Rationale for Thromboprophylaxis in Lower Joint Arthroplasty

Clifford W. Colwell, Jr., MD

Abstract

Without prophylaxis, rates of deep vein thrombosis (DVT) after major orthopedic surgery range from 40% to 60%. Randomized clinical trials over the past 30 years have provided evidence that primary thromboprophylaxis reduces DVT, pulmonary embolism (PE), and fatal PE, and prophylaxis to prevent venous thromboembolism (VTE) in patients at risk has been ranked as the highest safety practice for hospitalized patients. Since 1986, some type of prophylaxis has been recommended for total knee arthroplasty (TKA), total hip arthroplasty (THA), and hip fracture surgery. Orthopedic guidelines published in *Chest* provide a current evidence-based guide for prophylaxis for TKA, THA, and hip fracture surgery. In addition to following these recommendations for routine prophylaxis, surgeons should assess patients for additional VTE risk. Patients at higher risk may need more intense prophylaxis. Data from meta-analyses and placebo-controlled, blinded, randomized clinical trials have demonstrated little or no increase in rates of clinically important bleeding with prophylaxis.

Since the first National Institutes of Health Thrombosis Conference in 1986,[1] when it was reported that patients undergoing major lower extremity orthopedic surgery were in the group at highest risk for venous thromboembolic (VTE) events, some type of prophylaxis has been recommended for total knee arthroplasty (TKA), total hip arthroplasty (THA), and hip fracture surgery. Appropriate endpoints for thromboprophylaxis studies, as defined by physicians, differ widely. Some believe that contrast venography for deep vein thrombosis (DVT) should be used as the endpoint, whereas others argue that reduction in all-cause mortality should be used. Although it is widely recognized that use of venographic, duplex ultrasound, or clinically symptomatic DVT is not a perfect endpoint, DVT is an endpoint that can be documented in a manageable number of patients. Proving reduction in all-cause mortality or fatal pulmonary embolism (PE) as the objective of a thromboprophylaxis trial is problematic. PE as an endpoint would require more patients than could be reasonably examined in a study situation. Obtaining autopsy confirmation of PE as cause of death is increasingly difficult. No reported study has used PE as the endpoint for determining the advantage of using prophylaxis. Using mortality as the endpoint dismisses the significant burden on the health care system of illness caused by symptomatic or objectively proven VTE with possible long-term problems from these events, such as pulmonary hypertension and chronic venous insufficiency.

Endpoints for thromboprophylaxis differ widely, but DVT, though not perfect, is an endpoint that can be documented.

Without prophylaxis, rates of DVT after major orthopedic surgery range from 40% to 60%.[2,3] Between 25% and 33% of these thrombi occur in the proximal deep veins, which are more likely to produce symptoms and result in PE. Although improved patient care and surgical techniques have reduced some risk factors, the majority of patients undergoing major orthopedic surgery still have many risk factors, including advanced age, comorbidities (eg, cancer, peripheral vascular disease, high blood pressure), and more extensive surgical procedures.

Most studies of VTE and its prevention have used sensitive diagnostic tests to detect DVT. The majority of diagnosed DVT cases in TKA were distal, below

Dr. Colwell is Director, Shiley Center for Orthopaedic Research and Education, Scripps Clinic, La Jolla, California.

the knee, and remained unchanged without any adverse outcomes.[4-7] Approximately 10% to 20% of distal DVT cases propagate to the proximal veins,[5,8-10] particularly in patients having major hip surgery.[11,12] Randomized clinical trials over the past 30 years have provided evidence that primary thromboprophylaxis reduces DVT, PE, and fatal PE.[13,14,15] Prophylaxis to prevent VTE in patients at risk has been ranked as the highest safety practice for hospitalized patients.[16]

In response to the high incidence of VTE in patients who did not receive prophylaxis before 1986, a series of guidelines was developed and published in the journal *Chest*. These guidelines are reviewed and modified every few years and are presently undergoing their eighth modification. In these guidelines, the evidence and its strength are delineated. A grade 1 rating means that evidence in a study clearly shows that the benefit of a specific modality outweighs the risk; a grade 2 rating means that the benefit versus risk is not clear. Ratings A through C refer to the quality of studies, with A representing randomized prospective studies with consistent hard endpoints that apply to most patients most of the time and C representing cohort studies in nature with results that are not consistent.

VTE prevention recommendations rated grade 1A in *Chest* guidelines for THA are low-molecular-weight heparin (LMWH) started 12 hours before surgery or 12 to 24 hours after surgery, fondaparinux started 6 to 8 hours after surgery, and adjusted-dose warfarin started preoperatively or the evening after surgery. Routine TKA prophylaxis recommendations rated grade 1A are LMWH started 12 to 24 hours after surgery, fondaparinux started 6 to 8 hours after surgery, and adjusted-dose warfarin started preoperatively or the evening after surgery. For patients undergoing hip fracture surgery, fondaparinux is grade 1A. LMWH (grade 1C+) and adjusted-dose warfarin (grade 2B) also appear to be reasonable for DVT prophylaxis in hip fracture surgery, though the evidence from clinical trials is not as strong as for fondaparinux. Optimal use of mechanical prophylaxis may be employed in TKA (grade 1B) and hip fracture surgery (grade 1C+) if the patient is at high risk for bleeding. Aspirin alone for VTE prophylaxis is not recommended (grade 1A) for any major lower extremity surgery.[15]

In addition to following these recommendations for routine prophylaxis, surgeons should assess patients for additional VTE risk. Patients at higher risk may need more intense prophylaxis. Use of both the recommendations and the documented assessment of each patient has been adopted by the National Quality Forum (NQF), the Surgical Care Improvement Project (SCIP), and the Joint Commission on Accreditation of Healthcare Organizations (JCAHO).

Appropriately used thromboprophylaxis appears to have desirable risk-benefit ratio.

The major concern in thromboprophylaxis is the complication of bleeding. However, data from meta-analyses and placebo-controlled, blinded, randomized clinical trials have demonstrated little or no increase in rates of clinically important bleeding with prophylaxis.[17,18] One study found an incidence of 1.1% postoperative hemorrhage or hematoma with a death rate of 4.5% and an 11.3% incidence of postoperative PE or DVT with a death rate of 6.5% in reporting on all surgical patients in 2002.[19] Appropriately used thromboprophylaxis appears to have a desirable risk–benefit ratio and is reported as cost-effective.[20-22] Thromboprophylaxis in major lower extremity orthopedic surgery provides an opportunity to improve patient outcomes and long-term sequelae of VTE by using established, validated outcome measures. This represents the best method of using evidence-based medicine in clinical practice.

Author's Disclosure Statement

The author wishes to note he is a consultant for Bayer Healthcare Pharmaceuticals, DePuy Inc., and Stryker Orthopaedics.

(*References continued on next page*.)

References

1. National Institutes of Health. Prevention of venous thrombosis and pulmonary embolism. NIH Consensus Development. *JAMA*. 1986;256:744-749.
2. Anderson FA Jr, Wheeler HB, Goldberg RJ, et al. A population-based perspective of the hospital incidence and case-fatality rates of deep vein thrombosis and pulmonary embolism. The Worcester DVT Study. *Arch Intern Med*. 1991;151:933-938.
3. Geerts WH, Heit JA, Clagett GP, et al. Prevention of venous thromboembolism. *Chest*. 2001;119(1 suppl):132S-175S.
4. Agnelli G, Cosmi B, Radicchia S, et al. Features of thrombi and diagnostic accuracy of impedance plethysmography in symptomatic and asymptomatic deep vein thrombosis. *Thromb Haemost*. 1993;70:266-269.
5. Kakkar VV, Howe CT, Flanc C, Clarke MB. Natural history of postoperative deep-vein thrombosis. *Lancet*. 1969;2:230-232.
6. Lotke PA, Ecker ML, Alavi A, Berkowitz H. Indications for the treatment of deep venous thrombosis following total knee replacement. *J Bone Joint Surg Am*. 1984;66:202-208.
7. Philbrick JT, Becker DM. Calf deep venous thrombosis. A wolf in sheep's clothing? *Arch Intern Med*. 1988;148:2131-2138.
8. Kearon C. Natural history of venous thromboembolism. *Circulation*. 2003;107(23 suppl 1):I22-I30.
9. Lohr JM, Kerr TM, Lutter KS, Cranley RD, Spirtoff K, Cranley JJ. Lower extremity calf thrombosis: to treat or not to treat? *J Vasc Surg*. 1991;14:618-623.
10. Maynard MJ, Sculco TP, Ghelman B. Progression and regression of deep vein thrombosis after total knee arthroplasty. *Clin Orthop*. 1991;273:125-130.
11. Ascani A, Radicchia S, Parise P, Nenci GG, Agnelli G. Distribution and occlusiveness of thrombi in patients with surveillance detected deep vein thrombosis after hip surgery. *Thromb Haemost*. 1996;75:239-241.
12. Stamatakis JD, Kakkar VV, Sagar S, Lawrence D, Nairn D, Bentley PG. Femoral vein thrombosis and total hip replacement. *BMJ*. 1977;2:223-225.
13. Collins R, Scrimgeour A, Yusuf S, Peto R. Reduction in fatal pulmonary embolism and venous thrombosis by perioperative administration of subcutaneous heparin. Overview of results of randomized trials in general, orthopedic, and urologic surgery. *N Engl J Med*. 1988;318:1162-1173.
14. Sevett S, Gallagher NG. Prevention of venous thrombosis and pulmonary embolism in injured patients. A trial of anticoagulant prophylaxis with phenindione in middle-aged and elderly patients with fractured necks of femur. *Lancet*. 1959;2:981-989.
15. 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.
16. Shojania KG, Duncan BW, McDonald KM, Wachter RM, eds. *Making Health Care Safer: A Critical Analysis of Patient Safety Practices* [Evidence Report/Technology Assessment 43]. Rockville, Md: US Dept of Health and Human Services, Agency for Healthcare Research and Quality; 2001. AHRQ publication 01-E058. Available at http://www.ahrq.gov/clinic/ptsafety/. Accessed August 6, 2007.
17. Nurmohamed MT, Rosendaal FR, Buller HR, et al. Low-molecular-weight heparin versus standard heparin in general and orthopaedic surgery: a meta-analysis. *Lancet*. 1992;340:152-156.
18. Thomas DP. Does low molecular weight heparin cause less bleeding? *Thromb Haemost*. 1997;78:1422-1425.
19. Health Grades, Inc. *Patient Safety in American Hospitals*. Available at: http://www.healthgrades.com/media/english/pdf/HG_Patient_Safety_Study_Final.pdf. Accessed July 11, 2007.
20. Caprini JA, Botteman MF, Stephens JM, et al. Economic burden of long-term complications of deep vein thrombosis after total hip replacement surgery in the United States. *Value Health*. 2003;6:59-74.
21. Davidson BL, Sullivan SD, Kahn SR, Borris L, Bossuyt P, Raskob G. The economics of venous thromboembolism prophylaxis: a primer for clinicians. *Chest*. 2003;124(6 suppl):393S-396S.
22. Sullivan SD, Kahn SR, Davidson BL, Borris L, Bossuyt P, Raskob G. Measuring the outcomes and pharmacoeconomic consequences of venous thromboembolism prophylaxis in major orthopaedic surgery. *Pharmacoeconomics*. 2003;21:477-496.