Venous Thromboembolism Prevention: The Evidence for Aspirin?

To the Editor:

I read with interest the study published recently by Eikelboom *et al.*[1] in Anesthesiology. Because venous thromboembolism (VTE) is infrequently discussed in the anesthesia literature and is the leading cause of preventable death in surgical patients, certain aspects of the publication by Eikelboom *et al.*[1] merit additional discussion. I believe someone who does not review the entire article, but simply glances through the "What This Article Tells Us That Is New" section will leave with the erroneous impression that there is no benefit of aspirin in VTE prevention. Histological studies unequivocally confirm that, whereas fibrin is crucial to initiation of the venous thrombus, continued growth and propagation are primarily platelet-driven phenomena.[2,3] Because thrombus growth with or without embolization is required for the demonstration of clinical symptoms, it follows that platelet inhibitors must play a key role. Indeed, Eikelboom *et al.*[1] themselves remark, "Exploratory analyses…suggest that aspirin is more effective in preventing large than preventing small thrombi." Recent pathophysiologic studies on venous thromboembolism also emphasize the importance of platelets, and numerous clinical publications have demonstrated the effectiveness of aspirin after hip and knee arthroplasty, traditionally considered very high-risk procedures with respect to thromboembolic complications. Also distressing is the growing body of evidence demonstrating that increased use of pharmacologic agents has not reduced VTE morbidity or mortality rates but has resulted in increased bleeding, infection, and other serious complications, such as heparin-induced thrombocytopenia. In a recent study, 11% of patients experiencing an anticoagulant-associated adverse drug reaction died within 30 days.[4] Sharrock *et al.*,[5] in a literature review of more than 28,000 patients, found an increase in all-cause mortality using potent anticoagulants compared with aspirin in hip and knee arthroplasties. A surgical site infection after knee or hip arthroplasty is another catastrophic complication, and recent evidence notes an increased risk of infection after pharmacologic VTE prophylaxis with rivaroxaban, one of the newer factor X inhibitors. Because formation of the initial thrombotic nidus formation results from valve cusp hypoxia, which may be minimized to a significant degree by maintenance of pulsatile flow (*e.g.*, with sequential compression devices), anticoagulants should be reserved only for those patients at the very greatest risk. In summary, the anesthesia provider can and should play a more significant role in the prevention of VTE after noncardiac surgery, including maintenance of pulsatile flow and promotion of aspirin as the anticoagulant of choice in all but the highest-risk patients. Blind adherence to American College of Chest Physicians guidelines using the Caprini score, which itself is based solely on intuition and experience, far overestimates the likelihood of a VTE event. Pharmacologic agents for VTE prophylaxis should no longer be the default course of action for the perioperative physician.

Competing Interests

The author declares no competing interests.

Ronald J. Gordon, M.D., Ph.D., University of California San Diego, San Diego, California. rjgordon@ucsd.edu

References

1. Eikelboom JW, Kearon C, Guyatt G, Sessler DI, Yusuf S, Cook D, Douketis J, Patel A, Kurz A, Allard R, Jones PM, Dennis RJ, Painter TW, Bergese SD, Leslie K, Wijeysundera DN, Balasubramanian K, Duceppe E, Miller S, Diedericks J, Devereaux PJ: Perioperative aspirin for prevention of venous thromboembolism: The PeriOperative ISchemia Evaluation-2 Trial and a pooled analysis of the randomized trials. Anesthesiology 2016; 125:1121–9
2. Hume M, Sevitt S, Thomas DP. Venous thrombosis and pulmonary embolism. Cambridge, Harvard University Press, 1970
3. Bovill EG, van der Vliet A: Venous valvular stasis-associated hypoxia and thrombosis: What is the link? Annu Rev Physiol 2011; 73:527–45
4. Piazza G, Nguyen TN, Cios D, Labreche M, Hohlfelder B, Fanikos J, Fiumara K, Goldhaber SZ: Anticoagulation-associated adverse drug events. Am J Med 2011; 124:1136–42
5. Sharrock NE, Gonzalez Della Valle A, Go G, Lyman S, Salvati EA: Potent anticoagulants are associated with a higher all-cause mortality rate after hip and knee arthroplasty. Clin Orthop Relat Res 2008; 466:714–21

(Accepted for publication May 8, 2017.)

In Reply:

Gordon comments on the importance of platelets in the propagation of venous thrombosis and suggests that this may explain our findings,[1] that aspirin is more effective in preventing large *versus* small thrombi. He also expresses concern about the widespread use of anticoagulant prophylaxis because of the risk of bleeding, infection, and other serious complications, such as heparin-induced thrombocytopenia. We agree that critical reevaluation of benefits and risks of pharmacologic prophylaxis and in particular the use of anticoagulant compared with aspirin prophylaxis is warranted. The Comparative Effectiveness of Pulmonary Embolism Prevention after Hip and Knee Replacement trial currently ongoing in the United States is comparing aspirin plus intermittent pneumatic compression, low-intensity warfarin, and rivaroxaban for prevention of venous thromboembolism in 25,000 patients undergoing elective total hip or total knee replacement (clinicaltrials.gov No. NCT02810704). The results of this trial are expected in 2021.

We believe that the concerns raised by Madi-Jebara and Sleilaty are misplaced. Although the primary outcome for the aspirin *versus* placebo comparison in PeriOperative ISchemic Evaluation-2 (POISE-2) was death or nonfatal myocardial infarction at 30 days, venous thromboembolism was a prespecified outcome and was systematically collected and reported. Formal testing found no evidence to contradict the

assumption of proportionality in the Cox regression models. Exploratory subgroup analyses demonstrated similar results irrespective of whether participants received anticoagulant prophylaxis or whether they received anticoagulant prophylaxis in the first 3 days after surgery. Results were consistent across age and diabetes subgroups, and there is no basis for speculating that these subgroups "would have been potentially significant" if the trial had been larger. It is not the 95% CI that informs a subgroup; rather, it is the interaction *P* value. As reported in the article,[1] the interaction *P* values were 0.13 and 0.81 for the age and diabetes subgroups, respectively. These nonsignificant results do not support a subgroup effect.

The low rate of venous thromboembolism in POISE-2 limited power to detect an effect of aspirin, but the point estimate was consistent with the results of earlier trials, and the pooled analysis presented in the article[1] provides readers with what we believe are the best estimates of the efficacy of aspirin for venous thromboembolism prevention in surgical patients. This approach has previously been taken by others[2] and is also the approach that we took in the original publication of POISE.[3] As presented in our article,[1] the best evidence indicates that aspirin compared with placebo reduces the risk of postoperative venous thromboembolism by approximately one third.

Competing Interests

The authors declare no competing interests.

John W. Eikelboom, M.B.B.S., P. J. Devereaux, Ph.D. McMaster University and Population Health Research Institute, Hamilton, Ontario, Canada (J.W.E.). eikelbj@mcmaster.ca

References

1. Eikelboom JW, Kearon C, Guyatt G, Sessler DI, Yusuf S, Cook D, Douketis J, Patel A, Kurz A, Allard R, Jones PM, Dennis RJ, Painter TW, Bergese SD, Leslie K, Wijeysundera DN, Balasubramanian K, Duceppe E, Miller S, Diedericks J, Devereaux PJ: Perioperative aspirin for prevention of venous thromboembolism: The PeriOperative ISchemia Evaluation-2 Trial and a pooled analysis of the randomized trials. Anesthesiology 2016; 125:1121–9
2. Pulmonary Embolism Prevention (PEP) Trial Collaborative Group: Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) trial. Lancet 2000; 355:1295–302
3. Devereaux PJ, Yang H, Yusuf S, Guyatt G, Leslie K, Villar JC, Xavier D, Chrolavicius S, Greenspan L, Pogue J, Pais P, Liu L, Xu S, Málaga G, Avezum A, Chan M, Montori VM, Jacka M, Choi P: Effects of extended-release metoprolol succinate in patients undergoing non-cardiac surgery (POISE trial): A randomized controlled trial. Lancet 2008; 371:1839–47

(Accepted for publication May 8, 2017.)