AAOS
American Academy of Orthopaedic Surgeons
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American Academy of Orthopaedic Surgeons Peer Review Comments on AHRQ's "Venous Thromboembolism Prophylaxis in Major Orthopedic Surgery: Systematic Review Update"

The American Academy of Orthopaedic Surgeons (AAOS) has multiple concerns regarding this "Venous Thromboembolism Prophylaxis in Major Orthopedic Surgery: Systematic Review Update" because:

(1) the definition of sufficient evidence excludes level I therapeutic evidence for aspirin;
(2) the choice of clinical outcomes is not focused on clinically important outcomes;
(3) the use of network meta-analyses is inappropriate given the available evidence ;
(4) the conclusions and recommendations are not supported by a complete review of the evidence; and
(5) publishing this systematic review will generate more confusion than clarity for total hip replacement (THR), total knee replacement (TKR), and hip fracture surgery patients that are often co-managed by orthopaedic surgeons and hospitalists/internists.

In 2012, the American College of Chest Physicians (ACCP) released the "Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines" [1]. The ACCP Clinical Practice Guidelines (CPGs) recommended use of aspirin, as one of the pharmacologic agents, for anti-thrombotic prophylaxis for total hip arthroplasty (THA), total knee arthroplasty (TKA), and hip fracture surgery (HFS). ACCP's inclusion of aspirin as a recommendation for anti-thrombotic prophylaxis after THA, TKA, and HFS, brought the ACCP CPG into alignment with the AAOS clinical practice guideline [2]. This alignment between AAOS and ACCP resulted in aspirin being included as an acceptable prophylactic option under the Surgical Care Improvement Project (SCIP) Venous Thromboembolism (VTE) quality measure beginning January 1, 2014. The alignment between the AAOS and ACCP CPGs resolved a contentious debate that had lasted for over a decade [3]. This systematic review does not mention aspirin as an acceptable VTE prophylaxis agent after major orthopaedic surgery and threatens to nullify all of the collaborative efforts of the AAOS and the ACCP.

The systematic review's definition of "sufficient" evidence precludes the possibility of finding strong evidence supporting aspirin use for VTE prophylaxis. "*A priori*, we determined that specific comparisons with ≤2 analyzable studies provide insufficient evidence to evaluate strength of evidence." (Systematic Review p. 12) Industry intentionally selects comparators with a high adverse event rate profile in randomized controlled trials (RCTs) to increase the likelihood

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that the trial outcome will favor the sponsor's treatment [4]. Because aspirin is cost-effective [5] and has a lower operative site bleeding risk [6], pharma has never selected aspirin as an active comparator in RCTs studying low molecular weight heparin (LMWH), antithrombin III-mediated selective factor Xa inhibitors (ATIII), direct factor Xa inhibitors (FXaI), or direct thrombin inhibitors (DTI). This systematic review has endorsed industry's intentional exclusion of aspirin by their "*a priori*" definition of sufficient evidence and promulgate the industry bias prevalent in orthopaedic surgery VTE prophylaxis research [7]. It should also be noted that up until the 2012 ACCP guidelines, a surrogate for symptomatic Deep Vein Thrombosis (DVT) was used, that being ascending phlebography. The incidence of so-called "clots" on venogram was far in excess of what is seen clinically. Maintaining that study as an inclusion requirement for "good" evidence acted as a barrier to studies that involved aspirin. Although AAOS had completed a network meta-analysis in their full report, it was discounted as being dominated by this surrogate outcome. ACCP took a parallel path.

The Pulmonary Embolism Prevention (PEP) trial compared aspirin to placebo for VTE prophylaxis after HFS (13,356 subjects), THA (2,648 subjects), and TKA (1,440 subjects) [8]. This is the largest VTE prophylaxis randomized clinical trial in orthopaedic surgery with over 17,000 subjects. The Cochrane Review for HFS VTE prophylaxis noted "the recent PEP trial … can be a good example to follow." [9] The AHRQ systematic review did not include the PEP trial because there were ≤2 comparisons.

For a systematic review to be credible and clinically useful, the systematic review must focus on clinically important outcomes. The Centers for Medicare and Medicaid Services (CMS) Comprehensive Care for Joint Replacement (CJR) bundled payment program for lower extremity arthroplasty (and recently proposed extension to all hip and femur fractures) selected the National Quality Forum (NQF) 1550 quality measure as 50% of a quality score that must be met to qualify for any bundled care savings reimbursement from CMS. It is also used in the CMS hospital quality ratings (Hospital Compare) and will be applied to the outcomes quadrant for the Medicare Value-Based Purchasing Program (VBP) in 2019 for which it is currently being collected. The NQF 1550 quality measure includes:

(1) Mechanical complications (90 days)
(2) Periprosthetic joint infection (90 days)
(3) Wound infection (90 days)
(4) Surgical site bleeding (30 days)
(5) Pulmonary embolism (30 days)
(6) Death (30 days)

(7) Acute myocardial infarction (7 days)
(8) Pneumonia (7 days)
(9) Sepsis/septicemia (7 days)

Of note, symptomatic deep vein thromboses are not included in the list of complications. Also, this list was generated through a consensus process and did not involve weighting and the Delphi method. On the other hand, the AAOS work-group utilized the Delphi process in assigning the importance of outcome to the patient. Venogram only DVT did not rank as significant.

"For each of three surgeries (THR, TKR, and HipFx surgery) and for the two outcomes (total DVT and major bleeding), we conducted two analyses: …." (p. Executive Summary-19) Total DVT is defined as symptomatic and asymptomatic (p, Executive Summary-17). Major bleeding is defined as: fatal bleeding, bleeding leading to transfusion, major bleeding leading to reoperation, major bleeding leading to readmission, surgical site/joint bleeding, bleeding leading to infection, and "as defined by authors" (p. Executive Summary-17). We would emphasize that there is no evidence that asymptomatic DVTs have any clinical significance.

While the Executive Summary (ES) mentions concerns about surgical site bleeding, the ES does not reference a single citation on the clinical consequences of surgical site bleeding. References are cited for pulmonary embolus management [10], thromboembolic pulmonary hypertension [11, 12], and post-thrombotic syndrome [13-16]. Regarding the complications of operative site bleeding, Galat *et al* [17] reported that post-operative hematoma evacuation after total knee arthroplasty had a two-year cumulative probability of 12.3% for subsequent major surgery (component resection, muscle flap coverage, or amputation) or 10.5% for deep infection. This systematic review fails to focus on important outcomes that are needed for shared decision making discussions.

Based on the NQF 1550 quality measures and including symptomatic DVTs, appropriate outcomes for analyses would be:

(1) Pulmonary embolus
(2) Fatal pulmonary embolus
(3) Wound infection
(4) Periprosthetic joint infection
(5) Surgical site bleeding
(6) Death
(7) Symptomatic deep vein thrombosis

If the systematic review is to proceed to publication, new analyses must be restricted to these appropriate outcomes selected by CMS so that differences in important outcomes are not obscured by minimally relevant outcomes.

Since the Pulmonary Embolism Prevention trial [8] compares aspirin to placebo and no other orthopaedic VTE prophylaxis trial uses a placebo comparator, it is not possible to perform network meta-analyses including aspirin or placebo. Therefore, network meta-analyses are improper analytic tools for this systematic review. Because industry has not used aspirin as a comparator in orthopaedic VTE prophylaxis trials, industry bias [7] is worsened by the selection of network meta-analyses for comparative effectiveness. Pooled analyses of randomized controlled trials allow the comparison of treatments when direct comparisons are not available. A pooled analysis [6] comparing aspirin (ASA) to low molecular weight heparins (LMWH), pentasaccharides, and vitamin K antagonists (VKA) found no significant difference in rates of symptomatic DVT, PE, or fatal PE. However, the relative risks of surgical site bleeding are 6.38 (95% CI 4.56-8.92) for LMWH vs ASA, 4.88 (95% CI 3.28-7.27) for VKA vs ASA, and 4.16 (95% CI 2.83-6.13) for pentasaccharides vs ASA. Direct factor Xa inhibitors (FXaI) were not available at the time of the pooled analysis. However, a meta-analysis by Russel and Huo [18] found no difference in major bleeding, reoperation for bleeding, or post-operative wound infections when comparing FXaIs and LMWHs. Jameson *et al* [19] reported on English hospitals that switched from LMWHs to FXaIs and found a significant increase in total wound complications (LMWH vs FXaI relative risk 0.72, 95% CI 0.58-0.90). Therefore, FXaIs have a higher risk of wound complications than LMWH and LMWHs have the highest relative risk of surgical site bleeding in the above pooled analysis.

The systematic review update concludes by stating “While a large body of RCT evidence exists on comparative effectiveness and harms of venothromboprophylaxis interventions after major orthopedic surgery, none of the [key questions] are fully or adequately addressed.” Based on this conclusion, how can this review committee make recommendations that conflict with the American Academy of Orthopaedic Surgeons and American College of Chest Physicians evidence-based clinical practice guidelines [1, 2] that reviewed ALL the evidence and include aspirin for VTE prophylaxis after THA, TKA, and HFS? There is no additional evidence since these guidelines to warrant different conclusions. This “update” confuses existing evidence-based clinical practice guideline recommendations and recommends industry biased “evidence” to the detriment of our patients.

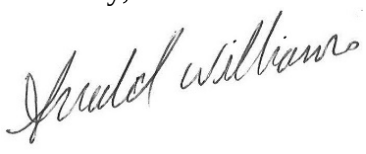
For patients undergoing THA, TKA, or HFS without additional VTE risk factors, aspirin is the most cost-effective VTE prophylaxis option [5]. Potent anticoagulants are associated with a higher all-cause mortality rate after THA and TKA [20]. The most important clinical question facing patients and orthopaedic surgeons is what VTE risk factors increase the risk of a VTE event to a level that the risks of surgical site bleeding and death are outweighed? Several protocols have been described for risk stratifying major orthopaedic surgery patients [21-23]. The systematic review update provides no evidence on additional VTE risk factors for THA, TKA, and HFS patients.

The triple aim outlined by Donald Berwick is: (1) improving the health of populations, (2) enhancing the patient experience of care, and (3) reducing the per capita cost of health care. The triple aim has been updated to the quadruple aim: (4) improving the work life of health care clinicians and staff [24]. Risk-stratified use of aspirin for major orthopaedic surgery VTE prophylaxis: (1) improves patient outcomes by reducing the rate of VTE events by 54% and 30 day non-elective re-admissions by 67% (study year 3) [23] and reduces 90 day all-cause mortality [20]; (2) improves the patient experience with shared decision making regarding VTE prophylaxis and reducing surgical site bleeding [6] and surgical site bleeding complications [17]; (3) reduces the per capita costs of orthopaedic surgery patients because aspirin is cost-effective [5] and reduces 30 day non-elective re-admissions [23]; and (4) improves the work life of orthopaedic surgeons by providing orthopaedic surgeons the autonomy to do what is best for their patients based on the evidence.

We respectfully request that AHRQ address these significant methodological flaws and not publish this “Systematic Review Update” because the exclusion of aspirin from the evidence review and analysis will harm our patients [19].

If you have any questions on our comments, please do not hesitate to contact William Shaffer, MD, AAOS Medical Director by email at shaffer@aaos.org.

Sincerely,



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