparin for thromboprophylaxis after a fracture? That is the question

Giuseppe Camporese,[1] Paolo Prandoni,[2] Walter Ageno[3]

[1]General Medicine Unit – Thrombotic and Hemorrhagic Disorders Unit, Department of Internal Medicine, Padua University Hospital; [2]Arianna Anticoagulazione Foundation, Bologna; [3]Department of Medicine and Surgery, University of Insubria, Varese, Italy

The recent publication of the PREVENT CLOT study in the New England Journal of Medicine has renewed the interest about the use of aspirin for prevention of venous thromboembolism (VTE) in orthopedic surgery that, at least in Europe, was virtually abandoned.[1] The PREVENT CLOT is an open-label, randomized controlled trial designed to test the role of aspirin, administered at the dose of 81 mg twice-daily, compared to enoxaparin, administered at the dose of 30 mg twice-daily for the prevention of VTE in more than 12,000 patients candidate to surgery for fracture of the lower limbs and/or the upper limbs, and for any pelvic or acetabular fracture. The trial presented pragmatic characteristics, respectful of any procedure in use in each of the 21 participating trauma centers in the USA and Canada. The administration of aspirin or enoxaparin was mandated by the protocol only during the hospital stay. The mean hospital duration was 5.3 days, and the mean number of in-patients doses of trial drugs was 8.6 in the aspirin group and 9.1 in the enoxaparin group. The decision to extend treatment after discharge was left to the discretion of the investigators according to existing local protocols and the median duration of thromboprophylaxis after hospital discharge was 21 days in both groups.

The overall 3-month mortality rate for any cause (indicated as the primary efficacy outcome) resulted similarly low in the two groups, either in the intention to treat analysis (0.78% in aspirin group, 0.73% in enoxaparin group; difference 0.05-96.2% confidence interval –0.27 to 0.38; P<0.001 for non-inferiority) or in the per-protocol analysis (0.75% in aspirin group, 0.72% in enoxaparin group; difference 0.03-96.2% confidence interval –0.31 to 0.38; P<0.001 for non-inferiority). Likewise, the mortality rate related to fatal and non-fatal pulmonary embolism, major bleedings, surgical wound complications, or infections were low and similar in the two arms. Even if the incidence of post-operative symptomatic deep-vein thrombosis (DVT) resulted higher in aspirin group, and the difference was statistically significant for the incidence of distal DVT, the authors concluded that for opportunity and cost reasons aspirin should be preferred compared to enoxaparin for VTE prevention in these patients.

The role of aspirin for the prevention of VTE in major orthopedic surgery (total hip and total knee replacement) has long been controversial. Historical studies using systematic venography of the lower limbs after 1-2 weeks from surgery found aspirin significantly less effective than anticoagulant prophylaxis for post-operative DVT prevention.[2] However, subsequent studies focusing on clinical endpoints reported favorable results, and the use of aspirin increased in this setting in some countries.[3]

The American College of Chest Physicians guidelines recognized aspirin as a beneficial antithrombotic treatment (if compared to the absence of any kind of thromboprophylaxis) and aspirin was included in the list of potential strategies, but recommended the low-molecular-weight heparin as the first line treatment for VTE prevention in patients undergoing major orthopedic surgery.[4] The more recent guidelines of the American Society of Hematology also included aspirin in the list of antithrombotic drugs for patients undergoing major elective surgery, but only suggested low-molecular-weight heparin for patients undergoing fracture repair.[5]

Two randomized controlled studies (EPCAT I and II) compared the role of aspirin for VTE prevention in patients undergoing major orthopedic surgery after an initial 10-day course of enoxaparin or 5-day course of rivaroxaban, against extended

Correspondence: Walter Ageno, Department of Medicine and Surgery, University of Insubria, Varese, Italy.
E-mail: walter.ageno@uninsubria.it

Citation: Camporese G, Prandoni P, Ageno W. Aspirin or low-molecular weight heparin for thromboprophylaxis after a fracture? That is the question. Bleeding, Thrombosis, and Vascular Biology 2023;2:82.

Key words: aspirin; low-molecular weight heparin; fracture; surgery; venous thromboembolism.

Contributions: the authors contributed equally.

Conflict of interest: the authors declare no potential conflict of interest.

Funding: none.

Received: 18 April 2023.
Accepted: 20 April 2023.

Licensee PAGEPress, Italy
Bleeding, Thrombosis and Vascular Biology 2023; 2:82
doi:10.4081/btvb.2023.82

enoxaparin or rivaroxaban, respectively.[6,7] Both studies only reported symptomatic VTE events, which occurred in similarly low rates between treatment groups.

The findings of the PREVENT CLOT and of the EPCAT I and II trials share similar conclusions and seem to indicate aspirin as an effective and safe thromboprophylactic agent in the setting of orthopedic surgery. In this sense, should we reconsider our guidance, in light of the practical use and the low cost of aspirin?

The assumption that aspirin is a valid alternative to anticoagulant drugs, either low-molecular-weight heparin or direct oral anticoagulants, originates from the low incidence of symptomatic, major VTE events after major orthopedic surgery and the absence of statistically significant differences between treatment arms. However, aspirin is clearly less effective than any anticoagulant (including low-molecular-weight heparin, fondaparinux, direct anti-Xa oral anticoagulants) when asymptomatic events are included. These events were usually assessed by venography of the lower limbs, and mainly included distal DVT. Are we sure that this finding is so irrelevant? In most cases, symptomatic DVT of the lower limbs start in the distal veins, where it can also remain asymptomatic for a long time. In other words, we can state that there is no symptomatic proximal DVT without a preceding stage of asymptomatic distal thrombosis. A systematic review of all the studies on post-operative VTE prevention after major orthopedic surgery published 15 years ago reported a consistent and reproducible relationship between the rate of asymptomatic DVT in the studies using venography and the rate of symptomatic DVT in those not using venography.[8] As a result, the only way to properly protect from symptomatic VTE is to systematically prevent distal DVT in its asymptomatic phase.

The results of the PREVENT CLOT trial confirm the superiority of enoxaparin versus aspirin for post-operative DVT prevention also in fracture surgery, extending the evidence of this benefit to some minor orthopedic surgical procedures, as well as to pelvic or acetabular fractures. Not surprisingly, due to the large cohort of patients included in the North American study, this difference also concerned clinically overt DVT and yielded the statistical significance when the analysis was related to distal DVT. Therefore, should we deliberately ignore this finding and rely only on the mortality rate, which was similarly low in both study groups? First of all, the early diagnosis and the subsequent early treatment of these DVT events certainly concurred to reduce the progression rate to the proximal vein system or to the pulmonary arteries with unpredictable outcomes. Second, recent studies have extensively reconsidered the clinical relevance of distal DVT, showing a risk of extension to the proximal veins and/or of recurrence unexpectedly high when treated for less than 3 months and a risk of long-term sequelae (post-thrombotic syndrome) only slightly lower than that expected for proximal DVT.[9,10]

Against the use of aspirin in major orthopedic surgery takes sides the recent CRISTAL study, that investigated more than 9000 patients undergoing total hip or knee replacement in 31 Australian hospitals. Patients were randomly assigned to receive aspirin 100 mg once-daily or enoxaparin 40 mg once-daily for 35 days after hip replacement and for 14 days after knee replacement. The 3-month rate of symptomatic VTE in the aspirin group was 3.4% *versus* 1.8% in enoxaparin group (difference 1.97%; 95%CI: 0.54-3.41; P=0.007).[11]

A recent editorial on the same issue, even if recognizing the role of aspirin in preventing VTE in patients with extremities fracture, at the same time highlighted some characteristics of the patients investigated in the PREVENT CLOT study, which placed them at low risk of developing thrombosis (*e.g.* relatively young patients with a mean age of 45 years, absence of history of previous VTE event, *etc*), wishing for further studies supporting an effective role of aspirin in VTE prevention in those patients.[12]

In summary, we believe that evidence is not sufficiently strong to justify the use of aspirin in patients undergoing orthopedic surgery, in the light of the superior efficacy of low molecular weight heparin for the prevention of VTE, with similarly low bleeding risk. The only advantage of aspirin is represented by the lower costs, is this enough? Based on available evidence aspirin should not be prescribed immediately after major orthopedic surgery, and its use in any case should be considered after an initial course of low molecular weight heparin or rivaroxaban. Aspirin should likely not even be considered in other surgical settings after the recent publication of the results of the PRONOMOS trial, that showed the superiority of rivaroxaban over enoxaparin for the prevention of symptomatic and asymptomatic VTE events in minor orthopedic surgery of the lower limbs.[13] Also in this setting, aspirin should not be considered as an alternative thromboprophylactic agent.

We still believe that the common European practice to use parenteral (low molecular weight heparin, fondaparinux) or oral anticoagulants (rivaroxaban, apixaban) is widely justified and well supported by current evidence.

References

1. O'Toole RV, Stein DM, O'Hara NN, et al. Aspirin or low-molecular-weight heparin for thromboprophylaxis after a fracture. N Engl J Med 2023;388:203-13.
2. Mohr DN, Silverstein MD, Murtaugh PA, Harrison JM. Prophylactic agents for venous thrombosis in elective hip surgery. Meta-analysis of studies using venographic assessment. Arch Intern Med 1993;153:2221-8.
3. No authors listed. Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) trial. Lancet 2000;355:1295-302.
4. Falck-Ytter Y, Francis CW, Johanson NA, et al. 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:e278-325S.
5. Anderson DR, Morgano GP, Bennett C, et al. American Society of Hematology 2019 guidelines for management of venous thromboembolism: prevention of venous thromboembolism in surgical hospitalized patients. Blood Adv 2019;3:3898-944.
6. Anderson DR, Dunbar MJ, Bohm ER, et al. Aspirin versus low-molecular-weight heparin for extended venous thromboembolism prophylaxis after total hip arthroplasty: a randomized trial. Ann Intern Med 2013;158:800-6.
7. Anderson DR, Dunbar M, Murnaghan J, et al. Aspirin or rivaroxaban for VTE prophylaxis after hip or knee arthroplasty. N Engl J Med 2018;378:699-70.
8. Quinlan DJ, Eikelboom JW, Dahl OE, et al. Association between asymptomatic deep-vein thrombosis detected by venography and symptomatic venous thromboembolism in

patients undergoing elective hip or knee surgery. J Thromb Haemost 2007;5:1438-43.
9. Ageno W, Bertù L, Bucherini E, et al. Rivaroxaban treatment for six weeks versus three months in patients with symptomatic isolated distal deep vein thrombosis: randomised controlled trial. BMJ 2022;379:e072623.
10. Turner BRH, Thapar A, Jasionowska S, et al. Systematic review and meta-analysis of the pooled rate of post-thrombotic syndrome after isolated distal deep venous thrombosis. Eur J Vasc Endovasc Surg 2023;65:291-7.
11. Sidhu VS, Kelly TL, Pratt N, et al. Effect of aspirin vs enoxaparin on symptomatic venous thromboembolism in patients undergoing hip or knee arthroplasty: the CRISTAL randomized trial. JAMA 2022;328:719-27.
12. Vergallo R, Patrono C. Aspirin for venous thromboprophylaxis after fracture: ready for prime time? Eur Heart J 2023;44:1299-300.
13. Samama CM, Laporte S, Rosencher N, et al. Rivaroxaban or enoxaparin in nonmajor orthopedic surgery. N Engl J Med 2020;382:1916-25.