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Bounameaux, Henri; Fontana, Pierre

EDITORIAL

Aspirin for venous thromboembolism prevention and treatment: a renewal?

Henri Bounameaux, Pierre Fontana

Division of Angiology and Hemostasis, University Hospitals of Geneva, Geneva, Switzerland

Over the past months, aspirin has suddenly moved from the backstage to the front of the scene of venous thromboembolism. Indeed, two features raised interest of the medical community. First, in 2012, the American College of Chest Physicians (ACCP) evidence-based clinical practice guidelines changed its former strong recommendation (Grade 1A) *against* use of aspirin for preventing venous thromboembolism after major orthopedic surgery[1] for a conditional Grade 1B recommendation *in favor of* its use in this particular indication.[2] Second, *The New England Journal of Medicine* has recently published the results of the Warfarin and Aspirin (WARFASA) study that convincingly demonstrate the efficacy of low-dose aspirin for preventing the long-term recurrence of venous thromboembolism in patients who received a course of 6 to 18 months of oral anticoagulant treatment for the initial event.[3] These features are in line with recent basic science data that emphasize the role of platelets in the pathogenesis of venous thrombosis. Indeed, the histological inspection of venous thrombi shows that cells such as red blood cells and leukocytes are in close vicinity of platelets. Of note, neutrophils stimulated with proinflammatory agents or activated platelets release their nuclear content (including histones) that form web-like structures designated as neutrophil extracellular traps,[4] which in turn promote the generation of thrombin through platelet-dependent mechanisms[5] as well as vein thrombi, at least in a murine model.[6] Taken together, these findings provide a rationale for clinical studies addressing the issue of the prevention of venous thrombosis by platelet function inhibitors, particularly aspirin.

However, both the new ACCP recommendation about thromboprophylaxis in major orthopedic surgery with the suggestion of aspirin as an alternative to anticoagulants, and the superiority of aspirin over placebo for secondary prophylaxis after a first venous thromboembolic event are essentially each based on a single study. In 2000, the Pulmonary Embolism Prevention (PEP) investigators[7] reported a significant risk reduction with aspirin 160 mg daily compared with placebo for symptomatic venous thromboembolism in a very large population undergoing surgery for hip fractures or elective hip arthroplasty. In the WARFASA multicenter, investigator-initiated, double-blind study, Beccatini et al.[3] concluded that aspirin is efficacious and safe for secondary long-term prophylaxis of venous thromboembolism in patients who had experienced a first unprovoked deep vein thrombosis (DVT) or pulmonary embolism.

Let us first consider the issue of aspirin for thromboprophylaxis in major orthopedic surgery. As early as 1994, the Antiplatelet Trialists' Collaboration meta-analysis[8] pooled data from 62 randomized studies totaling over 8000 patients and concluded that aspirin (various dosages) reduced the frequency of both pulmonary embolism (by two-thirds) and DVT (by 40%). However, the methodological quality of many studies included in the meta-analysis was poor, and diagnostic methods were far from optimal, which resulted in mixed opinions on its results. Therefore, the PEP trial was launched in the mid-1990s to test aspirin (160 mg daily for 35 days) vs. placebo in 17,444 patients with hip fracture or elective hip arthroplasty. The study had several methodological strengths, including a central randomization, a double-blind design, an independent blinded committee for adjudicating objectively confirmed endpoints, and a follow-up that was close to 100%. There was a statistically significant 28% but limited relative risk reduction in symptomatic DVT (relative risk [RR], 0.72; 95% confidence interval [CI], 0.53–0.96) with no beneficial effect on nonfatal pulmonary embolism, and no significant effect on overall mortality. The number needed to treat (NNT) to prevent one symptomatic DVT was 238 (P = 0.03). Despite the large sample size, major nonfatal bleeding was not significantly increased in patients given aspirin even

Correspondence to:
Prof. Henri Bounameaux, MD,
Division of Angiology and Hemostasis,
University Hospitals of Geneva,
Rue Michel Servet, 1 CH-1211
Geneva 4, Switzerland,
phone: +41-22-3795033,
fax: +41-22-3795002,
e-mail: henri.bounameaux@unige.ch
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TABLE Randomized controlled studies of long-term secondary prevention of venous thromboembolism recurrence after an initial course of anticoagulant treatment

Study	Number of patients	Investigational regimen arm (event rate, %/y) RRR	Comparator regimen arm (event rate, %/y)	VTE recurrence (RR, 95% CI) *P* NNT	Major bleeding (RR, 95% CI) *P* NNH
Ridker et al.[9] (PREVENT study)	508	warfarin INR 1.5–2 (2.6) 64%	placebo (7.2)	0.36 (0.19–0.67) <0.001 22	2.53 (0.49–13.03) 0.25 200
EINSTEIN Investigators[10]	1196	rivaroxaban (1.3) 82%	placebo (7.1)	0.18 (0.09–0.39) <0.001 17	0.7% (Riva) vs. 0 (placebo) 0.11 143
Beccatini et al.[3]	402	aspirin (6.6) 41%	placebo (11.2)	0.58 (0.36–0.93) 0.02 22	0.3% in both arms 0.97 indefinite
Kearon et al.[11] (ELATE study)	738	warfarin INR 1.5–1.9 (1.9) NA	warfarin INR 2–3 (0.7)	2.8 (1.1–7.0) 0.03 NA	1.2 (0.4–3.0) 0.76 NA

Abbreviations: CI – confidence interval, INR – international normalized ratio, NA – not applicable, NNH – number needed to harm, NNT – number needed to treat, RR – relative risk, RRR – relative risk reduction (compared with placebo), VTE – venous thromboembolism

though there was a trend in this direction (RR, 1.12; 95% CI, 0.94–1.34). Of note, a substantial proportion of the PEP population also received some sort of heparin, which may have offset the effect of aspirin. Altogether, the PEP trial confirmed a statistically significant but small thromboprophylactic effect of aspirin in major orthopedic surgery (mainly hip fracture) compared with placebo. Based on this evidence, the 8th ACCP consensus[1] admitted that aspirin provides some protection against venous thromboembolism, but did not recommend its use alone as prophylaxis primarily because more effective methods are readily available, e.g., low-dose unfractionated heparin and low-molecular-weight heparins (LMWH). This nuanced appreciation was, however, translated into a strong recommendation against aspirin. In turn, the 9th edition of the ACCP consensus concentrated their analysis on the so called patient-important (say symptomatic) outcomes and, therefore, rehabilitated aspirin as one prophylactic agent among others for patients undergoing major orthopedic surgery. However, the panelists state in the text that indirect evidence from trials of LMWH and aspirin against placebo also shows greater relative efficacy of LMWH and, in the end, suggest the use of LMWH in preference to the other options including aspirin. The controversy raised around the contradiction between the 8th and the 9th ACCP consensus recommendations thus seems to be largely artificial.

Let us now consider the issue of aspirin for long-term secondary prophylaxis after an initial 6- to 18-month period of anticoagulant treatment in patients with a first idiopathic DVT and/or pulmonary embolism, as tested in the WARFASA study.[3] In this trial, 205 patients were randomized to receive aspirin 100 mg daily and 197 patients were given placebo. Twenty-eight (6.6% per year) and 43 (11.2% per year) symptomatic venous thromboembolic events were adjudicated in the two groups, respectively, during a median follow-up of 2 years, resulting in a hazard ratio of 0.58 (95% CI, 0.36–0.93) ($P = 0.02$). Only 1 patient in each group experienced a major bleeding episode.

These results need to be viewed in the perspective of other large-scale, randomized controlled studies of long-term secondary prevention of venous thromboembolism recurrence – the Prevention of Recurrent Venous Thromboembolism (PREVENT) study,[9] the EINSTEIN Extension study,[10] and the Extended Low-Intensity Anticoagulation for Thromboembolism (ELATE) study.[11] Both PREVENT and EINSTEIN Extension were placebo-controlled trials while ELATE compared 2 intensities of warfarin therapy (TABLE). In all these studies, the main efficacy outcome was recurrent symptomatic, objectively confirmed DVT or pulmonary embolism. The active regimen in PREVENT and EINSTEIN Extension was warfarin with a target international normalized ratio (INR) of 1.5–2.0 and rivaroxaban (20 mg once daily, p.o), respectively. While the relative risk reduction of venous thromboembolism recurrence was 64% (95% CI, 19%–67%) and 82% (95% CI, 61%–91%), respectively, in these 2 trials, it was only 42% in WARFASA with a large CI (95% CI, 7%–64%). Even though the CIs in the 3 studies largely

overlap, its lower limit in WARFASA is compatible with almost no effect of aspirin. Admittedly, the NNT was very similar in the 3 placebo-controlled trials but for WARFASA this is mainly due to the high rate of events in the placebo group: 11.2% per year, compared with 7.2% and 7.1% in PREVENT and EINSTEIN Extension, respectively. There is no obvious reason for this difference since all trials included selected patients who had already been treated with anticoagulants during a prolonged period, and who were at low risk of bleeding. Cancer was rare in these populations and was an exclusion criterion for WARFASA. Because of the relatively small number of patients in the latter study, the margin of error around these 11.2% is quite high, and the aspirin effect may be overestimated. As a matter of fact, the incidence of recurrent venous thromboembolism in the active groups was 2.6% (PREVENT), 1.3% (EINSTEIN Extension), 1.9% (ELATE, low-intensity INR), and 0.7% (ELATE, standard-intensity INR), as compared with 6.6% in WARFASA. The ongoing placebo-controlled Aspirin to Prevent Recurrent Venous Thromboembolism (ASPIRE) study (ACTRN012 605 000 004 662) with more than 800 patients and the planned prespecified pooled analysis of WARFASA and ASPIRE (ACTRN12 611 000 684 921) should reduce this imprecision and provide the final word about the extent of the aspirin effects in the indication of long-term secondary prevention in patients with first idiopathic venous thromboembolism. As far as the post orthopedic surgery prophylaxis is concerned, the new ACCP recommendations will support to a degree the attitude of many surgeons, especially in the United States, to restrict prophylaxis to aspirin alone or in combination with compression devices[2,12] in patients undergoing major joint arthroplasty. While this policy might apply to selected patients with high bleeding risk, we doubt that it provides sufficient protection against venous thromboembolism and do not use it routinely in our practice. Nowadays, LMWH and, even more, the novel oral anticoagulants have almost eradicated this complication in providing safer care for this kind of surgery. Whether aspirin could be an option for extension of prophylaxis in such cases remains hypothetical. With respect to long-term secondary prevention after venous thrombosis, we feel that aspirin should still wait a while, which should not be a problem for a hundred-year-old drug.

REFERENCES

1 Geerts WH, Bergqvist D, Pineo GF, et al. Prevention of venous thromboembolism: American College of Chest Physicians evidence-based clinical practice guidelines. Chest. 2008; 133 (6 Suppl): 381S-453S.

2 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 (2 Suppl): e278S-e325S.

3 Becattini C, Agnelli G, Schenone A, et al.; WARFASA Investigators. Aspirin for preventing the recurrence of venous thromboembolism. N Engl J Med. 2012; 366: 1959-1967.

4 Brinkmann V, Zychlinsky A. Beneficial suicide: why neutrophils die to make NETs. Nat Rev Microbiol. 2007; 5: 577-582.

5 Semeraro F, Ammollo CT, Morrissey JH, et al. Extracellular histones promote thrombin generation through platelet-dependent mechanisms: involvement of platelet TLR2 and TLR4. Blood. 2011; 118: 1952-1961.

6 Brill A, Fuchs TA, Savchenko AS, et al. Neutrophil extracellular traps promote deep vein thrombosis in mice. J Thromb Haemost. 2012; 10: 136-144.

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

8 Collaborative overview of randomized trials of antiplatelet therapy – III: Reduction in venous thrombosis and pulmonary embolism by antiplatelet prophylaxis among surgical and medical patients. Antiplatelet Trialists' Collaboration. BMJ. 1994; 308: 235-246.

9 Ridker PM, Goldhaber SZ, Danielson E, et al.; PREVENT investigators. Long-term, low-intensity warfarin therapy for the prevention of recurrent venous thromboembolism. N Engl J Med. 2003; 348: 1425-1434.

10 Bauersachs R, Berkowitz SD, Brenner B, et al.; EINSTEIN Investigators. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med. 2010; 363: 2499-2510.

11 Kearon C, Ginsberg JS, Kovacs MJ, et al.; Extended Low-intensity Anticoagulation for Thrombo-Embolism Investigators (ELATE). Comparison of low-intensity warfarin therapy with conventional-intensity warfarin therapy for long-term prevention of recurrent venous thromboembolism. N Engl J Med. 2003; 349: 631-639.

12 Kearon C, O'Donnell M. Graduated compression stockings to prevent venous thromboembolism in hospital: evidence from patients with acute stroke. Pol Arch Med Wewn. 2011; 121: 40-43.