Comparative Effectiveness Review Disposition of Comments Report

Research Review Title: Venous Thromboembolism Prophylaxis in Major Orthopedic Surgery: Systematic Review Update

Draft review available for public comment from July 27, 2016 to August 23, 2016.

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Comments to Research Review

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The tables below include the responses by the authors of the review to each comment that was submitted for this draft review. The responses to comments in this disposition report are those of the authors, who are responsible for its contents, and do not necessarily represent the views of the Agency for Healthcare Research and Quality.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	General Comments	It was very helpful to view the original report from 2012 and rationale for the new study. The report is very clinically relevant and meaningful. VTE after major orthopaedic surgery is important to prevent as it can lead to mortality and chronic venous disease.	Thank you.
Peer Reviewer #1	General Comments	As a researcher, I have attempted to examine the methods of VTE prophylaxis in major orthopaedic surgery and found it very frustrating due to the numbers of variables involved. This study clearly outlines and defines all of those variables and clarifies various methods used in treatment and outcome measures.	Thank you
Peer Reviewer #1	General Comments	This study is very valuable as it helps the practitioner and researcher clarify those many variables into understandable and clear results. The overall organization is very logical based on all of those variables and easy to follow. The narrative portions are well labeled and summarized and the tables and figures visually summarize the data.	Thank you
Peer Reviewer #1	General Comments	All elements of a well written report are present leaving few questions for the reader to ponder the purpose, methods, results, search criteria, etc.	Thank you

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #2	General Comments	The report is clinical meaningful, and the key questions chosen by the authors are central to the investigation and use of different therapeutics for venous thromboembolism prophylaxis. The key questions are explicitly stated. The target population is explicitly stated; however, while I assume the audience for the report includes clinicians, researchers, and policy professionals, it is never explicitly stated.	Thank you. The front matter describes the purpose of this report: "This report is intended to help health care decisionmakers—patients and clinicians, health system leaders, and policymakers, among others—make well-informed decisions and thereby improve the quality of health care services."
Peer Reviewer #3	General Comments	This comprehensive update provides a methodologically excellent analysis of the current literature regarding VTE prophylaxis following arthroplasty and hip fracture.	Thank you

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	General Comments	There are two significant issues which limit the utility of this report: 1. The use of DVT as a proxy for clinically symptomatic PE (intro p. xii); given the documented risk of complications related to the development of hematoma/hemarthrosis especially following TKR, the orthopaedic community has adopted the latter as the appropriate outcome measure for efficacy of prophylaxis. The authors correctly point out that post-phlebitic syndrome can be a significant clinical problem however it is relatively rare and it trumped by risk of bleeding into a surgical wound with subsequent risk of infection and wound compromise.	Throughout the revised report we have made explicit the caveat that total DVT (including asymptomatic DVT) is an outcome of questionable clinical values, but also that total DVT was most commonly reported while symptomatic DVT and PE were more infrequently reported. These additions are in the abstract, start of the Introduction, the start of the Discussion, Evidence Limitations, and the Conclusions.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #3	General Comments	2. There has been a dramatic shift over the past five years in perioperative management of elective total joint patients with early mobilization and decreased use of narcotics (as part of a multi-model pain/nausea regimen). The National Surgical Quality Improvement Project (NSQIP) 2015 expected rate for orthopaedic VTE within 30 days of hospital discharge is 1.14% (CI 0.93-2.76%). Therefore, the risk of Doppler/venogram-proven DVT in the RCTs analyzed by the authors does not reflect current clinical practice in arthroplasty surgery. I encourage including the comments in (a) above [ie, this comment and the one immediately above].	Based on the 2012 VTE report and a non-systematic search for more recent evidence, it is not clear if or how the underlying rate of VTE has changed over time. Presumably today's rates of VTE reflect near-universal use of VTE prophylaxis, even if "only" mechanical or earlier mobilization. Without evidence of substantial differences in underlying VTE rates between existing studies and clinical practice, we remain silent on the issue. However, we have added a sentence to the start of the Introduction reflecting increasing use of early mobilization and decreasing use of narcotics. Throughout the revised report we have made explicit the caveat that total DVT (including asymptomatic DVT) is an outcome of questionable clinical value.
Peer Reviewer #3	General Comments	The authors are encouraged to incorporate this changing perspective on VTE into their final summary and conclusions to ensure a coherent view of current VTE prophylaxis following TJA.	Throughout the revised report we have made explicit the caveat that total DVT (including asymptomatic DVT) is an outcome of questionable clinical value.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	General Comments	This review is an update of the 2012 VTE report. The authors did a surveillance review of new studies to help determine the scope of the updated report. Standard systematic review methods were used and the outcomes were clearly delineated. The statistical analysis approach is generally sound and some specific comments are provided below.	Thank you
Peer Reviewer #4	General Comments	Overall, there are a large number of studies, but the number of studies in each meta-analysis is small. Many comparisons from the network MA are based on indirect comparison with one study, and the true value of such network MA seems to be limited	This statement is true.
TEP Reviewer #1	General Comments	The report addresses critical questions in the area of VTE prophylaxis in orthopedic surgery. It is very well focused and writte4n.	Thank you
TEP Reviewer #2	General Comments	Overall it is a good report. The used defendable methods and described things pretty well so as to avoid ambiguity.	Thank you
TEP Reviewer #3	General Comments	The report is clinically meaningful with the population and audience clearly defined. The key questions are appropriate.	Thank you

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #4	General Comments	This report was a Herculean effort to analyze the extant literature on the important issue of VTE following hip and knee arthroplasty, and hip fracture surgery. The authors are to be commended for their work.	Thank you very much.
TEP Reviewer #4	General Comments	The target populations are not sufficiently defined: did the analyses include both primary and revision THR?, primary and revision TKR? Tricompartmental knee replacement and unicompartmental knee replacement There is a major difference in the complexity, operative time, soft tissue injury association with revision surgery and partial knee replacement.	We did not exclude studies based on details regarding the type of eligible surgery, related anesthesia management, or perioperative care. Therefore, both primary and revision arthroplasty and unicompartmental and tricompartmental TKR are included. We made explicit in the Methods that different surgical techniques were all eligible and searched for regarding subgroup analysis. We also made more explicit in the Discussion the limitation due to lack of subgroup analyses, including regarding these surgery types.
TEP Reviewer #4	General Comments	Furthermore, "hip fracture surgery" runs the gamut from a simple in situ pinning of a non-displaced fracture with minimal blood loss, to an intramedullary nailing of a complex comminuted fracture with substantial blood loss, to a total hip arthroplasty for a displaced femoral neck fracture. The tissue injury and operative interventions in these situations can be quite different.	We made explicit in the Methods that different surgical techniques were all eligible and searched for regarding subgroup analysis. We also made more explicit in the Discussion the limitation due to lack of subgroup analyses, including regarding these surgery types.

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TEP Reviewer #5	General Comments	The review provides useful analyses and results for management of individuals undergoing major lower extremity surgery. The report is well organized and well written. The syntheses, and discussion provide important recommendations for future research and reporting, which is critical for maximizing the value of research in this area for providers and patients. I did not find any areas of weakness, nor did I have any suggestions for improvement.	Thank you
TEP Reviewer #6	General Comments	This is an important time to update the data for prevention of VTE in major orthopedic surgery. The last update was in 2012 and the data for DOACs was sparse. This now includes this data.	Thank you.

Commentator & Affiliation	Section	Comment	Response
Public reviewer #1. American Academy of Orthopaedic Surgeons (Gerald Williams, Jr., MD; William A. Jiranek, MD, FACS)	General Comments	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	Please see our responses to the more specific comments.

Commentator & Affiliation	Section	Comment	Response
Public reviewer #1. American Academy of Orthopaedic Surgeons (Gerald Williams, Jr., MD; William A. Jiranek, MD, FACS)	General Comments	In 2012, the American College of Chest Physicians (ACCP) released the "Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians EvidenceBased 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.	This systematic review addressed the specific research questions as laid out a priori in the protocol. We included all interventions used for VTE prophylaxis after major orthopedic surgery, including aspirin. We set eligibility criteria to address these questions. Principally, these included RCTs with comparisons of different interventions, for the most part not including placebo or no intervention; we also included larger nonrandomized comparative studies. The lack of comparative evidence regarding aspirin resulted in a lack of evidence-based conclusions regarding aspirin, in the context of the research questions and study eligibility. We did not base conclusions on expert opinion or physiological assumptions. This review is one piece of evidence and does not attempt to cover all evidence that might be of interest to guideline development organizations. We have re-reviewed the very large observational study from the UK with over 100,000 study participants (Jameson 2011). Based on this study, we have added low strength of evidence findings regarding LMWH vs. aspirin in THR patients (similar risks of DVT, PE, and major bleeding).

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Public reviewer #1. American Academy of Orthopaedic Surgeons (Gerald Williams, Jr., MD; William A. Jiranek, MD, FACS)	General Comments	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 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 IIImediated selective factor Xa inhibitors (ATIII), direct factor Xa inhibitors (FXaI), or direct thrombin inhibitors (DTI).	We agree with the concern about biases that determine what interventions get studied and which studies get reported and have added this concern to the discussion section. Specifically, we discuss how LMWH (enoxaparin especially) are relatively over-researched and aspirin, warfarin, and mechanical devices are under-researched. We also highlight potential sources of bias related to industry funding (thus potentially favoring LWMH etc.). It was beyond the scope of this review to examine indirect evidence beyond the comparisons described in the scope of the *a priori* protocol criteria, namely direct comparison studies (RCTs and large nonrandomized). These are the same basic criteria as used in 2012. However, guideline groups may often consider other indirect evidence in making their recommendations. However, we re-reviewed the very large observational study from the UK with over 100,000 study participants (Jameson 2011). Based on this study, we have added low strength of evidence findings regarding LMWH vs. aspirin in THR patients.

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Public reviewer #1. American Academy of Orthopaedic Surgeons (Gerald Williams, Jr., MD; William A. Jiranek, MD, FACS)	General Comments	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].	We highlight the preponderance of industry funded studies and some of the weaknesses in the literature, including the lack of clinically meaningful outcomes, and the lack of appropriate comparisons. However, this report reviews the evidence as it exists, comments on problems with the evidence, and suggests future research.
Public reviewer #1. American Academy of Orthopaedic Surgeons (Gerald Williams, Jr., MD; William A. Jiranek, MD, FACS)	General Comments	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.	Despite the concerns and limitations of total DVT as an outcome, we decided to keep it as an outcome of interest after discussion with our key informants, technical experts, and other informants, including members of AAOS and ACCP. Despite it's being commonly thought of as a poor proxy for PE, it is most commonly reported in studies and remains of interest, at least in the research community. Users of our review, including guideline development organizations, are free to use or discount various analyses and findings of this review. Throughout the revised report we have made explicit the caveat that total DVT (including asymptomatic DVT) is an outcome of questionable clinical values.

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Public reviewer #1. American Academy of Orthopaedic Surgeons (Gerald Williams, Jr., MD; William A. Jiranek, MD, FACS)	General Comments	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.	As per the protocol for our review, this RCT did not meet eligibility criteria. In contrast with the 2012 review, we did not have a Key Question regarding interventions versus placebo. This is why this trial did not meet criteria. However, regarding the broader concern of a bias against aspirin, the revised report has more explicit conclusions about LMWH versus aspirin, based on available observational data.

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Public reviewer #1. American Academy of Orthopaedic Surgeons (Gerald Williams, Jr., MD; William A. Jiranek, MD, FACS)	General Comments	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).	The current systematic review includes clinical and patient-centered outcomes. The list of included outcomes was decided with input from KIs and TEP and was defined in the publicly posted surveillance review, which included the preliminary protocol. They include the listed NQF 1550 quality measure outcomes, except for acute myocardial infarction and pneumonia (which were rarely, if at all, reported in the research studies).

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Public reviewer #1. American Academy of Orthopaedic Surgeons (Gerald Williams, Jr., MD; William A. Jiranek, MD, FACS)	General Comments	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	Symptomatic DVT was an outcome of interest included in the review This review was not restricted to evaluation of NQF measures/outcomes, or only to outcomes that a single organization is interested in.
Public reviewer #2. Medtronic (Michael Tarnoff, MD, FACS)	General Comments	Appendix Table F4 This table is mentioned several times throughout the document but is not available for review. Would like to request opportunity to review Appendix Table F4 as well as the other Appendices referenced in the Text.	Thank you for noting this typo. Appendix F has now been correctly labeled in the Appendix file.

Commentator & Affiliation	Section	Comment	Response
Public reviewer #1. American Academy of Orthopaedic Surgeons (Gerald Williams, Jr., MD; William A. Jiranek, MD, FACS)	Executive Summary	"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 there may be problems with the concept of total DVT, as the report highlights, it is the predominant outcome reported by studies. This is problematic, as the report highlights. Throughout the revised report we have made explicit the caveat that total DVT (including asymptomatic DVT) is an outcome of questionable clinical value. We have added additional information about the (lack of) possibility of performing network meta-analyses on other outcomes (Results/KQ 5/Key Points, and other places) . We did not include asymptomatic DVTs (alone) as an outcome of interest. Of note, vascular surgeons, who deal with the long term sequelae of DVTs (whether initially symptomatic or not) disagree that asymptomatic DVTs have no clinical significance.

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Public reviewer #1. American Academy of Orthopaedic Surgeons (Gerald Williams, Jr., MD; William A. Jiranek, MD, FACS)	Executive Summary	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.	Thank you for noting this omission. We have added some text linking major bleeding to adverse clinical outcomes (and increased resource use). We have included some relevant references, some from the 2012 VTE report to the Introduction. Unfortunately, as we note repeatedly, the evidence fails to focus on many important outcomes of interest to clinicians and policymakers.

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Public reviewer #2. Medtronic (Michael Tarnoff, MD, FACS)	Executive Summary	TEXT ES 13: "Comparisons of mechanical VTE prophylaxis versus no VTE prophylaxis did not provide strong evidence that mechanical prophylaxis reduced the risk of VTE, including, specifically, DVT." COMMENT: It is unclear which studies were used that compared mechanical VTE prophylaxisvs. no VTE prophylaxis for this review and the type of orthopedic surgery to which this finding applies.	In the Introduction we are summarizing the findings of the 2012 VTE report in regard to placebo and no treatment comparisons. The specific details and findings of those studies can be found in the 2012 VTE report.
Public reviewer #2. Medtronic (Michael Tarnoff, MD, FACS)	Executive Summary	TEXT: ES-24 Table A THA. Summary of Sufficient evidence lists Mechanical vs. UFH as 3 RCTs (N=434). COMMENT: Is this correct, or is this meant to be Mechanical vs. VKA? Per sections earlier, only one RCT compared Mechanical and UFH, and 3 were Mechanical vs. VKA.	Thank you for noting this typo (This has been changed to VKA per the results from KQ1
Peer Reviewer #1	Introduction	This section is well organized and clear—especially the reason for revisiting the 2012 study.	Thank you
Peer Reviewer #2	Introduction	The introduction discusses the background and importance of venous thromboembolism prophylaxis. Key questions are stated succinctly. The authors' analytic framework and scope of the review are all addressed.	Thank you

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #1	Introduction	Introduction: Very clear with appropriate references.	Thank you.
TEP Reviewer #2	Introduction	Page 6; Line 16 — use term unfractionated heparin vs. UFH even after defined (this happens in a few other places in the report as well and they should check for use of the abbreviations).	The main report repeats definitions of abbreviations in each "chapter". In the executive summary we removed most of the duplication of abbreviations across executive summary "chapters". However, we redefined the intervention abbreviations in the Methods/Interventions of Interest section. In addition, when we talk about unfractionated heparins as a class we use the abbreviation UFH. To improve clarity, when we talk about heparin as a specific drug, we use the term "heparin".
TEP Reviewer #2	Introduction	Page 16; Line 29 — "Interior" Vena Cave should be "Inferior". This also speaks to the need to re-read the report for consistency and for typos such as these which are not uncommon.	Thank you for pointing it out; this typo has been fixed.
TEP Reviewer #2	Introduction	PTS or Post-thrombotic syndrome is called in intro post-phlebitis syndrome which is not consistent with the rest of the paper.	This has been fixed
TEP Reviewer #3	Introduction	The introduction explained clearly the report and its intent.	Thank you
TEP Reviewer #4	Introduction	No additional concerns	Thank you

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #5	Introduction	The introduction presents the necessary background and rationale for the work and is well written	Thank you
TEP Reviewer #6	Introduction	Scope of the problem well defined.	Thank you
Peer Reviewer #1	Methods	This section is very complete and clear. All elements are present and outlined logically. The organization around the Key Questions and then by surgery type is also very clear and logical.	Thank you
Peer Reviewer #1	Methods	I have twosuggestions both of which will add to clarity in this section. 1)For the Grading and Strength of Evidence include a reference to the EP (Evidence Profile) tables.	To add clarity, we have repeated the reference to the relevant AHRQ Methods paper at the end of the Grading the Strength of the Evidence section.
Peer Reviewer #1	Methods	2) I also suggest that in the narrative of this section to include (SoE) refers to Strength of Evidence.	Thank you for noting that we were not consistent in our abbreviating strength of evidence and defining the abbreviation (SoE). We have fixed this.

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Peer Reviewer #2	Methods	The statistical methods are appropriate. Inclusion and exclusion criteria are discussed in a straight forward manner and are justifiable. The authors' search strategy is explicitly stated, logical, and appropriate to this review. My only concern involves the authors' grouping of studies in which A: Industry funding was not addressed by the authors with B: Non-industry funded studies as explicitly stated by the authors. While the number of studies in which the authors explicitly stated they received no funding from industry was only 13%, the results of these studies, as a separate category, would be useful to report due to concern over biased data resulting from industry funding. Otherwise, the reader cannot judge for himself the role, if any, industry funding played in study results.	In the "Cross-Study Subgroup Analyses" sections we provide the results of just the industry funded and no industry funding studies . Using statistical techniques we did not find significant evidence of bias (significant differences between industry-funded and other studies). This is described in the Results. However, in the Discussion we do talk about the possibility of bias related to selective outcome reporting and selective choice of treatment comparisons that may relate to possible industry bias. The industry funding status of studies is cited in the overall description of the RCTs and NRCSs and all data are available in the appendixes.
Peer Reviewer #3	Methods	the study appears methodologically sound but beyond the scope of expertise of this reviewer to assess	Thank you
Peer Reviewer #4	Methods	Risk of Bias for observational studies: any assessment for the adjustment of other potential confounding variables, other than different lengths of follow-up?	As noted in the Methods section for NRCS we evaluated "questions from the Newcastle Ottawa Scale about comparability of cohorts, representativeness of the population, and adjustment for different lengths of follow-up".

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Methods	For KQ1, for trials containing arms with different doses, compared to picking the arm with the largest sample size, why not considering combining all the arms? The different arms may have similar sample sizes. It helps to include all relevant data.	There are multiple reasonable approaches for how to deal with multi-arm trials in pairwise meta-analyses. Both this approach and what we did are reasonable options. There is no standard approach for this situation. We chose this one because it's analogous with what we did when we knew the FDA approved dose. We did not think a more complex method was worthwhile. Combining the arms of trials pre-meta-analysis is reasonable but would have required first meta-analyzing the event rates of these together and then incorporating this value into the final meta-analysis. We decided this was not worth the effort or revision to meta-analytic techniques that would have been required. Pooling of the arms would have been simple, but, we believe, inappropriate. Our approach is clean, simple, and appropriate, even if it does not fully incorporate all available evidence.
Peer Reviewer #4	Methods	Pairwise Meta-analysis Based on the literature, REML random effect model likely provides a 95% CI that is too narrow. Peto's method is fine for rare events.	REML is one of the preferred methods for meta-analysis. Simulation studies suggest only small numerical differences in the estimates between REML and profile likelihood. We do not think it is necessary to revise our methodology. We agree about use of Peto.

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Peer Reviewer #4	Methods	Network Meta-analysis Please specify the specific Bayesian model used for network meta-analysis and how to define direct and indirect parameters.	Further details about the Bayesian model have been added to the NMA methods section. In particular, we reference the source of the code, which provides parameter definitions.
Peer Reviewer #4	Methods	Network Meta-analysis Given the data, it is likely very underpowered to test the consistency assumption. The heterogeneity also impacts the power to detect inconsistency. Comment on the implications of such tests	Thank you. We have added this point in the Methods: “However, the inability of the models to detect inconsistency in our evidence base with sparse data may be due to the lack of power rather than suggestive of consistent networks.”

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Methods	Network Meta-analysis Again, compared to using the arm of largest sample size, may combine data from all the arms.	There are multiple reasonable approaches for how to deal with multi-arm trials in pairwise meta-analyses. Both this approach and what we did are reasonable options. There is no standard approach for this situation. We chose this one because it's analogous with what we did when we knew the FDA approved dose. We did not thing a more complex method was worthwhile. Combining the arms of trials pre-meta-analysis is reasonable but would have required first meta-analyzing the event rates of these together and then incorporating this value into the final meta-analysis. We decided this was not worth the effort or revision to meta-analytic techniques that would have been required. Pooling of the arms would have been simple, but, we believe, inappropriate. Our approach is clean, simple, and appropriate, even if it does not fully incorporate all available evidence.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Methods	It is very helpful to add event rates for each section. These are reported in most sections, but still missing in some.	Estimated event rate ranges are provided for all comparisons with meta-analyses (and the network meta-analyses). We did not report these for the many comparisons with only a small number of studies for which we did not conduct meta-analysis. These data can be found in Appendix Table F.
Peer Reviewer #4	Methods	Page 16, DTI vs. UFH, provide the 95% CI for the OR.	This omission has been corrected. The 95% CI has been added.
Peer Reviewer #4	Methods	Network Meta-analysis If the model does not converge, it may indicate the data are not adequate for the net-work MA and the fixed effects model may provide estimates that are over-precise.	When models do not converge, this indicates that the evidence is insufficient to draw inferences/conclusions. Therefore, we do not think such secondary analyses are informative, or would change our conclusions.
TEP Reviewer #1	Methods	The methods are clearly described and complete. In particular, the statistics section is excellent.	Thank you

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #1	Methods	One issue should be considered further. An important consideration in interpreting these results is the use (or not) of imaging techniques (US and venography) to screen for asymptomatic VTE, primarily call DVT. Such VTE often have represented the majority of the positive findings in studies, but their significance is debated. I think the methods should address this issue which should also be reflected in the Results and Discussion.	Throughout the revised report we have made explicit the caveat that total DVT (including asymptomatic DVT) is an outcome of questionable clinical values.
TEP Reviewer #2	Methods	Seuloparin should be semuloparin throughout the manuscript.	Thank you; this typo has been fixed throughout
TEP Reviewer #2	Methods	Why search for TAK422, it is not FDA approved for any indication?	We included in the search and review all relevant interventions, regardless of FDA approval in part because we and the TEP wanted to include all interventions under investigation, including those that may in the future be FDA approved. This was not the only unapproved (or not-yet-approved) drug that was searched.
TEP Reviewer #3	Methods	The inclusion/exclusion criteria is justified with the research strategies explained. The search strategies and outcome measures were explained and understood.	Thank you.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #4	Methods	The major issue with this review that detracts from its clinical utility is that "total DVT" is a determinative end point, and is likely the basis for the comparative efficacy of LMWH in some of the analyses. Following THR and TKR, asymptomatic DVT, particularly those distal to the popliteal fossa, are typically ignored in clinical practice because of their lack of clinical relevance.	Throughout the revised report we have made explicit the caveat that total DVT (including asymptomatic DVTs and DVTs distal to the popliteal fossa) is an outcome of questionable clinical values.
TEP Reviewer #4	Methods	What would happen to these analyses if only the clinically relevant DVTs (symptomatic and/or proximal DVTs) were the end point? Would there be any meaningful differences?	We have added additional information about the (lack of) possibility of performing network meta-analyses on other outcomes (Results/KQ 5/Key Points, and other places). Analyses of symptomatic and proximal DVTs are analyzed throughout as the evidence allows.
TEP Reviewer #5	Methods	Yes to all of the above. I had no concerns about inc/excl criteria. The search strategies were explicitly described, and were appropriate for the key questions. The outcomes were appropriate. Although I cannot comment on the more sophisticated methods, I had no concerns about the more traditional methods.	Thank you

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #6	Methods	My only question here is for page 18 l26. Disagreements were discussed within the team. Was there a process for this? Was it consensus? How was coersion avoided? was there a tie-breaker?	. We have revised the wording to "Disagreements were resolved by open, free-flowing discussion among the team to achieve consensus."
Public reviewer #1. American Academy of Orthopaedic Surgeons (Gerald Williams, Jr., MD; William A. Jiranek, MD, FACS)	Methods	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 4 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.	The listed 8 outcomes were all included in the review, although most had insufficient evidence regarding them. We strongly disagree with the concept that our review should be restricted to NQF 1550 quality measures/outcomes. However, users of the review are welcome to focus on the outcomes of interest to them.
Public reviewer #1. American Academy of Orthopaedic Surgeons (Gerald Williams, Jr., MD; William A. Jiranek, MD, FACS)	Methods	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.	Just because an intervention of interest is not adequately included in network meta-analysis does not make the tool improper for this systematic review. We have better emphasized that the conclusions are relevant only to subsets of the interventions (and outcomes) that were adequately included in the analyses.

Commentator & Affiliation	Section	Comment	Response
Public reviewer #1. American Academy of Orthopaedic Surgeons (Gerald Williams, Jr., MD; William A. Jiranek, MD, FACS)	Methods	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.	We would instead suggest that industry bias (in choice of outcomes and interventions) is made more transparent by the process of network meta-analysis. The sparseness of connections within the network to aspirin (and mechanical devices) is presented graphically. Simply because an intervention of interest in not adequately included in network meta-analysis does not make the tool improper for this systematic review. Furthermore, network meta-analysis was only one method for evaluating comparative effectiveness.

Commentator & Affiliation	Section	Comment	Response
Public reviewer #1. American Academy of Orthopaedic Surgeons (Gerald Williams, Jr., MD; William A. Jiranek, MD, FACS)	Methods	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.	Pooled analyses are highly flawed analyses that do not meet any current standards of appropriate systematic review (except under certain rare conditions). Pooling and directly comparing interventions across studies that have no common comparator is highly problematic. In the cited analysis [PMID 19628366] the individual study arms from the RCTs were analyzed as single group cohorts and chi squared tests were used to compare interventions (from one set of studies) to other interventions (for another, mostly non-overlapping, set of studies). There is no way to account for large differences in populations, settings, and so forth across single-group studies. There is serious confounding bias by indication. As an example, a possible explanation of Brown's findings is that aspirin studies are more likely to include patients at low risk for VTE than LMWH studies (who possibly recruited patients at higher risk for VTE). Therefore similar rates of VTE between aspirin and LMWH arms may indicate that LMWH is more effective (reducing risk of VTE in high-risk patients down to the level of low-risk patients [who got aspirin]). This is [response continued in next row]

Commentator & Affiliation	Section	Comment	Response
			[response continued from prior row] clearly speculative, but highlights the flaws to pooling analyses. The trials included in Russell and Huo were included in our systematic review, but we did not combine THA and TKA studies. Jameson et al 2012 (PMID 22832942)., unfortunately, combined TKA and THA (and included “hip resurfacing”), and thus did not meet our eligibility criteria. Our review is considerably more inclusive and expansive than these given examples. While it may be appropriate for a guideline development organization to use a more expansive set of evidence to support their guidelines (e.g., inclusion of single group studies, pathophysiological concepts, single studies), we conducted our review and based our conclusions on a specific, protocol-driven comparative effectiveness review.

Commentator & Affiliation	Section	Comment	Response
Public reviewer #2. Medtronic (Michael Tarnoff, MD, FACS)	Methods	In general, we support the sound methodology, through review and analysis that AHRQ has prepared. However, we would like to make note that the requirement for randomized, prospective or retrospective studies to be 750 patients per surgery type, per study, is extremely limiting for the evidence on mechanical devices. Device studies are typically smaller in size than pharmaceutical studies and thus most mechanical prophylaxis evidence is excluded by this requirement. Therefore, the AHRQ systematic review misses evidence that is relevant to clinician decision making and patient centered benefit.	We agree that this is an important limitation that pertains particularly to mechanical devices. We have added this specific limitation to the discussion. We suggest for a possible future updated AHRQ review of this topic, that smaller observational studies of mechanical devices (and possibly other interventions) be included.
Public reviewer #2. Medtronic (Michael Tarnoff, MD, FACS)	Methods	Noting that the date in the draft for the final search reads “December 23, 2015 [to be updated]”, and given the relative infrequency of review updates of this caliber, Medtronic would like to request AHRQ consider a search of the databases for updates since December 2015. Importantly, two new studies have been published since the search was completed and provide quality evidence for mechanical prophylaxis.	We have updated the search to June 3, 2016 and new studies have been added. Thank you for noting the two additional studies. Eisele 2007 (PMID 17473143) has been added. Unfortuntely, Nam 2016 (PMID 26777547) did not report hip and knee arthroplasty separately; therefore this study was not eligible for our review. Nam was primarily interested in evaluating risk stratification, which is an interesting related topic, but not a research question addressed by this review.

Commentator & Affiliation	Section	Comment	Response
Public reviewer #2. Medtronic (Michael Tarnoff, MD, FACS)	Methods	Nam et al. (2016)1 presented the use of a risk stratification protocol prior to assignment of the patients to either mechanical compression (IPC) with aspirin (for routine risk) or warfarin (for high-risk) after THA (N=1859). The rate of VTE was 0.5% in the routine versus 0.5% in the high-risk cohort within 6 weeks postoperatively (P=1.00). However, patients in the routine risk cohort had a lower rate of major bleeding (0.5% versus 2.0%, P=0.006) and fewer wound complications (0.2% versus 1.2%, P=0.01). The authors concluded that use of the risk stratification and mechanical prophylaxis allowed avoidance of complications associated with use of warfarin. Odeh et al. (2016)2 retrospectively reviewed 2611 total joint replacements and found similar results to Nam et al., although the manuscript failed to separate the analysis for TKA from THA and would therefore not meet the inclusion criteria for AHRQ's analysis. Nevertheless, we have provided it for your consideration to substantiate the findings of Nam et al.	While we agree that the question of risk stratification is important, such strategies (as opposed to specific interventions) were not part of our Key Questions and thus were not part of our eligibility criteria. If AHRQ determines that it is of value to update the current review, we believe this will be an important topic to discuss; whether the next update should include an expansion to cover this topic.

Commentator & Affiliation	Section	Comment	Response
Public reviewer #2. Medtronic (Michael Tarnoff, MD, FACS)	Methods	Additionally, one large trial (Eisele et al., 2007) is older than the dates of this search, but it was not included in the 2012 review, and thus was not carried over to this analysis. This large randomized trial is considered Level I evidence in support of mechanical prophylaxis. A total of 1803 patients in this study were prospectively randomized to LMWH or LMWH and IPC. Significantly fewer DVTs occurred in the group randomized to the LMWH and IPC group (p=0.007). While the study enrolled patients undergoing several types of surgery (THA, TKA, Fracture, etc.) the results are delineated by surgery category in the manuscript.3	We have included this study in the update.
Public Reviewer #3. American Association of Hip and Knee Surgeons (Michael J. Zarski, JD)	Methods	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.	We have added further discussion and highlighting regarding the outcomes that include asymptomatic DVTs. However, these outcomes were included after input from our TEP and in our protocol and could not be dropped arbitrarily.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #3. American Association of Hip and Knee Surgeons (Michael J. Zarski, JD)	Methods	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.	This review does not formally rank the relative importance of outcomes. The review did engage stakeholders in determining key outcomes. . The report does elaborate much more fully on which outcomes are (and are not) reported by studies. There is also discussion about the limitations of the evidence in regard to relatively limited reporting of clinically important VTE as opposed to the problematic outcome total DVT. The conclusions are based on the evidence that address the Key Questions, as stated. The lack of evidence about most outcomes is problematic, as discussed.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #3. American Association of Hip and Knee Surgeons (Michael J. Zarski, JD)	Methods	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.	That the majority of studies used LMWH is no more a challenge to the validity of the network than that many studies had a placebo comparator. We have added more explicit information about our attempt to run network meta-analyses for outcomes other than total DVT (and major bleeding), including symptomatic DVT, proximal DVT, and all PE outcomes. However, due to reporting bias, these networks are too sparse to be interpretable.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #3. American Association of Hip and Knee Surgeons (Michael J. Zarski, JD)	Methods	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 antiplatelet controls in most studies is also limiting.	Inclusion of ascending phlebography (or of asymptomatic DVT) was not an inclusion criterion for meta-analysis. The placebo arms of otherwise included studies were included in the network meta-analyses. Comparisons between all active interventions (including aspirin) were included, although there was a dearth of such studies.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #3. American Association of Hip and Knee Surgeons (Michael J. Zarski, JD)	Methods	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.	We have reviewed and presented all data and conclusions for all outcomes that were predetermined to be of clinical interest, including major bleeding (overall) and specific major bleeding events (eg, requiring transfusion). It is the case that major bleeding was heterogeneously defined (or in many cases undefined) by studies. Too few studies reported specific major bleeding events to allow meaningful conclusions about these important outcomes. These deficiencies are discussed in the Limitations part of the Discussion. We have also added language to our eligibility criteria that we relied on studies to define the outcomes of interest and that we sometimes needed to use our judgment to categorize poorly defined outcomes.

Commentator & Affiliation	Section	Comment	Response
Public Reviewer #3. American Association of Hip and Knee Surgeons (Michael J. Zarski, JD)	Methods	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.	There is very limited comparative evidence on anti-platelet agents. This report represents a systematic review of the existing evidence. It is neither a narrative review that discusses all interventions regardless of evidence nor a clinical practice guideline that must make recommendations regarding all interventions, again regardless of evidence. We have made more explicit throughout the report that aspirin (and mechanical devices, and others) were not adequately studied We have re-reviewed the very large observational study from the UK with over 100,000 study participants (Jameson 2011). Based on this study, we have added low strength of evidence findings regarding LMWH vs. aspirin in THR patients. We reviewed the systematic review in the Bone & Joint Journal (Wilson 2016 PMID 27482017). We used stricter eligibility criteria, particularly related to excluding smaller observational studies and requiring separate analyses in THR, TKR, and HFx surgery. Nevertheless, Wilson included two additional relevant studies, one of which was picked up in [response continued in next row]

Commentator & Affiliation	Section	Comment	Response
			[response continued from prior row] our literature search update and one of which was excluded from the 2012 VTE report for unclear reasons. These have been added. Furthermore, we have re-reviewed the very large observational study from the UK with over 100,000 study participants (Jameson 2011). Based on this study, we have added low strength of evidence findings regarding LMWH vs. aspirin in THR patients.
Peer Reviewer #1	Results	The Results section is also very complete and clear. The only suggestion that I have is that since there is so many results addressed under each Key Question that sub headings include a reference to the Key Question just to refresh the memory of the reader. For example, under Key Question 1 and THR, when the TKR results are presented, I suggest that you label and maybe even restate Key Question #1. There are many pages in-between the results for THR and TKR for KQ1.	KQ (and surgeries in places) have been added to subheads.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	Results	The narrative summaries are clear and concise. I was quite impressed by the number and variety of tables and figures outlining results. They are both clear and helpful.	Thank you
Peer Reviewer #2	Results	Especially within the results section, would recommend showing results for studies separately for A: industry funded studies; B: studies in which industry funding is not addressed; C: studies in which the authors explicitly stated funding was from non-industry sources. If for statistical purposes, it is necessary to group B and C together to draw conclusions, at least these results could be shown separately in the Results section. Otherwise, characteristics of the studies is clearly described. Key messages are explicit, and figures are adequate and descriptive. Inclusion criteria are appropriate.	We have clarified, via citations, which studies are and are not industry funded. Where analyzable, we describe and present results for industry vs. non-industry funded studies. Since we did not find differences, we do not further separate out study results by funding source.
Peer Reviewer #3	Results	succinct and well presented	Thank you
Peer Reviewer #4	Results	In some cases, the range of event rates is large, for example, for total VTE (page 18, lines 53-54), the event rate could be 1.1 – 43.8% -- different definition of VTE? Different patient populations?	We have added in a comment that the different rates could not be explained and that both lowest and highest rates were found in studies that both used mandatory bilateral venography (page 19).
Peer Reviewer #4	Results	Page 37, subgroup analysis: p < 0.03? P <0.20? Provide exact P-values.	The P values were extracted from the full text, they only reported as P<0.03, P <0.20.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Results	The application of REML RE model vs. Peto's FE model does not seem to be very consistent. For example, Figure 1. tkr.3., the RE model is used, and Figure 1. tkr.9., a Peto's FE model is used. Figure 3.dose.tkr.5., RE model is used. In these cases, the event rates are all pretty rare. Figure 3duration.thr.3, Peto FE model is used, but the event rate is not that rare. Conduct sensitivity analysis using either model to see how the model choice might impact the outcomes.	We have reviewed our application of our criteria for using Peto or not and have made corrections. Where the Peto method was used, we now comment on results with alternative models (no differences in conclusions were found).
Peer Reviewer #4	Results	Page 61, lines 16-17: 300 specific comparison-outcome pairs evaluated by only one single study? Clarify?	We have clarified the language (p. 61): "**Each of the** more than 300 specific comparison-outcome pairs that were evaluated by only a single study are presented only in Appendix F."
Peer Reviewer #4	Results	Results for network MA For each net-work MA, clarify whether the RE vs. FE models were used.	All network meta-analyses use random effects model. We do not know of any instance where a fixed effect model network meta-analysis would be appropriate. The use of random effects model network meta-analysis is stated in the Methods section.
Peer Reviewer #4	Results	Results for network MA The topology maps are very helpful to see the overall evidence base for the network MA. It will be useful to provide the number of events and the number of patients for each node.	We have improved the topology maps. The node sizes are related to total sample size. This is standard for presenting these maps. We think this is adequate.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Results	Results for network MA One general comment is that for many significant comparisons from the network MA, even for THP where there are the most studies, they are purely based on indirect evidence (given the node-splitting method often could not detect inconsistency) and quite a few of such comparisons are based on only one study. It is doubtful that such significant comparisons are reliable and provide useful insights on the indirect comparison. For example, Figure 5.thr.7., most comparisons have only one study. Another example is Figure 5.tkr.3. that are associated with many significant comparisons, but the true value of such network MA is limited. Similarly for Figure 5.hfx.3., 5.hfx.1 and other comparisons.	We agreed that this was an important issue in regards to deriving conclusions from the network meta-analyses. For this reason, we restricted our conclusions to those interventions (or classes) for which there were a "sufficient" number of direct comparisons within the network. Therefore, we did not come to conclusions about interventions with only a single study (connection) in the network.
Peer Reviewer #4	Results	Results for network MA For the many significant comparisons, do the FE model provide a role to make is easier to see significant comparisons?	We do not conduct fixed effect analyses except under rare circumstances where the relevant assumptions are reasonable. We do not think that the assumptions for fixed effects models are plausible for network meta-analyses and therefore, have not done these. It is unclear why we would choose an analytic method for the purpose of making it easier to see significant comparisons.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #4	Results	Results for network MA More helpful to focus on results that are based on more studies.	This is what is done. We base our conclusions regarding the network meta-analyses on those interventions with more direct comparisons ("ignoring" single-study nodes).
Peer Reviewer #4	Results	Results for network MA Estimated event rates are very useful information and could provide the comparative results into context.	Thank you.
TEP Reviewer #1	Results	The results are clearly presented. I have 2 suggestions: In sections relating to anticoagulant dose, a distinction is made between "high" and "low" dose. However, these are not defined and many doses may have been used. This should be explained better.	Thank you for this suggestion. We have added in information about the relative doses in the Key Points.
TEP Reviewer #1	Results	2. Similarly, prophylaxis for "short" and "longer" is compared. These times need to be defined.	Thank you for this suggestion. We have added in information about the relative durations in the Key Points.
TEP Reviewer #2	Results	Page 22 Key Points in ES: Sometimes VTE is defined but sometimes it is not.	In the Key Points we have better clarified when we mean VTE overall or specific types/definitions of VTE.
TEP Reviewer #2	Results	Page 23, Line 31: How many RCTs for the "symptomatic VTE comparison?	We have added the number of RCTs (throughout). Thank you.
TEP Reviewer #2	Results	Page 23, Line 44: "The" spelled incorrectly and "with VKA" is redundant. The entire sentence is a bit awkward as written.	This has been corrected. Thank you

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #2	Results	Page 23, Line 47-48: Is this UFH or VKA that is being compared. It is impossible to tell but there is at least one error here. This underscores the need to recheck the data presented to assure it is true and accurate.	This was a typo. It should have been VKA and has been corrected.
TEP Reviewer #2	Results	Page 24, Line 15-16 and in Lines 53-54. Why only report a range of estimates with four RCTs? That seems a violation of your stated methods.	We have added footnotes throughout to explain when there are 4 or more RCTs but too few with events to allow meta-analysis, per protocol. Frequently for PE and major bleeding, numerous studies had no events.
TEP Reviewer #2	Results	Page 25; Line 10: Add "stage" between CKD and 3A.	This has been added.
TEP Reviewer #2	Results	Page 32, Lines 46-50: Enoxaparin was said to not have been compared to dalteparin but in KQ2 it says that is was (KQ2, lines 40-41). This seems to be an error either here of in the above section and should be reassessed.	The comparison between enoxaparin and dalteparin in KQ 2 was for patients with hip fracture surgery. The lack of comparison between the two drugs for KQ 5 related to total hip replacement. The direct comparison between the two drugs is included in the network meta-analysis for hip fracture surgery.
TEP Reviewer #3	Results	The results are presented in great detail. Unfortunately, with the variety of comparisons in the research, it is difficult to determine which dvt prophylaxis provides the best outcome for the surgery-this is not a reflection of the study but rather a reflection of the research available.	We agree that limitations in the evidence make it difficult to determine which intervention provides the best outcomes. The Discussion summarizes the evidence as it is and we discuss the limitations and make future research recommendations based on these limitations.. Thank you.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #5	Results	The results are well described: comprehensive and well organized. I found nothing missing.	Thank you
TEP Reviewer #6	Results	I found that the supplemental materials were very complete and enhanced the main article. For most reading this, the abbreviated form was good and the summary row for each recommendation describing the evidence was excellent. I felt that the explanations of the reasons why some modalities were favored (in the cases were there was not strong evidence or not concurring evidence) was well done	Thank you
Public reviewer #2. Medtronic (Michael Tarnoff, MD, FACS)	Results	TEXT P33-35: Table X1. THA COMMENT: According to this table, 3 RCTs addressed Mechanical vs. UFH. However, on page 32 (see line below) only one RCT is listed for Mechanical Device vs. UFH. (Ref 78). We believe review of all 3 RCTs is essential for a comprehensive comparative evaluation.	Thank you for noticing this error. We left out the words “Mechanical vs. VKA” in the appropriate cell of the table to state that the last 7 rows referred to mechanical vs. VKA. This has been corrected.

Commentator & Affiliation	Section	Comment	Response
Public reviewer #2. Medtronic (Michael Tarnoff, MD, FACS)	Results	TEXT P 32: Mechanical Device vs. UFH, One RCT (N=132) compared a mechanical device and UFH. (Ref 78) COMMENT: Table EP1 on page 136 for Mechanical vs. UFH. lists 3 RCTs (N=434) and the comment in the column to the right states "favors VKA". Is the Intervention column mislabeled in this table as Mechanical vs. UFH instead of Mechanical vs. VKA? Based on references reviewed, this seems to be the case. If this is mislabeled, then the analysis of Mechanical vs. UFH is missing from the table EP1	Thank you for noticing this error. We left out the words "Mechanical vs. VKA" in the appropriate cell of the table to state that the last 7 rows referred to mechanical vs. VKA. This has been corrected.
Public reviewer #2. Medtronic (Michael Tarnoff, MD, FACS)	Results	TEXT P 32:: Mechanical Device vs. VKA, Three RCT (N=434) compared a mechanical device and VKA. COMMENT: (Ref 79-81). See above, mislabeled?	Thank you for noticing this error. We left out the words "Mechanical vs. VKA" in the appropriate cell of the table to state that the last 7 rows referred to mechanical vs. VKA. This has been corrected.

Commentator & Affiliation	Section	Comment	Response
Public reviewer #2. Medtronic (Michael Tarnoff, MD, FACS)	Results	TEXT P 32: Mechanical Device vs. VKA, Three RCT (N=434) compared a mechanical device and VKA. (Ref 79-81)….A U.S.- based registry NRCS of 14,657 THR patients found no significant difference in total PE between mechanical devices and LMWH (OR 1.34, 95% CI 0.51 to 3.53), controlling for age, sex, anesthesia risk category, and use of general anesthesia… COMMENT: Is this an error to include LMWH in this section? Perhaps was meant to read VKA. Is the data correct for VKA or LMWH?	Thank you for noticing this error. We left out the words “Mechanical vs. VKA” in the appropriate cell of the table to state that the last 7 rows referred to mechanical vs. VKA. This has been corrected.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	Discussion /Conclusion	It is very clearly stated that not all of the key questions were answered which answeres the purpose of the study. Major findings are well summarized outlining the most effective methods based on evidence. Limitations of the Evidence are clear stating that despite the large number of studies the researches could draw conclusions from only a small subset of studies. This I also found to be true when attempting to draw conclusions about this topic. The future research section challenges VTE prevention researchers to design a study with a clear comparative intervention and a clear outcome measurement.	Thank you
Peer Reviewer #2	Discussion /Conclusion	The authors clearly and adequately discuss problems and limitations with data from current research, and at the same time, make clear where new research is needed, and what types of study design would be most helpful in further answering the key questions. Limitations are discussed. No important literature that I know of has been omitted.	Thank you
TEP Reviewer #1	Discussion /Conclusion	Discussion/ Conclusion: No further suggestions.	Thank you

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Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #2	Discussion /Conclusion	The discussion seemed to me to be a rehash of the results without really putting the results into perspective as well as they could have. If they reduced some redundancy in the discussion vs. the results they could have more space for more context. The content experts might be especially helpful I this regard.	We have added a paragraph to the Conclusions (now Conclusions and Clinical Implications) to put our findings into context. We aimed to focus on decisionmaking in the face of incomplete evidence rather than make any comments that could be perceived as practice recommendations.
TEP Reviewer #3	Discussion /Conclusion	The implications and limitations are clearly stated and understood.	Thank you
TEP Reviewer #4	Discussion /Conclusion	The authors should discuss the issue raised above regarding the limitation of use of "total DVT". Total DVT overstates the risk of clinically relevant DVT.	Throughout the revised report we have made explicit the caveat that total DVT (including asymptomatic DVT) is an outcome of questionable clinical values.
TEP Reviewer #4	Discussion /Conclusion	Furthermore, this issue of heterogeneity of the surgery involved should be addressed.	We agree and have added this concept to the Discussion.
TEP Reviewer #5	Discussion /Conclusion	Yes, the implications and limitations are addressed.	Thank you
TEP Reviewer #6	Discussion /Conclusion	The discussion clearly discussed the limitations in making recommendations for hip fracture. There was most data for hip replacement and a good amount for knee replacement. Does any of this CHANGE current recommendations? that should be addressed	Thank you. However, this review does not make (or change) recommendations.

Commentator & Affiliation	Section	Comment	Response
Public reviewer #1. American Academy of Orthopaedic Surgeons (Gerald Williams, Jr., MD; William A. Jiranek, MD, FACS)	Discussion /Conclusion	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 evidencebased clinical practice guideline recommendations and recommends industry biased "evidence" to the detriment of our patients.	The review is an update of the 2012 VTE comparative effectiveness review. This review highlights where there is and is not direct comparative effectiveness evidence. This review is restricted to the evaluated Key Questions and thus the *a priori* eligibility criteria. Other forms of evidence that were not included in the systematic review may be appropriate for clinical practice guideline groups to consider in developing their guidelines.

Commentator & Affiliation	Section	Comment	Response
Peer Reviewer #1	Clarity and Usability	This is one of the most well structured, organized, logical and clear reports that I have ever encountered. The report does help to clarify the numerous treatment options and outcome results available to prevent VTE in major orthopaedic surgery that will help the practitioner make decisions based on the evidence.	Thank you very much.
Peer Reviewer #2	Clarity and Usability	The report is well structured and organized. Conclusions are quite relevant to practice decisions that orthopedic surgeons and other clinical personnel make every day. Limitations of current evidence, and, therefore, the need and direction of future research are also clearly presented.	Thank you
Peer Reviewer #3	Clarity and Usability	Clarity and Usability: yes it is	Thank you
TEP Reviewer #1	Clarity and Usability	The report is well formulated and clear. The network meta-analysis is especially useful.	Thank you
TEP Reviewer #2	Clarity and Usability	Clarity and Usability: I would say it is clear and useable. A better discussion might make the entire paper more useable though. Think about the practicing clinician and the healthcare decision-maker, what can be done to the discussion focusing on these stakeholders.	We have added a paragraph to the Conclusions (now Conclusions and Clinical Implications) to put our findings into context. We aimed to focus on decisionmaking in the face of incomplete evidence rather than make any comments that could be perceived as practice recommendations.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #2	Clarity and Usability	Working in orthopedics, I feel the conclusions are relevant to practice. Unfortunately, with the variety of comparisons in the research, it is difficult to determine which dvt prophylaxis provides the best outcome-this is not a reflection of the report, but rather a reflection of the research available.	Thank you. We agree.
TEP Reviewer #4	Clarity and Usability	The report is well structured and organized. The clinical utility will be limited due to the poor state of the literature, particularly concerning clinically relevant end points. This is inherent to the topic under investigation and the situation has not materially changed since the 2012 review.	Thank you.
TEP Reviewer #5	Clarity and Usability	Very much so. I applaud the team. This is an exemplary report.	Thank you very much.
TEP Reviewer #6	Clarity and Usability	I like the structure, points are clearly defined and the rationale for each point is described clearly. For the poor clinician: I am often asked is there a benefit to chemoprophylaxis? Is one better than the other? I think the latter question was answered well, but the first needs to be reinforced.	We have added a short summary of the evidence from the 2012 VTE report on thromboprophylaxis vs. placebo (no prophylaxis) to the start of the Discussion. This review did not directly evaluate that question.

Commentator & Affiliation	Section	Comment	Response
TEP Reviewer #6	Clarity and Usability	There are a few typographical errors that I noted: P23 L25 (p171 L7) Trials is spelled as Tirals P23 L44 (P171 L7) The is spelled as Teh P23 L47 (P171 L30) I was confused by the statement that in "mechanical versus UFH, favors VKA"?? P30 L15 (P184 L19) there is an extra period mark	These typos have all been fixed. Thank you
Public reviewer #1. American Academy of Orthopaedic Surgeons (Gerald Williams, Jr., MD; William A. Jiranek, MD, FACS)	Clarity and Usability	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.	It is true that this systematic review did not address questions beyond its scope such as additional VTE risk factors for THA, TKA, and HFx surgery patients. It may be worthwhile to suggest these Key Questions for any update to the current review.

Commentator & Affiliation	Section	Comment	Response
Public reviewer #1. American Academy of Orthopaedic Surgeons (Gerald Williams, Jr., MD; William A. Jiranek, MD, FACS)	Clarity and Usability	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.	These comments relate to issues beyond the scope of our systematic review.

Commentator & Affiliation	Section	Comment	Response
Public reviewer #1. American Academy of Orthopaedic Surgeons (Gerald Williams, Jr., MD; William A. Jiranek, MD, FACS)	Clarity and Usability	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].	We understand the concerns about the lack of direct comparative studies on aspirin. Additional analyses and assessments regarding LMWH vs. aspirin, based on observational studies, were added. The review is methodologically rigorous in adhering to the scope of the review as described in the protocol. The limitations of the evidence, particularly related to the gaps in direct comparative studies of aspirin have been described in this review and highlighted as a needed area for future research in order to be able to answer the key questions. In the meantime, the review describes the available evidence and guideline developers may consider this and other evidence not included in the scope of this comparative effectiveness review in making their guideline recommendations.