VTE prevention in major orthopedic surgery

(SUPPLEMENT 3 TO VOLUME 75, APRIL 2008)

EDITOR'S NOTE: *These letters concern an article in a* Cleveland Clinic Journal of Medicine *supplement* (Preventing Venous Thromboembolism Throughout the Continuum of Care*) distributed to only a portion of the* Journal's *regular readership, owing to the terms of the grant supporting the supplement. The supplement is available free to all online at* ***www.ccjm.org/ccjm_pdfs_supplements/vte.asp.***

TO THE EDITOR: I must strongly disagree with Deitelzweig and colleagues' recommendations against the use of aspirin for thromboprophylaxis in elective joint replacement surgery.[1] The references cited[2–5] are outdated. In the last few years, in patients undergoing minimally invasive hip replacement (done either posterolaterally or via an anterior approach with epidural anesthesia), early ambulation and thromboprophylaxis with compression boots and enteric-coated aspirin (or alternative antiplatelet agents in patients allergic to aspirin) has been associated with a lower incidence of deep vein thrombosis (DVT) and postoperative bleeding than either enoxaparin or fondaparinux.[6–9]

Our experience in Los Angeles under the direction of Dr. Lawrence Dorr, past president of the Hip Society, is also instructive: minimally invasive hip replacement performed via a posterior approach with a 2- to 3-day length of stay and with the use of multimodal thromboprophylaxis including aspirin (or an alternate antiplatelet) has resulted in a low incidence of proximal DVT and no deaths from pulmonary embolism.[10] Our experience with total knee replacement is similar but has included a slightly higher rate of DVT in patients older than 75 years of age.[10]

The American Academy of Orthopaedic Surgeons has clearly supported the use of aspirin as an effective modality for DVT prophylaxis.[11] We are patiently awaiting the newest recommendations from the American College of Chest Physicians, which I believe should incorporate aspirin in DVT prophylaxis and thus get medical physicians on the same page as orthopedic surgeons.

ANDREW FISHMANN, MD
The Good Samaritan Hospital
Los Angeles, CA

TO THE EDITOR: I must make several comments regarding the review by Deitelzweig and colleagues.[1]

First, all but one of the article's six authors report having received honoraria, consulting fees, or research funding from companies that market medical products; therefore, their observations are not going to be "clean."

Second, the most worrisome part of the article is that the authors downplay the issue of bleeding. As recently reported by surgeons from the Rothman Institute of Orthopedics at Thomas Jefferson University, there is a very clear connection in their practice between periprosthetic infection and an international normalized ratio (INR) greater than 1.5.[12] All of us in the Hip Society and the American Association of Hip and Knee Surgeons have seen cases with infection directly related to hematoma formation. This has been totally underreported and understated, and was thought not to be scientific until this recent report from the Rothman Institute.[12]

Third, as an orthopedic surgeon, I have to follow the guidelines of the American Academy of Orthopaedic Surgeons.[11] To blindly follow the guidelines of the Surgical Care Improvement Project (http://www.medqic.org) is asking for less than ideal results in orthopedic cases.

I see a very strong trend toward aspirin. A number of academics in prominent institutions are using aspirin, particularly in knee surgery.

I personally have experience with a group of 350 orthopedic surgery patients whom I have managed based on the approach recently reported by Bern et al—ie, warfarin 1 mg/day for 7 days prior to surgery, followed by variable warfarin dosing during the hospital stay to achieve a target INR of 1.5 to 2.0, followed by a maintenance warfarin dose of 1 mg daily for 30 days after discharge.[13] I am very pleased with the results of this regimen. I have not encountered any wound issues, unlike my prior experience when using warfarin dosed to an INR of 2.0 to 3.0. I have currently modified this approach so that all male patients first receive two 325-mg aspirin tablets daily for 2 weeks, then warfarin 1 mg/day for the 7 days before surgery, followed by postoperative warfarin dosed to an INR of 1.5 to 2.0 during hospitalization,

and then warfarin 2 to 5 mg/day for 30 days based on the patient's INR response during hospitalization. The postoperative warfarin dosing requires monitoring, of course.

The results have been far superior to the bleeding rates reported from the Rothman Institute.[12] It is unfortunate that an approach such as this, as well as the rationale behind it, was not discussed in your supplement.

HAROLD S. BOYD, MD
Willamette Orthopedic Group
Salem Memorial Hospital
Salem, OR

IN REPLY: We appreciate the comments by Drs. Fishmann and Boyd, but we strongly disagree with their suggestion that aspirin monotherapy is an appropriate option for the prevention of venous thromboembolism (VTE) following major orthopedic surgery.

As discussed in our original article,[1] multiple large-scale clinical trials in patients undergoing elective hip arthroplasty, knee arthroplasty, or hip fracture surgery have demonstrated the thromboprophylactic efficacy of warfarin, unfractionated heparin, low-molecular-weight heparin (LMWH), fondaparinux, and oral direct thrombin inhibitors. The relative risk reduction with these agents has been greater than 50% in most studies. In contrast, in a large meta-analysis of VTE prophylaxis following total hip replacement, which included data from 56 randomized trials published between 1966 and 1993, aspirin was not beneficial in preventing DVT.[14]

The largest prospective randomized trial comparing aspirin with placebo for VTE prevention was conducted between 1992 and 1998 among 17,444 patients in five countries.[5] It involved 13,356 patients requiring hip fracture surgery and 4,088 patients requiring elective hip arthroplasty. Patients were randomized to receive aspirin 160 mg/day or placebo for 35 days. However, additional forms of VTE prophylaxis were allowed if deemed necessary by the clinician. In fact, 26% of patients received LMWH in addition to aspirin, and dual therapy was probably more common in those patients at highest thromboembolic risk. As such, the 36% relative risk reduction in VTE ascribed to aspirin should be viewed with caution. Further, this is a smaller risk reduction than that observed in trials of other anticoagulant agents.

A large, well-designed, randomized clinical trial comparing aspirin to LMWH or fondaparinux remains to be conducted.

Dr. Fishmann cites a small study of patients undergoing knee arthroplasty who received spinal anesthesia and intermittent calf compression devices.[7] In this underpowered study, 275 patients were randomized to receive aspirin 325 mg twice daily or enoxaparin 30 mg twice daily for 3 weeks. The overall DVT rates were 14.1% in the enoxaparin group vs 17.8% in the aspirin group (P = .27).[7] Patients who received aspirin had significantly more postoperative drainage than those randomized to enoxaparin. In addition, the protocol for scheduling enoxaparin 48 hours postoperatively is not consistent with recommendations of the American College of Chest Physicians (ACCP) and may have reduced the efficacy of enoxaparin.

The other evidence in support of aspirin cited by Dr. Fishmann includes an editorial,[9] an uncontrolled retrospective analysis,[8] a single-center retrospective review,[10] and a review article.[6] Although there is evidence that the use of aspirin is probably associated with a modest reduction in postoperative VTE risk, it has been unequivocally surpassed in efficacy by other anticoagulants.

Both the latest (2004) ACCP guidelines on VTE[2] and the 2006 International Consensus Statement on VTE prevention and treatment[15] advise against aspirin monotherapy as VTE prophylaxis in any patient groups. It is likely that the upcoming 2008 ACCP guidelines will also advocate against using aspirin as well.

Lastly, the most recent guideline from the American Academy of Orthopaedic Surgeons advocating aspirin as monotherapy[11] is based on the assumption that the major important clinical end point in the orthopedic surgery patient is clinical pulmonary embolism, an end point that was not included as a lone primary end point in any of the modern randomized controlled studies in major orthopedic surgery. This represents a flawed logic for the development of evidence-based guideline recommendations, and this recommendation has not been advocated by well-respected bodies such as the ACCP and the international groups that developed the International Consensus Statement. Furthermore, if this practice is going to be advocated by the American Academy of Orthopaedic Surgeons, then large rig-

orously designed randomized trials must be conducted to compare aspirin to currently available anticoagulants, and the type of joint surgery should be clearly defined.

STEVEN B. DEITELZWEIG, MD
Ochsner Health System
New Orleans, LA

ALPESH N. AMIN, MD, MBA
University of California, Irvine

DANIEL J. BROTMAN, MD
Johns Hopkins Hospital
Baltimore, MD

SYLVIA C. McKEAN, MD
Brigham and Women's Hospital
Boston, MA

ALEX C. SPYROPOULOS, MD
Lovelace Medical Center
Albuquerque, NM

AMIR K. JAFFER, MD
University of Miami
Miami, FL

EDITOR'S NOTE: *One of the above letters suggests that the authors' observations "are not going to be 'clean'" because some of the authors disclosed receiving honoraria, consulting fees, or research funding from industry. The* Journal *strictly requires that such relationships with industry be disclosed, as they were in this case, but we do not agree that such relationships imply academic impropriety.*

The integrity of editorial content must be judged on the basis of the content itself and the degree to which it is evidence-based. The supplement in which this article appeared underwent an independent review by a content expert unaffiliated with the project and without commercial ties to the funding source; this expert attested that the supplement was evidence-based, balanced, and free of commercial bias. Such a review is required by the Cleveland Clinic Center for Continuing Education, our CME partner, for all CME-certified supplements with commercial support from a single industry grantor.

Obviously, with some of the issues discussed here relating to the efficacy of aspirin as an antithrombotic agent following orthopedic surgery, there is a difference of opinion regarding the strength of the data.

■ REFERENCES

1. **Deitelzweig SB, McKean SC, Amin AN, Brotman DJ, Jaffer AK, Spyropoulos AC.** Prevention of venous thromboembolism in the orthopedic surgery patient. Cleve Clin J Med 2008; 75(suppl 3):S27–S36.
2. **Geerts WH, Pineo GF, Heit JA, et al.** Prevention of venous thromboembolism: the Seventh ACCP Conference on Antithrombotic and Thrombolytic Therapy. Chest 2004; 126(3 suppl):338S–400S.
3. **Geerts WH, Heit JA, Clagett GP, et al.** Prevention of venous thromboembolism. Chest 2001; 119(1 suppl):132S–175S.
4. **Zimlich RH, Fulbright BM, Friedman RJ.** Current status of anticoagulation therapy after total hip and total knee arthroplasty. J Am Acad Orthop Surg 1996; 4:54–62.
5. **PEP Trial Collaborative Group.** Prevention of pulmonary embolism and deep vein thrombosis with low dose aspirin: Pulmonary Embolism Prevention (PEP) trial. Lancet 2000; 355:1295–1302.
6. **Berend KR, Lombardi AV Jr.** Multimodal venous thromboembolic disease prevention for patients undergoing primary or revision total joint arthroplasty: the role of aspirin. Am J Orthop 2006; 35:24–29.
7. **Westrich GH, Bottner F, Windsor RE, Laskin RS, Haas SB, Sculco TP.** VenaFlow plus Lovenox vs VenaFlow plus aspirin for thromboembolic disease prophylaxis in total knee arthroplasty. J Arthroplasty 2006; 21(6 suppl 2):139–143.
8. **Lotke PA, Lonner JH.** The benefit of aspirin chemoprophylaxis for thromboembolism after total knee arthroplasty. Clin Orthop Relat Res 2006; 452:175–180.
9. **Callaghan JJ, Dorr LD, Engh GA, et al.** Prophylaxis for thromboembolic disease: recommendations from the American College of Chest Physicians—are they appropriate for orthopaedic surgery? J Arthroplasty 2005; 20:273–274.
10. **Dorr LD, Gendelman V, Maheshwari AV, Boutary M, Wan Z, Long WT.** Multimodal thromboprophylaxis for total hip and knee arthroplasty based on risk assessment. J Bone Joint Surg Am 2007; 89:2648–2657.
11. American Academy of Orthopaedic Surgeons Clinical Guideline on Prevention of Symptomatic Pulmonary Embolism in Patients Undergoing Total Hip or Knee Arthroplasty: Summary of Recommendations. http://www.aaos.org/Research/guidelines/PE_summary.pdf. Accessed April 16, 2008.
12. **Parvizi J, Ghanem E, Joshi A, Sharkey PF, Hozack WJ, Rothman RH.** Does "excessive" anticoagulation predispose to periprosthetic infection? J Arthroplasty 2007; 22(6 suppl 2):24–28.
13. **Bern M, Deshmukh RV, Nelson R, et al.** Low-dose warfarin coupled with lower leg compression is effective prophylaxis against thromboembolic disease after hip arthroplasty. J Arthroplasty 2007; 22:644–650.
14. **Imperiale TF, Speroff T.** A meta-analysis of methods to prevent venous thromboembolism following total hip replacement. JAMA 1994; 271:1780–1785.
15. **Cardiovascular Disease Educational and Research Trust; Cyprus Cardiovascular Disease Educational and Research Trust; European Venous Forum; International Surgical Thrombosis Forum; International Union of Angiology; Union Internationale de Phlébologie.** Prevention and treatment of venous thromboembolism. International Consensus Statement (guidelines according to scientific evidence). Int Angiol 2006; 25:101–161.