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**2010**

**President**

Hal Broxmeyer, PhD  
Walther Oncology Center  
Indiana University School of Medicine  
950 W. Walnut Street, Room 302  
Indianapolis, IN 46202  
phone 317-274-7510  
fax 317-274-7592  
hbroxmey@iupui.edu

**President-Elect**

J. Evan Sadler, MD, PhD  
Washington University Medical School  
660 South Euclid Avenue, Box 8126  
Saint Louis, MO 63110-1093  
phone 314-362-9029  
fax 314-454-3012  
esadler@wustl.edu

**Vice President**

Armand Keating, MD  
Princess Margaret Hospital  
610 University Avenue, Suite 5-303  
Toronto, ON M5G 2M9  
CANADA  
phone 416-946-4595  
fax 416-946-4530  
armand.keating@uhn.on.ca

**Secretary**

Charles Abrams, MD  
University of Pennsylvania  
School of Medicine  
421 Curie Boulevard, #912  
Philadelphia, PA 19104-6140  
phone 215-573-3288  
fax 215-573-7400  
abrams@mail.med.upenn.edu

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Linda Burns, MD  
Division of Hematology,  
Oncology, and Transplantation  
University of Minnesota  
420 Delaware Street, SE  
Mayo MC 286/Room 14-154A Moos Tower  
Minneapolis, MN 55455-0341  
phone 612-624-8144  
fax 612-625-9988  
burns019@umn.edu

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Martha L. Liggett, Esq.  
mliggett@hematology.org

Effective Health Care Program  
Agency for Healthcare Research and Quality  
540 Gaither Road  
Rockville, MD 20850

RE: VTE prophylaxis in orthopedic surgery

To Whom It May Concern:

The American Society of Hematology (ASH) appreciates the opportunity to comment on the Agency for Healthcare Research and Quality (AHRQ) key questions for VTE prophylaxis in orthopedic surgery. The Society represents more than 16,000 clinicians and scientists committed to the study and treatment of blood and blood-related diseases such as thrombosis, leukemia, lymphoma, and anemia. ASH appreciates that the AHRQ recognizes the public health impact of venous thromboembolism (VTE) and that it is focusing on this issue. Below, please find ASH's comments on the key questions that AHRQ proposes to use to address VTE prophylaxis in orthopedic surgery.

***Major orthopedic surgery (total hip or knee replacement, hip fracture surgery):***

***Key Question 1: In patients undergoing major orthopedic surgery what is the overall baseline risk of VTE and bleeding outcomes?***

ASH would like clarification about how "baseline" is defined and assumes that "baseline" means the rates of VTE and bleeding in patients not receiving thromboprophylaxis (TP). If this assumption is correct, ASH does not believe that the baseline rates of VTE can be determined - there are no recent studies that can provide this information since control groups without TP have been considered unethical in major orthopedic surgery (MOS) for more than 25 years.<sup>1</sup> Every randomized controlled trial (RCT) done over this time (except for subsets of patients in the PEP trial<sup>2</sup>) has compared two active interventions. Furthermore, in the clinical trials, highly selected patient groups were used (excluding patients felt to have greater risks of VTE). In addition, surgical techniques, post-operative care and rehabilitation services have changed drastically over the past 25 years.

In addition, ASH would like clarification of the definition of "bleeding". There are numerous definitions of bleeding used in the MOS prophylaxis trials with no consensus on which definition is optimal and with limited ability to determine the rates of bleeding using one particular definition if another definition was used in the trial.<sup>3,4</sup> For example, whether surgical site bleeding is included or not significantly affects the reported rates of bleeding, and there is no standard definition for what constitutes surgical site bleeding. Furthermore, patients considered to be high risk for bleeding were also excluded from all of the relevant RCTs.

***Key Question 2: In patients undergoing MOS what patient characteristics predict or differentiate patient risk of VTE and bleeding outcomes?***

ASH suggests that the question be clarified to refer to VTE and bleeding risks in patients that are receiving thromboprophylaxis. There are studies in MOS patients that have assessed predictors of TP “failures” – i.e. patients who develop VTE despite TP or who develop bleeding while on TP. Although this could be summarized in a systematic review, ASH is unsure of the utility of this question. The rates of clinically-important VTE and clinically-important bleeding are both low in recent MOS clinical trials.<sup>1,5</sup> Predictors of asymptomatic deep vein thrombosis (DVT) in MOS include: bilateral arthroplasty, previous VTE, increased age, reduced postoperative mobility, obesity, use of warfarin as prophylaxis, and failure to provide post-discharge prophylaxis.<sup>1,6</sup> The studies that have assessed bleeding risk factors in MOS are few in number and quite heterogeneous. ASH is not aware of any studies in MOS that have specifically identified patients at high risk of VTE or bleeding and then assessed some modification of usual TP.

***Key Question 3: In patients undergoing MOS in the absence of important patient outcomes, can the risk for such outcomes reliably be estimated by measuring surrogate outcomes, such as DVT (asymptomatic or symptomatic, proximal or distal) as detected by venography or ultrasound?***

ASH suggests increasing the clarity of the question and recommends the following: “Is asymptomatic DVT, assessed by routine contrast venography or DUS, a reasonable and appropriate surrogate outcome for “clinically-important VTE?” There are articles in the current literature to help answer this question .<sup>1,7</sup>

***Key Question 4: In patients undergoing MOS, what is the relative impact of thromboprophylaxis [any pharmacologic agent within the defined classes (oral antiplatelet agents, injectable low molecular weight heparins (LMWH), injectable unfractionated heparin, injectable or oral factor Xa antagonists, injectable or oral direct thrombin inhibitors, oral vitamin K antagonists (VKAs)) or any external mechanical intervention within the defined classes (graduated compression, intermittent pneumatic compression, or venous foot pump)] compared with no thromboprophylaxis on VTE [asymptomatic or symptomatic, proximal or distal DVT detected by venography or ultrasound, proximal DVT, non-fatal pulmonary embolism (PE), fatal PE, symptomatic objectively confirmed VTE, major VTE (proximal DVT, non-fatal PE or VTE-related mortality)], post-thrombotic syndrome; bleeding (major, major leading to re-operation, minor, bleeding leading to infection, bleeding leading to transfusion), immune-mediated thrombocytopenia, discomfort, re-admission, re-operation, total mortality, mortality due to bleeding?***

ASH believes this question is problematic for several reasons. First, there are no trials comparing one of the modalities of interest to no TP in the past 25 years. Furthermore, the data on antiplatelet agents is well-established. The 2008 ACCP guidelines gave a Grade 1A recommendation against aspirin as TP for any patient group and the 2010 UK NICE guidelines do not include aspirin as TP for any patient group.<sup>1,8</sup> There are no injectable DTIs approved for TP, and there are no data looking at PTS after a specific modality of TP. There appears to be an association between wound bleeding and infection but there is no direct evidence linking any prophylaxis modality to wound infection. Finally, there are no useful data related to the following proposed outcomes in MOS: fatal PE, readmission, discomfort, all-cause mortality, re-operation, or fatal bleeding. Therefore, this question cannot be directly answered and the use of indirect comparisons is not acceptable.

***Key Question 5: In patients undergoing MOS what is the comparative efficacy between classes of agents on outcomes: VTE [asymptomatic or symptomatic, proximal or distal DVT detected by venography or ultrasound, proximal DVT, non-fatal PE, fatal PE, symptomatic objectively confirmed VTE, major VTE (proximal DVT, non-fatal PE or VTE-related mortality)], post-thrombotic syndrome; bleeding (major, major leading to re-operation, minor, bleeding leading to infection, bleeding leading to transfusion), immune-mediated thrombocytopenia, discomfort, re-admission, re-operation, total mortality, mortality due to bleeding? Classes include oral antiplatelet agents, injectable low molecular weight heparins (LMWH), injectable unfractionated heparin, injectable or oral factor Xa antagonists, injectable or oral direct thrombin inhibitors, oral vitamin K antagonists (VKAs), and mechanical interventions?***

This is a clinically relevant question. Please refer to the numerous systematic reviews, meta-analyses and evidence-based guidelines that have addressed this question.<sup>1,8</sup>

***Key Question 6: In patients undergoing MOS what is the comparative efficacy of individual agents within classes on VTE [asymptomatic or symptomatic, proximal or distal DVT detected by venography or ultrasound, proximal DVT, non-fatal PE, fatal PE, symptomatic objectively confirmed VTE, major VTE (proximal DVT, non-fatal PE or VTE-related mortality)], post-thrombotic syndrome; bleeding (major, major leading to re-operation, minor, bleeding leading to infection, bleeding leading to transfusion), immune-mediated thrombocytopenia, discomfort, re-admission, re-operation, total mortality, mortality due to bleeding? Classes include LMWH and mechanical devices.***

Again, ASH considers this to be a potentially very important question but ASH is also aware that there are very few direct comparisons between agents within one class of TP modalities.

***Key Question 7: In patients undergoing MOS what are the effect estimates of combined pharmacologic and mechanical modalities vs. single modality on VTE [asymptomatic or symptomatic, proximal or distal DVT detected by venography or ultrasound, proximal DVT, non-fatal PE, fatal PE, symptomatic objectively confirmed VTE, major VTE (proximal DVT, non-fatal PE or VTE-related mortality)], post-thrombotic syndrome; bleeding (major, major leading to re-operation, minor, bleeding leading to infection, bleeding leading to transfusion), immune-mediated thrombocytopenia, discomfort, re-admission, re-operation, total mortality, mortality due to bleeding?***

Again, ASH considers this to be a potentially important question but is also aware that there are very few direct comparisons of combined vs. single modality TP and most of the listed outcomes have never been assessed in trials. Therefore, this question cannot be definitively answered.

***Key Question 8: In patients undergoing MOS regardless of thromboprophylaxis method, what are the effects of prolonging thromboprophylaxis for 30 days or longer compared to thromboprophylaxis for 7 days on VTE [asymptomatic or symptomatic, proximal or distal DVT detected by venography or ultrasound, proximal DVT, non-fatal PE, fatal PE, symptomatic objectively confirmed VTE, major VTE (proximal DVT, non-fatal PE or VTE-related mortality)], post-thrombotic syndrome; bleeding (major, major leading to re-operation, minor, bleeding leading to infection, bleeding leading to transfusion), immune-mediated thrombocytopenia, discomfort, re-admission, re-operation, total mortality, mortality due to bleeding?***

ASH notes that the effects of post-discharge TP on both surrogate and clinically-important outcomes have been reasonably well studied and there are multiple systematic reviews/meta-analyses on this subject.<sup>1,9</sup> However, even in these trials, only asymptomatic DVT, symptomatic VTE and bleeding have been assessed. The other outcomes have not been assessed.

***Key Question 9: In patients undergoing MOS who have known contraindications to antithrombotic agents, what is the relative impact of prophylactic inferior vena cava filter (IVC) placement compared to any external mechanical intervention on VTE [asymptomatic or symptomatic, proximal or distal DVT detected by venography or ultrasound, proximal DVT, non-fatal PE, fatal PE, symptomatic objectively confirmed VTE, major VTE (proximal DVT, non-fatal PE or VTE-related mortality)], post-thrombotic syndrome; bleeding (major, major leading to re-operation, minor, bleeding leading to infection, bleeding leading to transfusion), immune-mediated thrombocytopenia, discomfort, re-admission, re-operation, total mortality, mortality due to bleeding or IVC filter placement-associated insertion site thrombosis?***

ASH notes that there are no data on this issue. Not a single randomized trial has specifically addressed MOS patients with a contra-indication to antithrombotic agents. Furthermore, there is not a single RCT of the role of IVC filter use for any patient group as primary prophylaxis (with or without a contraindication to anticoagulant TP).

*Other orthopedic conditions (e.g., distal to knee injuries, conditions requiring knee arthroscopy, or elective spine surgery) & VTE*

***Key Question 10: In patients with other orthopedic conditions, what is the relative impact of thromboprophylaxis (any agent, any mechanical intervention) compared to no thromboprophylaxis intervention on VTE [asymptomatic or symptomatic, proximal or distal DVT detected by venography or ultrasound, proximal DVT, non-fatal PE, fatal PE, symptomatic objectively confirmed VTE, major VTE (proximal DVT, non-fatal PE or VTE-related mortality)], post-thrombotic syndrome; bleeding (major, major leading to re-operation, minor, bleeding leading to infection, bleeding leading to transfusion), immune-mediated thrombocytopenia, discomfort, re-admission, re-operation, total mortality, mortality due to bleeding?***

ASH suggests that these patient populations be considered separately. The data are limited in these populations and ASH suggests that you refer to existing reviews of the literature.<sup>1</sup>

***Key Question 11: In patients with other orthopedic conditions what is the relative impact of injectable antithrombotic agents (LMWH versus unfractionated heparin vs. factor Xa antagonists vs. direct thrombin inhibitors) compared to mechanical interventions on VTE [asymptomatic or symptomatic, proximal or distal DVT detected by venography or ultrasound, proximal DVT, non-fatal PE, fatal PE, symptomatic objectively confirmed VTE, major VTE (proximal DVT, non-fatal PE or VTE-related mortality)], post-thrombotic syndrome; bleeding (major, major leading to re-operation, minor, bleeding leading to infection, bleeding leading to transfusion), immune-mediated thrombocytopenia, discomfort, re-admission, re-operation, total mortality, mortality due to bleeding?***

ASH notes that there are inadequate data to be able to answer this question.

**Additional Comment:**

Throughout the AHRQ questions, the term “immune-mediated thrombocytopenia” is used. ASH suggests that the correct terminology is “heparin-induced thrombocytopenia”.

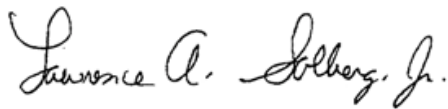
**Overall Comments:**

While there are clearly gaps in the knowledge on orthopedics and thromboembolism, there are also existing evidence-based resources that can save AHRQ time by avoiding duplication of efforts. Specifically, ASH recommends that AHRQ review references 1 and 8 below. For the questions where there is clearly data lacking, it will be useful for AHRQ to review these topics in the context of driving future research.

One of the reasons that AHRQ is reconsidering the use of TP in MOS may have arisen from the differences in the recommendations from the 8<sup>th</sup> ACCP Antithrombotic Guidelines and the document produced by the American Academy of Orthopedic Surgery. ASH recommends that you also review references 10 and 11 below which compare these two sets of guidelines. The AAOS has stated that it plans to update its guidelines in 2010 and there may be substantial changes.

Again, ASH appreciates the opportunity to submit these comments. ASH would be interested in working with the AHRQ on issues related to thrombosis. If you have any questions or require any additional information, please contact ASH Senior Manager of Policy and Practice Carol Schwartz at or 202-776-0544.

Sincerely,



Lawrence A. Solberg, Jr., MD, PhD  
Chair, Committee on Practice

NOTE: ASH appreciates the assistance of Dr. William Geerts and several reviewers in the development of this document.

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