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Agency for Healthcare Research and Quality
U.S. Department of Health and Human Services
c/o Scientific Resource Center
Portland VA Research Foundation
3170 SW U.S. Veterans Hospital Road
Mail code: R&D 71
Portland, Oregon 97239

RE: Venous Thromboembolism Prophylaxis in Major Orthopedic Surgery: Systematic Review Update

To Whom It May Concern,

The leadership, the Research Committee, and the Evidence Based Medicine Committee of the American Association of Hip and Knee Surgeons (AAHKS) have had the opportunity to read the Draft manuscript entitled "Comparative Effective Review: Venous Thromboembolism Prophylaxis in Major Orthopaedic Surgery: Systematic Review Update". VTE prophylaxis is a topic of great interest to our organization and our members. We have previously worked with the American Academy of Orthopaedic Surgeons to develop guidelines for prevention of VTE following total joint arthroplasty. We would like to commend you for producing the above named document that attempts to summarize the findings of the published literature on VTE following total joint arthroplasty. We do, however, have some major concerns regarding the review in its current state.

First, an area of significant concern with respect to the literature review is the fact that studies that assessed both asymptomatic and symptomatic events were included in the analysis. Asymptomatic clots diagnosed on venogram or by ultrasound have questionable clinical relevance, and are surrogates for disease. Therefore, we do not believe that an analysis that assesses the efficacy of VTE prophylaxis regimens should contain data that includes asymptomatic clots. There does not appear to be a patient centric process to determine the importance of various outcomes to the patient, which is not in keeping with EBM methodologies such as GRADE. Your report states that 80% of the studies used reported on the total number of DVT's without further description. Registry data shows a far lower rate of symptomatic DVT than those reported in industrial studies using venogram findings of all DVT as the end-point. If the symptomatic DVT /PE is accepted as the more critical end-point, the use of all DVT's challenges the face validity of the conclusions. In addition, the majority of the studies use LMWH as the comparator challenging the validity of the network analysis. This concern is supported by the methods and conclusions of the most recent American College of Chest Physician Guidelines: Prevention of VTE in Orthopaedic Patients; that guideline downgraded previous 1A recommendation for LMWH to a 1B level and included ASA one of the 1B alternatives. A similar decision was made by the workgroup for The American Academy of Orthopaedic Surgeons Clinical Practice Guidelines: Preventing Venous Thromboembolic Disease in Patients Undergoing Elective Hip and Knee Arthroplasty. The results of an extensive network meta-analysis for that study was discounted because of the use of the surrogate outcome of radiographic DVT, which resulted in recommendations not far removed from that of the ACCP. It would be useful to repeat your analysis and remove studies that did not include asymptomatic events and see if this has an impact on your conclusions.

Although your analysis showed no industrial bias, it should be recognized that the great cost of the RCT's requiring ascending phlebography has been, in effect, a barrier to entry in terms of studies that could meet previous criteria for inclusion in meta-analysis. The historical rejection of either placebo or anti-platelet controls in most studies is also limiting.

A second concern regards the balance between efficacy and safety in selecting a prophylactic regiment. Surgeons have great concerns about bleeding associated with over anticoagulation of patients. Hematoma formation, persistent bleeding, and periprosthetic joint infection are important end-points for patients as well, and their preferences should be considered. Mechanical protection with or without aspirin is accepted by most surgeons as having less risk of bleeding complications; at one time, this combination was an 1A recommendation of the ACCP. Your review might not take into account all of the serious events that can occur as a result of administration of anticoagulation agents because the vast majority of the selected studies carry significant exclusion criteria not always as carefully adhered to in actual practice; this can be because of inaccurate records and/or EMR interfaces that do not have the advantage of study coordinators. Although the review made an attempt to evaluate the risk of bleeding with each agent, it is unclear from the methodology how an adverse bleeding event was identified and, in fact, the definition of such event is missing. Surgeons are particularly concerned about bleeding events that require a return to the operating room. At minimum you should attempt to capture the rate of reoperation related to hematoma formation or persistent drainage with each agent.

Third, there is a very limited discussion about anti-platelet agents in this study. In the most recent ACCP guideline, aspirin was one of the recommended agents for prevention of VTE following total joint arthroplasty with a 1B grade endorsement. The popularity of aspirin as a prophylaxis agent for VTE after total hip and knee arthroplasty has increased significantly over the past five years. Therefore, it is essential that one assess the impact of anti-platelet prophylaxis on the frequency of symptomatic events after total joint replacement. Your review has missed numerous publications related to the efficacy of aspirin for prevention of VTE following total joint arthroplasty. In fact, a recent systematic review published in British Joint Journal on the efficacy of various anticoagulation agents for prevention of VTE following total joint arthroplasty came up with different conclusions than what is stated in your review. The latter may arise from the exclusion of many studies from your review that endorse the value of aspirin as an effective VTE prophylaxis after TJA. It should be noted that Jameson was able to compare ASA and LMWH in over one hundred thousand patient cohorts for both THA and TKA and estimated that, to have sufficient power, a prospective RCT would require approximately 30,000 patients to discern a difference in efficacy and safety between ASA and LMWH.

In conclusion, despite the immense work that your organization has invested to produce the above systematic review, AAHKS is sufficiently concerned with the conclusions of your article to urge you to consider implementing some of the suggestions made above.

Sincerely,



Michael J. Zarski, JD
Executive Director

CC: William A. Jiranek, MD, President
Jay R. Lieberman, MD, Immediate Past President
Adolph J. Yates, MD, Chair, Evidence Based Medicine Committee
Javad Parvizi, MD, Chair, Research Committee