AHRQ Comparative Effectiveness Review Surveillance Program

CER # 49:

Comparative effectiveness review of Venous Thromboembolism Prophylaxis in Orthopedic Surgery

Original release date:
March 2012

Surveillance Report:
December 2012

Key Findings:

- Key questions (KQs) 1-4,7-11 are uptodate
- 1 of 12 conclusions for KQ5 are possibly out of date
- 4 of 8 conclusions for KQ6 are possibly out of date
- Expert opinion: Three of the fourth experts said conclusions for majority of KQs were still valid.
- There are no safety concerns

Summary Decision:

This CER's priority for updating is **Low**.

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Contents

Tables

Appendices

1. Introduction

The purpose of this mini-report is to apply the methodologies developed by the Ottawa and RAND EPCs to assess whether the CER No. 49 (Comparative effectiveness review of Venous Thromboembolism Prophylaxis in Orthopedic Surgery), is in need of updating. [1] This CER was originally released in March, 2012. When the Surveillance program began in the summer of 2011, this CER was selected to be in the last wave of reports to go through the assessment. This first assessment of this CER was completed in December 2012.

This CER included 154 unique studies identified by using searches through May, 2009 and addressed eleven key questions to compare comparative effectiveness of Venous Trhomboemoblism prophylaxis in Orthopedic surgery. The key questions of the original CER were as follows:

1. In patients undergoing major orthopedic surgery (total hip or knee replacement or hip fracture surgery) what is the baseline postoperative risk of venous thromboembolism and bleeding outcomes in contemporary practice?

2. In patients undergoing major orthopedic surgery (total hip or knee replacement or hip fracture surgery) what patient, surgical or postsurgical characteristics predict or differentiate patient risk of venous thromboembolism and bleeding outcomes in contemporary practice?

3. In patients undergoing major orthopedic surgery (total hip or knee replacement or hip fracture surgery), in the absence of final health outcomes, can the risk for such outcomes reliably be estimated by measuring surrogate outcomes, such as deep vein thrombosis (asymptomatic or symptomatic, proximal or distal) as detected by venography or ultrasound?

4. In patients who had major orthopedic surgery (total hip or knee replacement, hip fracture surgery), what is the relative impact of thromboprophylaxis compared with no thromboprophylaxis on symptomatic objectively confirmed venous thromboembolism, major venous thromboembolism (proximal deep vein thrombosis, pulmonary embolism or venous thromboembolism-related mortality), pulmonary embolism, fatal pulmonary embolism, nonfatal pulmonary embolism, post thrombotic syndrome, mortality, mortality due to bleeding, deep vein thrombosis (asymptomatic or symptomatic, proximal or distal deep vein thrombosis), asymptomatic deep vein thrombosis, symptomatic deep vein thrombosis, proximal deep thrombosis, distal deep vein thrombosis, major bleeding, major bleeding leading to reoperation, minor bleeding, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, heparin-induced thrombocytopenia, discomfort, readmission, and reoperation? Thromboprophylaxis includes any pharmacologic agent within the defined classes (oral antiplatelet agents, injectable low molecular weight heparins, injectable unfractionated heparin, injectable or oral factor Xa inhibitors, injectable or oral direct thrombin inhibitors, oral vitamin K

antagonists) or any external mechanical intervention within the defined classes (graduated compression stockings, intermittent pneumatic compression devices, or venous foot pumps)]?

5. In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery), what is the comparative efficacy between classes of agents on outcomes: symptomatic objectively confirmed venous thromboembolism, major venous thromboembolism, pulmonary embolism, fatal pulmonary embolism, nonfatal pulmonary embolism, post thrombotic syndrome, mortality, mortality due to bleeding, deep vein thrombosis (asymptomatic or symptomatic, proximal or distal deep vein thrombosis), asymptomatic deep 3 vein thrombosis, symptomatic deep vein thrombosis, proximal deep thrombosis, distal deep vein thrombosis, major bleeding, major bleeding leading to reoperation, minor bleeding, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, heparin-induced thrombocytopenia, discomfort, readmission, and reoperation? Classes include oral antiplatelet agents, injectable low molecular weight heparins, injectable unfractionated heparin, injectable or oral factor Xa inhibitors, injectable or oral direct thrombin inhibitors, oral vitamin K antagonists, and mechanical interventions.

6. In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery), what is the comparative efficacy of individual agents within classes (injectable low molecular weight heparin or mechanical) on symptomatic objectively confirmed venous thromboembolism, major venous thromboembolism (proximal deep vein thrombosis, pulmonary embolism or venous thromboembolism related mortality), pulmonary embolism, fatal pulmonary embolism, nonfatal pulmonary embolism, post thrombotic syndrome, mortality, mortality due to bleeding, deep vein thrombosis (asymptomatic or symptomatic, proximal or distal deep vein thrombosis), asymptomatic deep vein thrombosis, symptomatic deep vein thrombosis, proximal deep thrombosis, distal deep vein thrombosis, major bleeding, major bleeding leading to reoperation, minor bleeding, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, heparin-induced thrombocytopenia, discomfort, readmission, and reoperation?

7. In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery), what are the effect estimates of combined pharmacologic and mechanical modalities versus single modality on symptomatic objectively confirmed venous thromboembolism, major venous thromboembolism (proximal deep vein thrombosis, pulmonary embolism or venous thromboembolism related mortality), pulmonary embolism, fatal pulmonary embolism, nonfatal pulmonary embolism, post thrombotic syndrome, mortality, mortality due to bleeding, deep vein thrombosis (asymptomatic or symptomatic, proximal or distal deep vein thrombosis), asymptomatic deep vein thrombosis, symptomatic deep vein thrombosis, proximal deep thrombosis, distal deep vein thrombosis, major bleeding, major bleeding leading to reoperation, minor bleeding, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, heparin-induced thrombocytopenia, discomfort, readmission, and reoperation?

8. In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery), regardless of thromboprophylaxis method, what are the effects of prolonging thromboprophylaxis for 28 days or longer compared with thromboprophylaxis for 7 to 10 days on symptomatic objectively confirmed venous thromboembolism, major venous thromboembolism (proximal deep vein thrombosis, pulmonary embolism or venous thromboembolism related mortality), pulmonary embolism, fatal pulmonary embolism, nonfatal pulmonary embolism, post thrombotic syndrome, mortality, mortality due to bleeding, deep vein thrombosis (asymptomatic or symptomatic, proximal or distal deep vein thrombosis), asymptomatic deep vein thrombosis, symptomatic deep vein thrombosis, proximal deep thrombosis, distal deep vein thrombosis, major bleeding, major bleeding leading to reoperation, minor bleeding, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, heparin-induced thrombocytopenia, discomfort, readmission, and reoperation?

9. In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery) who have known contraindications to antithrombotic agents, what is the relative impact of prophylactic inferior vena cava filter placement compared with any external mechanical intervention on symptomatic objectively confirmed venous thromboembolism, major venous thromboembolism (proximal deep vein thrombosis, pulmonary embolism or venous thromboembolism related mortality), pulmonary embolism, fatal pulmonary embolism, nonfatal pulmonary embolism, post thrombotic syndrome, mortality, mortality due to bleeding, deep vein thrombosis (asymptomatic or symptomatic, proximal or distal deep vein thrombosis), asymptomatic deep vein thrombosis, symptomatic deep vein thrombosis, proximal deep thrombosis, distal deep vein thrombosis, major bleeding, major bleeding leading to reoperation, minor bleeding, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, heparin-induced thrombocytopenia, discomfort, readmission, reoperation or IVC filter placement-associated insertion site thrombosis?

10. In patients requiring knee arthroscopy, surgical repair of a lower extremity injury distal to the hip, or elective spine surgery what is the relative impact of thromboprophylaxis (any agent, any mechanical intervention) compared with no thromboprophylaxis intervention on symptomatic objectively confirmed venous thromboembolism, major venous thromboembolism (proximal deep vein thrombosis, pulmonary embolism or venous thromboembolism related mortality), pulmonary embolism, fatal pulmonary embolism, nonfatal pulmonary embolism, post thrombotic syndrome, mortality, mortality due to bleeding, deep vein thrombosis (asymptomatic or symptomatic, proximal or distal deep vein thrombosis), asymptomatic deep vein thrombosis, symptomatic deep vein thrombosis, proximal deep thrombosis, distal deep vein thrombosis, major bleeding, major bleeding leading to reoperation, minor bleeding, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, heparin-induced thrombocytopenia, discomfort, readmission, and reoperation?

11. In patients requiring knee arthroscopy, surgical repair of a lower extremity injury distal to the hip, or elective spine surgery what is the relative impact of injectable antithrombotic agents (low molecular weight heparin agents, injectable unfractionated heparin, injectable factor Xa inhibitors, injectable direct thrombin inhibitors) compared with mechanical interventions on symptomatic objectively confirmed venous thromboembolism, major venous thromboembolism (proximal deep vein thrombosis, pulmonary embolism or venous thromboembolism related mortality), pulmonary embolism, fatal pulmonary embolism, nonfatal pulmonary embolism, post thrombotic syndrome, mortality, mortality due to bleeding, deep vein thrombosis (asymptomatic or symptomatic, proximal or distal deep vein thrombosis), asymptomatic deep vein thrombosis, symptomatic deep vein thrombosis, proximal deep thrombosis, distal deep vein thrombosis, major bleeding, major bleeding leading to reoperation, minor bleeding, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, heparin-induced thrombocytopenia, discomfort, readmission, and reoperation?

The conclusion(s) for each key question are found in the executive summary of the CER report. [1]

2. Methods

We followed *a priori* formulated protocol to search and screen literature, extract relevant data, and assess signals for updating. The identification of an updating signal (qualitative or quantitative) would be an indication that the CER might need to be updated. The Food and Drug Administration (FDA), Health Canada, and Medicines and Healthcare products Regulatory Agency (MHRA) surveillance alerts received from the Emergency Care Research Institute (ECRI) were examined for any relevant material for the present CER. The clinical expert opinion was also sought. All of this evidence was taken into consideration leading to a consensus-based decision on whether any given conclusion warrants updating (up to date, possibly out of date, or out of date). Based on this assessment, the CER was categorized into one of the three updating priority groups: high priority, medium priority, or low priority. Further details on the Ottawa EPC and RAND methods used for this project are found elsewhere.[2-4]

2.1 Literature Searches

The original CER search strategies were reconstructed in MEDLINE (1 November 2010 to 18 September 2012), Cochrane Central Register of Controlled Trials (CCRCT; search date: 18 September 2012), and Scopus (Elsevier) on 24 September 2012. The syntax and vocabulary, which include both controlled subject headings (e.g., MeSH) and keywords, were adjusted according to the three databases indicated in the appendix and in the search strategy section of the report. Journal titles were entered according to the style used by each of the selected OVID databases. The electronic searches in MEDLINE were limited to five general medical journals (Annals of Internal Medicine, BMJ, JAMA, Lancet, and New England Journal of Medicine) and several specialty journals (Journal of Bone & Joint Surgery (American volume), Clinical Orthopedics and Related Research, Journal of Thrombosis & Haemostasis, Journal of Arthroplasty, and Archives of Internal Medicine). Restricting by journal title was not possible in the Cochrane and Scopus searches and pertinent citations were instead selected from the results. Study design filters were not applied to any of the searches although the Cochrane Central Register only contains randomized or controlled clinical trials. Further details on the search strategies are provided in the Appendix A of this mini-report.

2.2 Study Selection

All identified bibliographic records were screened using the same inclusion/exclusion criteria as described in the original CER.

2.3 Expert Opinion

In total, 10 CER-specific (e.g., lead author, clinical content experts, and technical expert panel members) were requested to provide their opinion/feedback in a pre-specified matrix table on whether or not the conclusions as outlined in the Executive Summary of the original CER were still valid.

2.4 Check for Qualitative and Quantitative Signals

All relevant reports eligible for inclusion in the CER were examined for the presence of qualitative and quantitative signals using the Ottawa EPC method (see more details in Appendix B). CERs with no meta-analysis were examined for qualitative signals only, as was the case for this CER. For any CER that contains meta-analysis (es) we first assess for, the qualitative signal(s), and if no qualitative signal(s) are found, we then assess for quantitative signal(s). The identification of an updating signal (qualitative or quantitative) would be an indication that the CER might need updating. The definition and categories of updating signals are presented in Appendix B.

2.5 Compilation of Findings and Conclusions

All the information obtained during the updating process (i.e., data on qualitative/quantitative signals, the expert opinions, and safety surveillance alerts) was collated, summarized and presented into a table. We determined whether the conclusions of the CER warranted updating using a four category scheme:

- Original conclusion is still **up to date** and this portion of CER does not need updating
- Original conclusion is **possibly out of date** and this portion of CER may need updating
- Original conclusion is **probably out of date** and this portion of CER may need updating
- Original conclusion is **out of date** and this portion of CER is in need of updating

We used the following factors when making our assessments to categorize the CER conclusions:

- If we found no new evidence or only confirmatory evidence and all responding experts assessed the CER conclusion as still valid, we classified the CER conclusion as still up to date.
- If we found some new evidence that might change the CER conclusion, and /or a minority of responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the CER conclusion as possibly out of date.
- If we found substantial new evidence that might change the CER conclusion, and/or a majority of responding experts assessed the CER conclusion as having new evidence that might change the conclusion, then we classified the CER conclusion as probably out of date.
- If we found new evidence that rendered the CER conclusion out of date or no longer applicable, we classified the CER conclusion as out of date. Recognizing that our literature searches were limited, we reserved this category only for situations where a limited search would produce prima facie evidence that a conclusion was out of date, such as the withdrawal of a drug or surgical device from the market, a black box warning from FDA, etc.

2.6 Determining Priority for Updating

Determining the priority groups (i.e., Low, Medium, and High) for updating any given CER is based on the following two criteria:

- How many conclusions of the CER are up to date, possibly out of date, or certainly out of date?
- How out of date are conclusions (e.g., consideration of magnitude/direction of changes in estimates, potential changes in practice or therapy preference, safety issue including withdrawn from the market drugs/black box warning, availability of a new treatment)

3. Results

3.1 Update Literature Searches and Study Selection

A total of 56 bibliographic records were identified (MEDLINE=27, Central =4, and Scopus=25). After de-duping, 52 records remained (MEDLINE=27, Central=4, and Scopus=21) from which 22 potentially eligible records were selected for full text screening. Of these, two met the eligibility criteria and were included in this update.[5,6] We also identified one study [7] from the bibliography of one SR that itself was excluded because it contained all the studies that were already captured in the original CER. Four studies were suggested by the experts but were not included in this assessment because they did not meet the inclusion criteria of the original CER. [8-11]. A total of 3 studies are included in this assessment. [5-7]

3.2 Signals for Updating in Newly Identified Studies

3.2.1 Study overview

The study population demographics, treatment characteristics, and results for the five included studies are presented in Appendix C (Evidence Table). [5-7] In brief, all three studies were RCTs. The sample size of the studies ranged from 523 [6] to 2326 .[5] The included studies compared oral dabigartan (220mg/day) versus subcutaneous enoxaparin (40mg/day) [7] , edoxaban (5, 15, 30, and 60 mgs/day) versus placebo [6], and enoxaparin (30mg twice/day ,and 40 mg/day) versus semuloparin (20 mg/day) [5]. The outcomes assessed were including DVT (proximal, distal, symptomatic and total), symptomatic VTE, symptomatic PE, minor bleeding, major bleeding and death. [5-7]

3.2.2 Qualitative signals

Key question #1:

No new evidence was identified. **No Signal**

Key question #2:

No new evidence was identified. **No Signal**

Key question #3:

No new evidence was identified. **No Signal**

Key question #4

DVT : Consistent to the original CER finding, one RCT demonstrated that the number of patients (%) developed DVT (overall, proximal, and distal) events in pharmacologic treatment group were fewer than the placebo group:

- DVT (Overall): Number of patients with events (%) in placebo group was 43(43.3) versus in edoxaban group at different doses [5mg: 25(28.7), 15mg: 24(26.1), 30mg: 11(12.5), and 60mg: 8(9.1)]. [6] **No Signal**
- *DVT* (Proximal): Number of patients with events (%) in placebo group was 4(4.5) versus in edoxaban group at different doses [5mg: 0(0.0), 15mg: 0(0.0), 30mg: 1 (1.1), and 60mg:1 (1.1)]. [6] **No Signal**
- *DVT* (Distal): Number of patients with events (%) in placebo group was 43(48.3) versus edoxaban group at different doses [5mg: 25(28.7), 15mg: 24(26.1), 30mg: 11 (12.5), and 60mg: 7(8.0)]. [6] **No Signal**

The original CER did not provide data on symptomatic DVT events. One RCT reported only one event in the edoxaban 5mg group: Number of patients with events (%) in placebo group was 0(0.0) versus in edoxaban group at different doses [5mg: 1(1), 15mg: 0(0.0), 30mg: 0 (0.0), and 60mg:0 (0.0)]. [6] **No Signal**

VTE: In agreement with the original CER finding, one RCT demonstrated that the number of patients (%) developed VTE events in the pharmacologic treatment group were fewer than the placebo group: Number of patients with events (%); 95 % CI in placebo group was 43 (48.3); (37.9, 58.7) versus in edoxaban at different doses {[5mg: 26(29.5); (20.0, 39.1)], [15mg: 24(26.1); (17.1, 35.1)], [30mg: 11 (12.5); (5.6, 19.4)], and [60mg: 8(9.1); (3.1, 15.1)]}. [6] **No Signal**

Symptomatic PE: One RCT assessed this outcome but could not determine the effect of edoxaban versus placebo groups because no events occurred in either arm. [6] **No Signal**

Major Bleeding: One RCT demonstrated that only one patient developed major bleeding in the edoxaban versus placebo groups: Number of patients with events (%) in placebo group was 0(0.0) versus in edoxaban group at different doses [5mg: 0(0.0), 15mg: 0(0.0), 30mg: 0 (0.0), and 60mg: 1(0.9)]. [6] **No Signal**

Key question #5:

Major VTE and VTE related mortality: The original CER did not provide any information on this outcome for the group receiving oral direct thrombin inhibitors compared to LMWHs. However, one of the identified RCTs demonstrated that the absolute risk difference was significantly lower in patients receiving dabigatran (oral thrombin inhibitor) versus enoxaparin (subcutaneous LMWH): Number of patients with events/ total number (%, 95% CI) was 18/805 (2.2%, 1.2, 3.3%) versus 33/794 (4.2%, 2.8, 5.5%) and absolute risk difference of -1.9% with the 95% CI of -3.6, -2.2%, with p-value = 0.03 during the treatment period. However, no significant difference was identified during the follow-up period: The number of patients with event/total number (%) was 2/942 (0.2) versus 4/951 (0.4); p=0.69. [7] **1 Signal**

DVT: Consistent to the original CER finding, one RCT demonstrated that for DVT, and proximal DVT there were more events in the LMHW (enoxaparin) group compared to oral thrombin inhibitor (dabigatran) but not for distal DVT:

- Proximal DVT: Number of patients with events/ total number (%) was 17/804 (2.1) in dabigatran arm versus 31/792 (3.9) in enoxaparin, and the absolute risk difference was -1.8% with 95% CI of -3.5, 0.1%; and p-value =0.04 during treatment period. [7] **No Signal**
- Total DVT: Number of patients with events/ total number (%) was 60/791 (7.6) in dabigatran arm versus 67/783 (8.6) in enoxaparin, and the absolute risk difference was -1.0% with 95% CI of -3.7, 1.7% with p-value =0.48 during treatment period. [7] **No Signal**
- Distal DVT: Number of patients with events/ total number (%) was 43/792 (5.4) in dabigatran arm versus 35/785 (4.5) in enoxaparin arm. [7] **No Signal**

During treatment period: The original CER did not provide any data on Symptomatic VTE, Symptomatic non-fatal PE, and deaths, and the finding from one RCT did not demonstrate any significant difference between the groups:

- Symptomatic VTE: Number of patients with events/ total number (%) was 1/1,001 (0.1) in dabigatran arm versus 6/992 (0.6) in enoxaparin arm. [7] **No Signal**
- Symptomatic non-fatal PE: Number of patients with events/ total number (%) was 1/1,001 (0.1) in dabigatran group versus 2/992 (0.2) in enoxaparin group; p-value=0.62. [7] **No Signal**
- Deaths: Number of patients with events/ total number (%) was 0/1,001 (0.0) in dabigatran arm versus 1/992 (0.1) in enoxaparin arm; p-value=0.50. [7] **No Signal**

During follow up: The original CER did not provide any data on symptomatic VTE, and deaths, and the finding from one RCT did not demonstrate any significant difference between the groups:

- Symptomatic VTE: Number of patients with events/ total number (%) was 2/942 (0.2) in dabigatran arm versus 2/951 (0.2) in enoxaparin arm. [7] **No Signal**

- Death: Number of patients with events/ total number (%) was 0/942 (0.0) in dabigatran group versus 1/951 (0.1) in enoxaparin group. [7] **No Signal**

Total Study period (treatment +follow up): The original CER did not provide any data on symptomatic VTE+ all cause mortality, major bleeding, and minor bleeding. The finding from one RCT identified through update search did not demonstrate any significant difference between the groups:

- Symptomatic VTE+ all cause mortality: Number of patients with events/ total number (%) was 3/942 (0.3) in dabigatran arm versus 10/951 (1.1) in enoxaparin group. [7] **No Signal**

- Major bleeding: Number of patients [%, (95% CI)] was 14[1.4, (0.8, 2.3)] in dabigatran arm versus 9[0.9, (0.4,1.7)] in enoxaparin group, p-value= 0.40. [7] **No Signal**

- Minor bleeding: Number of patients (%) was 61 (6.0) in dabigatran group versus 54 (5.4) in the enoxaparin group. [7] **No Signal**

Key question #6:

DVT: The original CER compared enoxaparin versus other LMWH (dalteparin or tinzaparin) and found no significant difference between the groups. However, we identified one study that presented data from 3 RCTs comparing semuloparin versus enoxaparin and found significant differences among the groups:

- Any DVT: The OR= 0.54 and its 95% CI= 0.38, 0.76 favored significantly semulparin versus enoxaparin in Hip replacement RCT. However, no significant differences were observed in Hip surgery RCT (OR= 0.73, 95%CI= 0.50, 1.05), and in Knee replacement RCT (OR= 0.83, 95% CI= 0.61, 1.13). [5] **1 Signal**

- Any proximal DVT: The OR= 0.48 and its 95% CI= 0.23, 0.93 favored significantly semulparin versus enoxaparin in Hip surgery RCT. However, no significant differences were observed in Hip replacement RCT (OR= 0.87, 95%CI= 0.40, 1.86), and in Knee replacement RCT (OR= 1.74, 95% CI= 0.79, 3.99). [5] **1 Signal**

- Distal DVT: The OR= 0.49 and its 95% CI= 0.33, 0.72 favored significantly semulparin versus enoxaparin in Hip replacement RCT. However, no significant differences were observed in Hip surgery RCT (OR= 0.97, 95%CI= 0.63, 1.50), and in Knee replacement RCT (OR= 1.77, 95% CI= 0.55, 1.06). [5] **1 Signal**

Major bleeding: The original CER compared enoxaparin versus other LMWH (dalteparin or tinzaparin) and found no difference between the two groups. We identified one RCT comparing semuloparin versus enoxaparin and found significant differences among the groups: The OR= 0.28, and its 95% CI=0.08, 0.83 favored significantly semuloparin versus enoxaparin in hip replacement RCT. [5] **1 Signal**

However, no significant differences were observed in knee replacement RCT (OR= 0.74, 95%CI= 0.14, 3.61), and in hip surgery RCT (OR= 1.71, 95%CI= 0.39, 8.73) comparing enoxaparin versus semuloparin. [5] **No Signal**

All-cause death: The original CER did not provide any data on this outcome for MWHSs. No significant difference was observed among the patients receiving semuloparin versus enoxaparin in hip replacement RCT (OR= 0.50, 95%CI= 0.02, 6.59), and in hip surgery RCT (OR= 2.05, 95%CI= 0.36, 6.08). [5] **No Signal**

Major VTE or all-cause mortality: The original CER did not provide any data on this outcome for MWHSs. No significant differences were observed among the patients receiving semuloparin versus enoxaparin in hip replacement RCT (OR= 0.68, 95%CI= 0.35, 1.33), and in hip surgery RCT (OR= 0.71, 95%CI= 0.41, 1.24), and in knee replacement RCT (OR= 1.18, 95% CI= 0.67, 2.08). [5] **No Signal**

Non-fatal PE: The original CER did not provide any data on this outcome for MWHSs. The data from one study that included 3 RCTs was not determinable due to no or very low number of events. The number of patients with events/total patients (%) in semuloparin group versus enoxaparin group was:

- 0/1152 (0) versus 0/1150 (0) in hip replacement RCT
- 0/449 (0) versus 1/488 (0.2) in hip surgery RCT
- 1/568 (0.2) versus 0/573 (0) in knee replacement RCT

No Signal

Key question #7:

No new evidence was identified. **No Signal**

Key question #8:

No new evidence was identified. **No Signal**

Key question #9:

No new evidence was identified. **No Signal**

Key question #10:

No new evidence was identified. **No Signal**

Key question #11:

No new evidence was identified. **No Signal**

3.2.3 Quantitative signals

The presence of quantitative signals (B1 and B2) was checked only if the CER[1] included a meta-analysis and none of the studies identified through the update search indicated a qualitative signal. We found that three pooled estimates from three meta-analyses in the CER (key questions #4) were deemed to be potentially updatable given the relevant data from one study identified through the update search.[6]

3.3 FDA surveillance alerts

We did not identify any safety alerts on the interventions of interest.

3.4 Expert opinion

Four (all CER-specific) of the 10 contacted clinical experts provided their responses/feedback in the matrix table (Appendix D).

One of the experts said that the conclusions for all key questions (KQ) except KQ 2 were uptodate. He did not provide any evidence to support her response for KQ 2. She did reference one additional study for KQ 11 but we could not include it in this report because it failed to meet the eligibility criteria of the CER. [11]

Another expert stated that the conclusions for KQs 1- 6, and 11 are uptodate, but she does not know if the conclusions for KQs 7- 10 are uptodate or not.

The other expert said that conclusions for KQ 2-10 are uptodate, not sure about KQ 1, and does not know about currency of KQ 11. He had comment on KQ 1 which is not pertinent to our effort.

One another expert stated that the conclusions for four KQs (2, 6, 8, and 11) were uptodate. However, he disagreed with the methodological approach, analysis of the data, and conclusions of the original CER six KQs (1, 3-5, 7, and 10), and stated the conclusions for KQ9 were not still valid. For his disagreement, he referenced a publication in which he is the first author and preferred the methodology, analysis, and conclusion of that publication than the ones in the CER. [10] The referenced publication was a practice guideline that presents a systematic review. Most of the studies include in this publication are also included in the CER; however, some of the studies that has not met the eligibility criteria of the original CER and were excluded from the CER are included in his referenced publication. He referenced two studies to support his argument for KQ9, but we could not include these studies in this assessment because they did not meet the inclusion criteria of the original CER. [8,9]

In conclusion, of the four experts, the responses from three were in agreement for KQ 1-11 stating that either the conclusions were still valid or they did not know, except for KQ1(one expert was not sure), and for KQ2 (one expert said the conclusion was not still valid but did not support his/her view by any evidence). However, the fourth expert had consistent responses to other experts only for KQs 2, 6, 8, and 11. He disagreed with methodology, analysis, and conclusions of the KQs 1, 3, 4, 5, and 9.

Conclusion

Summary results and conclusions according to the information collated from different sources (updating signals from studies identified through the update search, safety surveillance alerts, and expert opinion) are provided in Table 1 (Summary Table). Based on the assessments, this CER is categorized in **Low** priority group for updating.

Key Question # 1

Signals from studies identified through update search: No new evidence was identified. **No Signal**
Experts: One of the four experts disagreed with methodology, analysis and conclusions, two experts said the conclusions were still valid and one expert was not sure.
Safety surveillance alerts: No safety alert was identified.
Conclusion: **The conclusions are uptodate**

Key Question # 2

Signals from studies identified through update search: No new evidence was identified. **No Signal**
Experts: One of the four experts stated that the conclusions were not still valid, but three said conclusions were still valid.
Safety surveillance alerts: No safety alert was identified.
Conclusion: **The conclusions are uptodate**

Key Question # 3

Signals from studies identified through update search: No new evidence was identified. **No Signal**
Experts: One of the four experts disagreed with methodology, analysis and conclusions, but three experts said the conclusions were still valid.
Safety surveillance alerts: No safety alert was identified.
Conclusion: **The conclusions are uptodate**

Key Question # 4

Signals from studies identified through update search: No qualitative signal met. **No Signal**

Experts: One of the four experts disagreed with methodology, analysis and conclusions, but three experts said the conclusions were still valid.
Safety surveillance alerts: No safety alert was identified.
Conclusion: **The conclusions are uptodate**

Key Question # 5

Signals from studies identified through update search: One qualitative signal met. **1 Signal**
Experts: One of the four experts disagreed with methodology, analysis and conclusions, but three experts said the conclusions were still valid.
Safety surveillance alerts: No safety alert was identified.
Conclusion: **1/12 conclusions are possibly out of date**

Key Question # 6

Signals from studies identified through update search: Four qualitative signals met. **4 Signals**
Experts: All of the four experts said that the conclusions were still valid.
Safety surveillance alerts: No safety alert was identified.
Conclusion: **4/8 conclusions are possibly out of date**

Key Question # 7

Signals from studies identified through update search: No new evidence was identified. **No Signal**
Experts: One of the four experts disagreed with methodology, analysis and conclusions, two experts said the conclusions were valid and one did not know.
Safety surveillance alerts: No safety alert was identified.
Conclusion: **The conclusions are uptodate**

Key Question # 8

Signals from studies identified through update search: No new evidence was identified. **No Signal**
Experts: Three of the four experts said that the conclusions were still valid, and one did not know.
Safety surveillance alerts: No safety alert was identified.
Conclusion: **The conclusions are uptodate**

Key Question # 9

Signals from studies identified through update search: No new evidence was identified. **No Signal**
Experts: One of the four experts disagreed with methodology, analysis and conclusions, two experts said conclusions were still valid and one expert did not know.
Safety surveillance alerts: No safety alert was identified.
Conclusion: **The conclusions are uptodate**

Key Question # 10

Signals from studies identified through update search: No new evidence was identified. **No Signal**
Experts: One of the four experts disagreed with methodology, analysis and conclusions, two experts said conclusions were still valid and one expert did not know.
Safety surveillance alerts: No safety alert was identified.
Conclusion: **The conclusions are uptodate**

Key Question # 11

Signals from studies identified through update search: No new evidence was identified. **No Signal**
Experts: Three of the four experts said that the conclusions were still valid, and one expert did not know.
Safety surveillance alerts: No safety alert was identified.
Conclusion: **The conclusions are uptodate**

Table 1. Summary Table

Conclusions from CER's Executive Summary	Update literature search results	Signals for updating		FDA surveillance alerts	Expert opinion (CER + local)	Conclusion on validity of CER conclusion(s)
		Qualitative	Quantitative			
Key Question 1: In patients undergoing major orthopedic surgery (total hip or knee replacement or hip fracture surgery) what is the baseline postoperative risk of VTE and bleeding outcomes in contemporary practice?						
Data were limited to placebo or control arms of trials for PE and DVT outcomes and placebo, control, or mechanical prophylaxis arms for bleeding outcomes. In contemporary surgical practice, the native postoperative incidence of DVT events was highest followed by PE and bleeding events. Follow up periods were defined in most trials as the postoperative period and may imply a more immediate rather than longer term follow up. The strength of evidence is predominately low for outcomes evaluated in hip and knee replacement surgery while all outcomes in hip fracture surgery were rated with insufficient evidence. Not all three surgeries had incidence data reported in clinical trials; therefore, the symbol "--" is used when no data were reported for the given surgery and outcome. In THR, TKR, and HFS, respectively, the incidences were: DVT (39 percent, 46 percent, 47 percent), proximal DVT (32 percent, 17 percent, --), distal DVT (30 percent, 22 percent, --), PE (6 percent, 1 percent, 3 percent), major bleeding (1 percent, 3 percent, 8 percent), minor bleeding (5 percent, 5 percent, --), major bleeding leading to reoperation (0 percent, 0 percent, --), and bleeding leading to transfusion (0 percent, 0 percent, --). Statistically significant levels of publication bias were detected for major bleeding and minor bleeding in THR, suggesting an underestimation of the incidence, which directionality of publication bias for proximal DVT in THR was unclear. Although RCTs and studies that used objective diagnostic means to	**No new evidence**	**NA**	**NA**	**None**	Two of the four experts said the conclusions were valid. One of the four expert was not sure if the conclusion was valid or not, and she commented, *"There are 3 issues: First, what is meant by "contemporary?" I think you go back to 1980. The baseline rate has probably decreased since then. Second, my view is that the important outcome is symptomatic VTE. That would include fatal and nonfatal PE and symptomatic DVT. This outcome is not clear from the numbers given. Third, are the baseline rates you cite for the period of 7-10 days or up to 28 days? Certainly, there are quite a few events after the 10 cutoff."* And one of the four experts said the conclusions for this question were not valid. He commented, *"I disagree with the assessment of baseline risk presented in that document. I believe that the baseline risk presented in the ACCP 2012 guideline is preferable".*	**Uptodate**

confirm efficacy outcomes were included as opposed to less rigorous criteria, a high degree of heterogeneity was present for most outcomes. This may be due to additional factors, such as different definitions of events, different ethnicities and countries in which trials were conducted, and undefined periods of postoperative followup and variation in duration of followup, potentially leading to insufficient length of followup for the outcomes being assessed. Our results are similar to that of previous pooled analyses of patients with total hip and total knee arthroplasty conducted between 1993 and 2001, in which 23 to 60 percent of patients had deep vein thrombosis, 23 to 26 percent had proximal deep vein thrombosis, 2 percent had pulmonary embolism, 1 percent had major bleeding, and 3 percent had minor bleeding.						
Key question 2: In patients undergoing major orthopedic surgery (total hip or knee replacement or hip fracture surgery) what patient, surgical, or postsurgical characteristics predict or differentiate patient risk of VTE and bleeding outcomes in contemporary practice?						
Several RCTs identified through our literature search evaluated different surgical characteristics on outcomes of interest, including anesthetic regimen, cemented arthroplasty, tourniquet use, limb positioning, and fibrin adhesive use. However, few trials evaluated each characteristic and subsequently did not address all major orthopedic procedures. Additionally, most trials evaluated intermediate health outcomes and did not address final health outcomes, and only one trial evaluated bleeding outcomes. As such, pooling was not possible. The surgical comparison with the most identified data was general anesthesia versus regional anesthesia. The impact of general versus regional anesthesia on several measures of DVT (overall, asymptomatic, proximal) was favorable to neutral for regional anesthesia while distal and symptomatic DVT, PE, and major bleeding were neutral. In a previous meta-analysis of 21 studies, regional anesthesia was associated with nonsignificantly reduced odds	**No new evidence**	**NA**	**NA**	**None**	Three of the four experts said the conclusions for this question were valid. One of the fourth expert said the conclusions was not valid but he did not support his opinion with evidence.	**Uptodate**

of pulmonary embolism and significantly reduced odds of deep vein thrombosis with no real impact on mortality versus general anesthesia. Although one trial compared spinal versus epidural anesthesia on the risk of deep vein thrombosis, no events occurred in the groups compared. The other characteristics were too limited to make any determinations. Patient characteristics were primarily evaluated in multivariate regression analyses of observational studies. Few characteristics were evaluated in multiple studies, and oftentimes when a significant finding was observed, the magnitude or direction of the effect was not reported. Patient characteristics found to significantly increase the odds of symptomatic objectively confirmed VTE in all available studies included congestive heart failure (two studies), inactive malignancy (one study), hormone replacement therapy (one study), living at home (one study), intertrochanteric fracture (one study), subtrochanteric fracture (one study), increased hemoglobin (one study), personal or familial history of VTE, (one study), and varicose veins (one study). Patient characteristics found to increase the odds of PE (evaluated in one study each) included age and genitourinary infection while cardiovascular disease was found to decrease the odds of PE. The following characteristics showed a mixed effect on DVT: age (two studies showed a significant increase while one study showed no effect), obesity (one study showed a significant increase while one study showed no effect), and gender (one study showed a significant increase in females while one study showed gender had no effect). Metabolic syndrome increased the odds of symptomatic DVT while congestive heart failure increased the odds of proximal DVT in the single study that evaluated each covariate. The one study that evaluated harms (major bleeding) suggested						

that age, gender, risk of bleeding, specific surgical procedure (total hip, knee replacement or hip fracture surgery), and prophylaxis administered in the hospital significantly impacted the risk of major bleeding. However, the magnitude and direction of the effect was not specified.						
Key question 3: In patients undergoing major orthopedic surgery (total hip or knee replacement or hip fracture surgery), in the absence of final health outcomes, can the risk for such outcomes reliably be estimated by measuring intermediate outcomes, such as DVT (asymptomatic or symptomatic, proximal or distal) as detected by venography or ultrasound?						
Pulmonary embolism was the only final health outcome with data depicting the relationship to the intermediate outcome DVT. In one observational study in TKR surgery, the overall occurrence of PE and the subset with symptomatic PE occurred more frequently in those with DVT. However, the data were not adjusted for confounders, and we cannot discern whether these variables are correlated or colinear. No trials or studies were available assessing whether DVT was correlated with or a multivariate predictor of PE. This data may be limited because the routine use of prophylaxis may have reduced the occurrence of DVT and the scheduled anticoagulant treatment for DVT, once it was detected, may have diminished the percentage that developed into PE.	**No new evidence**	**NA**	**NA**	**None**	Three of the four experts said the conclusions for this question were valid and one of them commented that the summary is very good. However, one of the four experts disagreed with the conclusion. He referenced the ACCP 2012 guideline (he is the first author) but it didn't pertain to the currency of conclusions.	**Uptodate**
Key question 4: In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery), what is the relative impact of thromboprophylaxis compared with no thromboprophylaxis on symptomatic objectively confirmed VTE, major VTE, PE, fatal PE, nonfatal PE, post thrombotic syndrome (PTS), mortality, mortality due to bleeding, DVT (asymptomatic or symptomatic, proximal or distal DVT), asymptomatic DVT, symptomatic DVT, proximal DVT, distal DVT, major bleeding, major bleeding leading to reoperation, minor bleeding, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, heparin-induced thrombocytopenia (HIT), discomfort, readmission, and reoperation? Thromboprophylaxis includes any pharmacologic agent within the defined classes (oral antiplatelet agents, injectable low molecular weight heparins [LMWHs], injectable unfractionated heparin [UFH], injectable or oral factor Xa inhibitors, injectable or oral direct thrombin inhibitors [DTIs], oral vitamin K antagonists [VKAs]) or any external mechanical intervention within the defined classes (graduated compression, intermittent pneumatic compression, or venous foot pump).						
Providing pharmacologic prophylaxis versus no prophylaxis has a better comparative balance of benefits and harms. There is high evidence that pharmacologic prophylaxis versus no prophylaxis significantly decreased risk of proximal and distal DVT (relative risk reduction [RRR] 47 percent and 41 percent, respectively), with moderate evidence	**1 RCT** [6]	**No Signal** **Placebo vs. Edoxaban (5, 15, 30, 60) mg** <u>VTE incidence [# of pts with events(%);</u>	**NA**	**None**	Three of the four experts said the conclusions for this question were valid. However, one of the four experts disagreed with the methodology, analyzes and conclusion of this question. He has did not referenced any evidence.	**Uptodate**

for the decrease in DVT overall and asymptomatic DVT (RRR 44 percent and 48 percent, respectively) in patients undergoing major orthopedic surgery. Higher levels of statistically heterogeneity were detected for the evaluation of DVT (I^2=52.8 percent). Statistically significant publication bias was detected in the evaluation of proximal DVT, suggesting an underestimation of benefit. There is low evidence that pharmacologic prophylaxis versus no prophylaxis significantly decreases major VTE in patients undergoing major orthopedic surgery (RRR 79 percent). Pharmacologic prophylaxis did not significantly impact PE versus no prophylaxis, although it was trending in that direction, and significantly reduced the risk of PE when the analysis was limited to the most stringent trials in which background prophylaxis (such as compression stockings) was not allowed in the experimental groups. There is high evidence that pharmacologic prophylaxis versus no prophylaxis significantly increases minor bleeding (relative risk increase 67 percent), and in a single observational study, pharmacologic prophylaxis increased the risk of reoperation. Pharmacologic prophylaxis versus no prophylaxis did not significantly impact nonfatal PE, mortality, symptomatic DVT, or major bleeding in patients undergoing major orthopedic surgery. Our results are in general agreement with the six previous meta-analyses of trials comparing pharmacologic prophylaxis versus placebo/control in patients with major orthopedic surgery. We could not determine the impact of pharmacologic prophylaxis on other endpoints either due to a lack of data or because there were no events in either experimental group. Providing mechanical prophylaxis versus no prophylaxis may have a better comparative balance of benefits and harms, but more data are needed to support this assumption. One RCT found that mechanical prophylaxis versus no		95% CI]: 43 (48.3); (37. 9, 58.7) versus {5mg: [26 (29.5); (20.0, 39.1)]; 15mg: [24 (26.1); (17.1, 35.1)]; 30mg:[11 (12.5); (5.6, 19.4)]; 60mg:[8 (9.1); (3.1, 15.1)]} VTE incidence difference from placebo [(%); 95% CI; p-value vs. placebo]: 5mg: 18.8; (4.7, 32.9); 0.01 15mg: 22.2; (8.5, 35.9); 0.002 30mg: 35.8; (23.3, 48.3); < 0.001 60mg: 39.2; (27.2, 51.2); < 0.001 Symptomatic PE [# of pts with events (%)] 0(0) vs. 0(0) in all groups Symptomatic PE difference from placebo (%)] 0.0 vs. 0.0 in all groups Symptomatic DVT[# of pts with events (%)] 0(0.0) vs.[5mg: 1(1) 15mg: 0(0.0) 30mg: 0(0.0)				

prophylaxis significantly decreased the occurrence of DVT in patients undergoing major orthopedic surgery. While mechanical prophylaxis versus no prophylaxis was not found to significantly impact proximal or distal DVT in patients undergoing major orthopedic surgery, the power to detect these differences was low. In the only previous meta-analysis comparing mechanical prophylaxis (intermittent pneumatic compression and venous foot pump) versus control, the risks of deep vein thrombosis (any, proximal, and distal) and pulmonary embolism were significantly reduced and the risk of fatal pulmonary embolism and mortality were nonsignificantly reduced. We could not adequately assess the other outcomes because there were either no trials or the available trials had no events in either group. Given the mechanism of action for these devices, bleeding should not result from their use, so benefits would likely overwhelm the risk of harms.		60mg: 0(0.0)] <u>Symptomatic DVT difference from placebo (%):</u> 5mg: -1.1 15mg: 0.0 30mg: 0.0 60mg: 0.0 <u>DVT total [# of pts with events (%)]</u> 43 (48.3) vs.[5mg: 25(28.7) 15mg: 24(26.1) 30mg: 11(12.5) 60mg: 8(9.1)] <u>DVT total; difference from placebo (%):</u> 5mg: 19.6 15mg: 22.2 30mg: 35.8 60mg: 39.2 <u>DVT Proximal [# of pts with events (%)]</u> 4 (4.5) vs.[5mg: 0(0.0) 15mg: 0(0.0) 30mg: 1(1.1) 60mg: 1(1.1)] <u>DVT Proximal; difference from placebo (%):</u> 5mg: 4.5 15mg: 4.5 30mg: 3.4 60mg: 3.4				

		DVT Distal [# of pts with events (%)] 43 (48.3) vs.[5mg: 25 (28.7) 15mg: 24 (26.1) 30mg: 11(12.5) 60mg: 7(8.0)] DVT Distal; difference from placebo (%): 5mg: 19.6 15mg: 22.2 30mg: 35.8 60mg: 40.4 Major Bleeding, n (%) Placebo: 0 (0.0) vs. [5mg: 0 (0.0) 15mg: 0 (0.0) 30mg: 0 (0.0) 60mg: 1.(0.9)] Major or clinically relevant non-major, n (%); p-value vs. placebo Placebo: 4 (3.9) vs. [5mg: 2 (1.9) ; 0.445 15mg: 4 (3.8); 1.000 30mg: 4 (3.9); 1.000 60mg: 5.(4.1);1.000]				
Key question 5: In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery), what is the comparative efficacy between classes of agents on outcomes: symptomatic objectively confirmed VTE, major VTE, PE, fatal PE, nonfatal PE, PTS, mortality, mortality due to bleeding, DVT (asymptomatic or symptomatic, proximal or distal DVT), asymptomatic DVT, symptomatic DVT, proximal DVT, distal DVT, major bleeding, major bleeding leading to reoperation, minor bleeding, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, HIT, discomfort, readmission, and reoperation? Classes include oral antiplatelet agents, injectable LMWHs, injectable UFH, injectable or oral factor Xa inhibitors, injectable or oral DTIs, oral VKAs, and mechanical interventions.						
While we sought to determine the impact of	**1 RCT**	**1 Signal**	**NA**	**None**	Three of the four experts said the	**Possibly out**

therapy on numerous outcomes, we were only able to discern significant differences between classes for relatively few outcomes. For the other outcomes, either there was a lack of evaluable data or no significant differences were found. Variable levels of statistical heterogeneity were detected in the base case analyses, and in a few cases, heterogeneity improved when each surgery was evaluated separately in subgroup analysis while other times the heterogeneity increased. However, in the majority of cases, the number of trials in a subgroup analysis was too low to evaluate statistical heterogeneity. We could not determine if this means that there is a lack of effect versus a lack of power to show that it is significant. The results of previous meta-analyses are in general agreement with the findings of our comparative effectiveness review. When compared directly with UFH, LMWH agents, as a class, have a better comparative balance of benefits and harms with significantly fewer PEs, DVTs, proximal DVTs, major bleeding, and HIT events. A higher level of statistical heterogeneity was detected in the evaluation of PE. <u>The comparative balance of benefits and harms for LMWHs with other classes could not be readily determined</u>. LMWH agents were also superior to VKAs at reducing measures of DVT (any, asymptomatic, proximal, and distal) but increased major, minor, and surgical site bleeding. A higher level of statistical heterogeneity was detected in the evaluation of DVT as was the presence of publication bias, which suggested an underestimation of the benefit of LMWH. Since no significant differences were found in important final health outcomes, the relevance of these reductions in DVT needs to be considered. LMWHs may be inferior to factor Xa inhibitors in terms of any, proximal, and distal DVTs but have a lower risk of major and minor bleeding. A higher	[7]	**Dabigatran vs. Enoxaparin** <u>*During Treatment Period:*</u> <u>Major VTE and VTE-related mortality[# of pts with event/total # (%, 95% CI)]:</u> 18/805 (2.2%, 1.2 to 3.3%) versus 33/794 (4.2%, 2.8 to 5.5%) <u>Absolute risk difference; 95% CI.; p-value:</u> – 1.9% (-3.6 to –0.2%); p=0.03 <u>Primary efficacy outcome [# of pts with event/total # (%, 95% CI)]:</u> 61/792 (7.7%, 5.8 to 9.6%) versus 69/785 (8.8%, 6.8 to 10.8%) <u>Absolute risk difference; 95% CI.; p-value:</u> – 1.1% (-3.8 to 1.6%); 0.43 <u>Total DVT[# of pts with event/total # (%)]:</u> 60/791 (7.6%) versus 67/783 (8.6%)			conclusions for this question were valid. However, one of the four experts disagreed with the methodology, analyzes and conclusion of this question. He has did not referenced any evidence.	**of date**

level of statistical heterogeneity was detected in the evaluation of proximal DVT and major bleeding. Observational data suggested LMWH agents had decreased mortality, although this was not supported by data pooled from RCTs, which showed no significant difference. Comparing LMWH agents with DTIs is difficult because the occurrence of DVT was greater, but the occurrence of distal DVT was less with LMWHs, and while surgical site bleeding is higher LMWH therapy, the overall risk of serious bleeding was not significantly altered. This part is taken from page 103 of CER: " While no significant differences occurred in the base case analysis, injectable low molecular weight heparin agents had significantly more proximal deep venous thrombosis events versus injectable or oral direct thrombin inhibitors in total hip replacement surgery." Finally, when LMWH agents were compared versus mechanical prophylaxis, the only significant difference is the lower occurrence for patient discomfort in the group receiving LMWHs. It is difficult to discern the comparative balance of benefits and harms for oral antiplatelet therapy versus mechanical prophylaxis or VKAs. Oral antiplatelet therapy had significantly greater occurrence of any and distal DVT versus mechanical prophylaxis. In a controlled observational study, oral VKAs had significantly fewer fatal PE events versus oral antiplatelet agents. In the only available RCT comparing VKAs to oral antiplatelet agents, the same direction of effect was found, suggesting VKA superiority, but this was not significant. Mortality was higher in patients receiving aspirin versus warfarin in one observational study and was nonsignificantly trending in that direction in another observational study, but showed no difference in a clinical trial.		Absolute risk difference; 95% CI.; p-value: – 1.0% (-3.7 to 1.7%); 0.48 Proximal DVT[# of pts with event/total # (%)]: 17/804 (2.1%) versus 31/792 (3.9%) Absolute risk difference; 95% CI.; p-value: – 1.8% (-3.5 to –0.1%); 0.04 Distal DVT[# of pts with event/total # (%)]: 43/792 (5.4%) versus 35/785 (4.5%) Symptomatic VTE [# of pts with event/total # (%)]: 1/1,001 (0.1%) versus 6/992 (0.6%) Symptomatic DVT[# of pts with event/total # (%); p-value]: 0/1,001 (0.0%) versus 4/992 (0.4%); 0.06 Symptomatic non-fatal PE[# of pts with event/total # (%); p-value]: 1/1,001 (0.1%) versus 2/992 (0.2%); p=0.62				

UFH, which was found to be inferior to LMWH agents in the balance of benefits and harms, had a greater occurrence of death and major bleeding versus factor Xa inhibitors in an observational study (with no clinical trial data to support or refute the findings), had a greater occurrence of any and proximal DVT versus DTIs, and had a greater occurrence of DVT versus mechanical prophylaxis. As such, it is likely inferior to factor Xa inhibitors in the balance of benefits and harms as well. Patients receiving VKAs had less occurrence of proximal DVT versus mechanical prophylaxis, but with no other differences in other health outcomes or bleeding, it is hard to discern a difference in the balance of efficacy to harms between them.		Death [# of pts with event/total # (%); p-value]: 0/1,001 (0.0%) versus 1/992 (0.1%); p=0.50 *During Follow-up Period:* Total VTE and all-cause mortality[# of pts with event/total # (%); p-value]: 2/942 (0.2%) versus 4/951 (0.4%); p= 0.69 Symptomatic VTE[# of pts with event/total # (%)]: 2/942 (0.2%) versus 2/951 (0.2%) Death [# of pts with event/total # (%)]: 0/942 (0.0%) versus 1/951 (0.1%) *Total study period (treatment + follow-up)* Symptomatic VTE + all-cause mortality[# of pts with event/total # (%)]: 3/942 (0.3%) versus 10/951 (1.1%) *Bleeding outcomes:*				

		Major bleeding, No. patients (%, 95% CI);p-value: 14 (1.4%; 0.8 to 2.3%) vs. 9 (0.9%; 0.4 to 1.7%); 0.40 Clinically overt leading to transfusion of 2 units of packed cells or whole blood (# of events): 12 vs. 6 Leading to re-operation (# of events): 0 vs. 0 Minor bleeding – No. patients (%) 61 (6.0%) versus 54 (5.4%)				
Key question 6: In patients undergoing major orthopedic surgery (total hip or knee replacement or hip fracture surgery), what is the comparative efficacy of individual agents within classes (LMWH and mechanical devices) on symptomatic objectively confirmed VTE, major VTE, PE, fatal PE, nonfatal PE, PTS, mortality, mortality due to bleeding, DVT (asymptomatic or symptomatic, proximal or distal DVT), asymptomatic DVT, symptomatic DVT, proximal DVT, distal DVT, major bleeding, major bleeding leading to reoperation, minor bleeding, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, HIT, discomfort, readmission, and reoperation?						
For both LMWHs and mechanical devices, there were no significant differences in PE (any, fatal, and nonfatal), mortality, and mortality due to bleeding between modalities within a class, but these evaluations were based on one or two trials with either no events or a very low number of events. The balance of benefits and harms from using enoxaparin versus another low molecular weight heparin within the class (dalteparin or tinzaparin) is similar. No difference in the occurrence of DVT or proximal DVT occurred between LMWHs (enoxaparin versus either tinzaparin or dalteparin). No significant difference was seen in	**3 RCTs** [5]	**3 Signals** **Semuloparin vs. Enoxaparin** Any DVT, OR [95% CI]: 0.54 [0.38–0.76] in Hip replacement RCT 0.73 [0.50–1.05] in Hip surgery RCT 0.83 [0.61–1.13] in Knee Replacement RCT	**NA**	**None**	All of the four experts said that the conclusions for this question were valid.	**Possibly out of date**

asymptomatic DVT between enoxaparin and dalteparin, symptomatic DVT between enoxaparin and tinzaparin, or distal DVT between enoxaparin and tinzaparin. For major bleeding, two trials compared LMWHs and found no differences between enoxaparin and either dalteparin or tinzaparin. For minor bleeding, one trial found no significant difference between enoxaparin and tinzaparin for this outcome. For surgical site bleeding, two trials compared LMWHs and found no differences between enoxaparin and either dalteparin or tinzaparin. For HIT, one trial found no significant difference between enoxaparin and tinzaparin for this outcome. The balance of benefits and harms for different mechanical modalities within a class could not be determined with the current literature base. The Venaflow pneumatic compression device significantly reduced the occurrence of DVT or distal DVT versus the Kendall pneumatic compression device in the only trial but did not significantly reduce proximal DVT. Intermittent compression stockings significantly reduced the occurrence of DVT or distal DVT versus graduated compression stockings but did not significantly reduce proximal DVT. In the only observational study, two intermittent compression devices were compared (ActiveCare system vs. Flowtron excel pump) and found to have a similar occurrence of DVT. Harms were not assessed in these trials or observational studies.		Any proximal DVT, OR [95% CI] 0.87 [0.40–1.86] in Hip replacement RCT 0.48 [0.23–0.93] in Hip surgery RCT 1.74 [0.79–3.99] in Knee Replacement RCT Distal DVT only, OR [95% CI] 0.49 [0.33–0.72] in Hip replacement RCT 0.97 [0.63–1.50]] in Hip surgery RCT 0.77 [0.55–1.06] in Knee Replacement RCT Non-fatal PE, n/N (%) 0/1152 (0) vs. 0/1150 (0) 0/499 (0) vs. 1/488 (0.2) 1/568 (0.2) vs. 0/573 (0) All-cause death, OR [95% CI] 0.50 [0.02–6.59] 2.05 [0.36–16.08] not estimable Secondary outcomes Major VTE or all cause mortality, OR (95% CI): 0.68 (0.35–1.33)				

		0.71 (0.41–1.24) 1.18 (0.67–2.08) Clinically relevant bleeding, OR (95% CI): 0.48(0.23–0.94) Major bleeding, OR (95% CI): 0.28 (0.08–0.83) **(Knee replacement RCT)** Clinically relevant bleeding, OR (95% CI): 1.5 (0.67–3.49) **(Hip surgery RCT)** Clinically relevant bleeding, OR (95% CI): 2.59, 95%CI 0.83–9.57 **Enoxaparin vs. Semuloparin** **(Knee replacement RCT)** Major bleeding incidence, n(%) 4 (0.7) vs. 3 (0.5) OR (95% CI): 0.74 (0.14–3.61) **(Hip surgery RCT)** Major bleeding incidence, n(%) 3 (0.6) vs. 5 (1.0) OR (95% CI):				

		1.71 (0.39–8.73)				
Key question 7: In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery), what are the effect estimates of combined pharmacologic and mechanical modalities versus single modality on symptomatic objectively confirmed VTE, major VTE, PE, fatal PE, nonfatal PE, PTS, mortality, mortality due to bleeding, DVT (asymptomatic or symptomatic, proximal or distal DVT), asymptomatic DVT, symptomatic DVT, proximal DVT, distal DVT, major bleeding, major bleeding leading to reoperation, minor bleeding, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, HIT, discomfort, readmission, and reoperation?						
The balance of benefits and harms for combining a pharmacologic and mechanical strategy versus using either strategy alone in patients undergoing major orthopedic surgery could not be determined. The use of a pharmacologic plus mechanical strategy versus either pharmacologic or mechanical prophylaxis did not significantly impact nonfatal PE, mortality, or DVT subsets (asymptomatic, symptomatic, proximal, or distal). The comparative impact of pharmacologic plus mechanical prophylaxis versus pharmacologic or mechanical prophylaxis on major or minor bleeding could not be determined. There was moderate evidence that the use of pharmacologic plus mechanical prophylaxis significantly decreases the occurrence of DVT versus pharmacologic prophylaxis alone. The impact of dual prophylaxis versus single modality on other outcomes could not be determined.	**No new evidence**	**NA**	**NA**	**None**	Two of the four experts said the conclusions for this question were valid. One of the four experts said she does not know if the conclusions are valid or not. However, one of the four experts disagreed with the methodology, analyzes and conclusion of this question and he did not referenced any evidence.	**Uptodate**
Key question 8: In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery), regardless of thromboprophylaxis method, what are the effects of prolonging thromboprophylaxis for 28 days or longer compared with thromboprophylaxis for 7 to 10 days on symptomatic objectively confirmed VTE, major VTE, PE, fatal PE, nonfatal PE, PTS, mortality, mortality due to bleeding, DVT (asymptomatic or symptomatic, proximal or distal DVT), asymptomatic DVT, symptomatic DVT, proximal DVT, distal DVT, major bleeding, major bleeding leading to reoperation, minor bleeding, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, HIT, discomfort, readmission, and reoperation?						
Prolonged prophylaxis had a better comparative balance of benefits and harms versus short-term prophylaxis in patients undergoing major orthopedic surgery. The impact of prolonging prophylaxis for 28 days or longer on events was compared with prophylaxis for 7 to 10 days in patients who had major orthopedic surgery. Prolonged prophylaxis reduced the occurrence of symptomatic objectively confirmed VTE, PE	**No new evidence**	**NA**	**NA**	**None**	Three of the four experts said the conclusions for this question were valid, and one of the four experts said she does not know if the conclusions are still valid or not.	**Uptodate**

(overall and nonfatal), and DVT (overall, symptomatic, asymptomatic, and proximal) versus shorter term prophylaxis. Statistically significant publication bias was detected in the evaluation of distal DVT and nonfatal PE although the directionality was unclear. While higher heterogeneity was found for symptomatic VTE and DVT, the direction of effect was consistent among all of the trials. In base case analyses, prolonged prophylaxis increases the occurrence of minor bleeding and surgical site bleeding versus shorter term prophylaxis. Four previous meta-analyses compared the impact of longer versus shorter duration pharmacologic prophylaxis and are in general agreement with our present comparative effectiveness review.						
Key question 9: In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery) who have known contraindications to antithrombotic agents, what is the relative impact of prophylactic inferior vena cava (IVC) filter placement compared with any external mechanical intervention on symptomatic objectively confirmed VTE, major VTE, PE, fatal PE, nonfatal PE, PTS, mortality, mortality due to bleeding, DVT (asymptomatic or symptomatic, proximal or distal DVT), asymptomatic DVT, symptomatic DVT, proximal DVT, distal DVT, major bleeding, major bleeding leading to reoperation, minor bleeding, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, HIT, discomfort, readmission, reoperation, and IVC filter placement associated insertion site thrombosis?						
There were no trials or studies that met our inclusion criteria.	**No new evidence**	**NA**	**NA**	**None**	Two of the four experts said the conclusions for this question were valid, and one of the four experts said she does not know if the conclusions are still valid or not. One of the four experts said the conclusions were not valid and he referenced a guideline that continued two studies as evidence for this question. However, both studies were not included in this assessment because they did not meet the eligibility criteria of the original CER.	**Uptodate**
Key question 10: In patients requiring knee arthroscopy, surgical repair of a lower extremity injury distal to the hip, or elective spine surgery, what is the relative impact of thromboprophylaxis (any agent, any mechanical intervention) compared with no thromboprophylaxis intervention on symptomatic objectively confirmed VTE, major VTE, PE, fatal PE, nonfatal PE, PTS, mortality, mortality due to bleeding, DVT (asymptomatic or symptomatic, proximal or distal DVT), asymptomatic DVT, symptomatic DVT, proximal DVT, distal DVT, major bleeding, major bleeding leading to reoperation, minor bleeding, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, HIT, discomfort, readmission, and reoperation?						
One trial was available for Achilles tendon rupture and for knee arthroscopy, but no literature met	**No new evidence**	**NA**	**NA**	**None**	Two of the four experts said the conclusions for this question were	**Uptodate**

inclusion criteria for elective spine surgery. Both of the available trials were small in size leading to limited power to detect differences between the groups compared. The comparative balance of benefits and harms for dalteparin therapy versus placebo or control was difficult to discern based on the scant data. In patients who had surgical repair of Achilles tendon rupture, the use of dalteparin versus placebo for 6 weeks did not significantly impact the incidence of total or proximal DVT. No patients developed a PE or major bleeding. In patients who had arthroscopic knee surgery, the use of dalteparin versus control led to significantly fewer patients with total or distal DVT. One patient in the dalteparin group developed a PE and also had a DVT. No patients had major bleeding, and the occurrence of minor bleeding was not significantly different between the two groups.					valid. One of the four experts said she does not know if the conclusions are valid or not. However, one of the four experts said the conclusions were not valid and he disagreed with the methodology, analyzes and conclusion of this question. He did not reference any evidence.	
Key question 11: In patients requiring knee arthroscopy, surgical repair of a lower extremity injury distal to the hip, or elective spine surgery, what is the relative impact of injectable antithrombotic agents (LMWH vs. UFH vs. factor Xa inhibitors vs. DTIs) compared with mechanical interventions on symptomatic objectively confirmed VTE, major VTE, PE, fatal PE, nonfatal PE, PTS, mortality, mortality due to bleeding, DVT (asymptomatic or symptomatic, proximal or distal DVT), asymptomatic DVT, symptomatic DVT, proximal DVT, distal DVT, major bleeding, major bleeding leading to reoperation, minor bleeding, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, HIT, discomfort, readmission, and reoperation?						
There were no trials or studies that met our inclusion criteria.	**No new evidence**	**NA**	**NA**	**None**	Three of the four experts said the conclusions were valid, and one of them referenced a study but we did not include it in this report because it did not meet the eligibility criteria of the original CER. One of the four experts said she does not know if the conclusions are still valid or not.	**Uptodate**
CER=comparative effectiveness review; FDA=food and drug administration; NA=not applicable; CI=confidence interval; DVT=Deep venous thrombosis; VTE: venous thromboembolism; PE= pulmonary embolism; OR= pulmonary embolism; RCT=Randomized Clinical Trial; mg= milligram; %= percentage						

Reference List

1. **Sobieraj DM, Coleman CI, Tongbram V et al. Venous Thromboembolism Prophylaxis in Orthopedic Surgery. 2012 Mar.**

2. **Shekelle P, Newberry S, Maglione M et al. Assessment of the need to update comparative effectiveness reviews: Report of an initial rapid program assessment (2005-2009) [Internet]. 2009 Sep 10.**

3. **Shojania KG, Sampson M, Ansari MT, et al. How quickly do systematic reviews go out of date? A survival analysis. Ann Intern Med 2007 Aug 21;147(4):224-33. [PMID: PM:17638714].**

4. **Shekelle PG, Newberry SJ, Wu H et al. Identifying signals for updating systematic reviews: A comparison of two methods [Internet]. 2011 Jun.**

5. **Lassen MR, Fisher W, Mouret P, et al. Semuloparin for prevention of venous thromboembolism after major orthopedic surgery: results from three randomized clinical trials, SAVE-HIP1, SAVE-HIP2 and SAVE-KNEE. J Thromb Haemost 2012 May;10(5):822-32. [PMID: 22429800].**

6. **Fuji T, Fujita S, Tachibana S, et al. A dose-ranging study evaluating the oral factor Xa inhibitor edoxaban for the prevention of venous thromboembolism in patients undergoing total knee arthroplasty. J Thromb Haemost 2010 Nov;8(11):2458-68. [PMID: 20723033].**

7. **Eriksson BI, Dahl OE, Huo MH, et al. Oral dabigatran versus enoxaparin for thromboprophylaxis after primary total hip arthroplasty (RE-NOVATE II*). A randomised, double-blind, non-inferiority trial. Thromb Haemost 2011 Apr;105(4):721-9. [PMID: PM:21225098].**

8. **Bass AR, Mattern CJ, Voos JE, et al. Inferior vena cava filter placement in orthopedic surgery. Am J Orthop (Belle Mead NJ) 2010 Sep;39(9):435-9. [PMID: PM:21290021].**

9. **Rajasekhar A, Lottenberg R, Lottenberg L, et al. Pulmonary embolism prophylaxis with inferior vena cava filters in trauma patients: a systematic review using the meta-analysis of observational studies in epidemiology (MOOSE) guidelines. J Thromb Thrombolysis 2011 Jul;32(1):40-6. [PMID: PM:21221716].**

10. **Falck-Ytter Y, Francis CW, Johanson NA, et al. Prevention of VTE in orthopedic surgery patients: Antithrombotic Therapy and Prevention of Thrombosis, 9th ed: American College of Chest Physicians Evidence-Based Clinical Practice Guidelines. Chest 2012 Feb;141(2 Suppl):e278S-e325S . [PMID: PM:22315265].**

11. **Maletis GB, Inacio MC, Reynolds S, et al. Incidence of symptomatic venous thromboembolism after elective knee arthroscopy. J Bone Joint Surg Am 2012 Apr 18;94(8):714-20. [PMID: PM:22517387].**

Appendix A: Search Methodology

Journal limits were incorporated into the OVID searches, and the equivalent limit was imposed manually by the search expert on the Central search results. All searches were limited to the following journals:

General biomedical - Annals of Internal Medicine, British Medical Journal, Journal of the American Medical Association, Lancet, and New England Journal of Medicine

Specialty journals - Journal of Bone & Joint Surgery (American volume), Clinical Orthopedics and Related Research, Journal of Thrombosis & Haemostasis, Journal of Arthroplasty, and Archives of Internal Medicine.

Database: Ovid MEDLINE(R)
Time period covered by the search: November 1st, 2012 to September 18th, 2012.

Database: Scopus
Time period covered by the search: January 1st, 2011to Sep 24th, 2012.

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>, EBM Reviews - Cochrane Central Register of Controlled Trials <September 2012>

Search Strategy:

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1 knee arthroscop*.mp. (1260)
2 (arthroscop* adj knee).mp. (661)
3 (meniscectomy adj arthroscop*).mp. (5)
4 (synovectomy adj arthroscop*).mp. (11)
5 (cruciate ligament and (arthroscop* or repair)).mp. (4675)
6 casts, surgical/ or casts, surgical.mp. (7963)
7 plaster cast.mp. (1355)
8 splint*.mp. or splints/ (15920)
9 (Achilles adj tendon).mp. (7131)
10 tibial plateau fracture.mp. (189)
11 (distal adj femur fracture).mp. (46)
12 (lumbar adj laminectomy).mp. (416)
13 (lumbar adj diskectomy).mp. (91)
14 (lumbar adj spinal fusion).mp. (329)
15 (fracture fixation, internal/ or fracture fixation, intramedullary/) and (femur or femor* or tibia* or ankle or foot).mp. (13074)
16 (osteotomy and (femur or femor* or tibia*)).mp. (9060)
17 or/1-16 (57859)
18 pulmonary embolism/ (30203)
19 pulmonary embol*.mp. (39712)
20 pulmonary thromboembol*.mp. (2648)
21 PE.mp. (23152)
22 deep vein thrombos*.mp. (11614)
23 deep venous thrombos*.mp. (8622)
24 deep venous thromboembol*.mp. (74)
25 deep vein thromboembol*.mp. (20)
26 DVT.mp. (6632)

27 venous thromboembolism/ (3262)
28 venous thromboembol*.mp. (12527)
29 VTE.mp. (4256)
30 venous thrombosis/ (16753)
31 venous thrombos*.mp. (31188)
32 clot.mp. (14309)
33 or/18-32 (106204)
34 anticoagulants/ (51481)
35 aspirin/ (40170)
36 aspirin.mp. (56931)
37 clopidogrel.mp. (8544)
38 ticlopidine.mp. (8457)
39 prasugrel.mp. (751)
40 heparin/ (49919)
41 heparinoids/ (779)
42 heparin.mp. (85560)
43 UFH.mp. (1762)
44 heparin, low-molecular weight/ (7099)
45 low molecular weight heparin.mp. (8489)
46 LMWH.mp. (3623)
47 enoxaparin.mp. (4217)
48 dalteparin.mp. (1294)
49 nadroparin.mp. (699)
50 ardeparin.mp. (45)
51 bemiparin.mp. (88)
52 certoparin.mp. (128)
53 parnaparin.mp. (60)
54 reviparin.mp. (174)
55 tinzaparin.mp. (434)
56 danaparoid.mp. (373)
57 fondaparinux.mp. (1341)
58 idraparinux.mp. (153)
59 rivaroxaban.mp. (722)
60 hirudins/ (2991)
61 desirudin.mp. (177)
62 argatroban.mp. (1117)
63 bivalirudin.mp. (1058)
64 lepirudin.mp. (546)
65 dabigatran.mp. (889)
66 warfarin/ (14015)
67 4-Hydroxycoumarins/ (678)
68 warfarin.mp. (20105)
69 acenocoumarol.mp. (1348)
70 dicoumarol.mp. (640)
71 dextran sulfate/ (2794)
72 dextran sulfate.mp. (4402)
73 or/34-72 (189892)
74 stockings, compression/ (877)
75 compression stocking.mp. (164)
76 compression stockings.mp. (1102)
77 compression boot.mp. (11)
78 graduated compression stocking.mp. (28)
79 graduated compression stockings.mp. (317)
80 elastic stocking.mp. (80)
81 elastic stockings.mp. (382)
82 GCS.mp. (7101)

83 venous foot pump.mp. (13)
84 intermittent pneumatic compression devices/ (377)
85 intermittent pneumatic compression.mp. (822)
86 pneumatic compression stocking.mp. (6)
87 pneumatic compression stockings.mp. (29)
88 pneumatic hose.mp. (1)
89 pneumatic compression hose.mp. (2)
90 IPC.mp. (2102)
91 or/74-90 (11695)
92 73 or 91 (200663)
93 17 and 33 and 92 (164)
94 lancet.jn. (129341)
95 jama.jn. (62989)
96 "annals of internal medicine".jn. (28788)
97 bmj.jn. (74597)
98 "new england journal of medicine".jn. (66322)
99 "journal of bone & joint surgery american volume".jn. (15288)
100 "clinical orthopaedics & related research".jn. (20096)
101 "journal of thrombosis & haemostasis".jn. (4636)
102 "journal of arthroplasty".jn. (4778)
103 "archives of internal medicine".jn. (20357)
104 or/94-103 (427192)
105 93 and 104 (22)
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107 105 and 106 (2)
108 107 use prmz (2)
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110 (arthroscop* adj knee).mp. (661)
111 (meniscectomy adj arthroscop*).mp. (5)
112 (synovectomy adj arthroscop*).mp. (11)
113 (cruciate ligament and (arthroscop* or repair)).mp. (4675)
114 casts, surgical/ or casts, surgical.mp. (7963)
115 plaster cast.mp. (1355)
116 splint*.mp. or splints/ (15920)
117 (Achilles adj tendon).mp. (7131)
118 tibial plateau fracture.mp. (189)
119 (distal adj femur fracture).mp. (46)
120 (lumbar adj laminectomy).mp. (416)
121 (lumbar adj diskectomy).mp. (91)
122 (lumbar adj spinal fusion).mp. (329)
123 (fracture fixation, internal/ or fracture fixation, intramedullary/) and (femur or femor* or tibia* or ankle or foot).mp. (13074)
124 (osteotomy and (femur or femor* or tibia*)).mp. (9060)
125 or/109-124 (57859)
126 pulmonary embolism/ (30203)
127 pulmonary embol*.mp. (39712)
128 pulmonary thromboembol*.mp. (2648)
129 PE.mp. (23152)
130 deep vein thrombos*.mp. (11614)
131 deep venous thrombos*.mp. (8622)
132 deep venous thromboembol*.mp. (74)
133 deep vein thromboembol*.mp. (20)
134 DVT.mp. (6632)
135 venous thromboembolism/ (3262)
136 venous thromboembol*.mp. (12527)
137 VTE.mp. (4256)

138 venous thrombosis/ (16753)
139 venous thrombos*.mp. (31188)
140 clot.mp. (14309)
141 or/126-140 (106204)
142 anticoagulants/ (51481)
143 aspirin/ (40170)
144 aspirin.mp. (56931)
145 clopidogrel.mp. (8544)
146 ticlopidine.mp. (8457)
147 prasugrel.mp. (751)
148 heparin/ (49919)
149 heparinoids/ (779)
150 heparin.mp. (85560)
151 UFH.mp. (1762)
152 heparin, low-molecular weight/ (7099)
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156 dalteparin.mp. (1294)
157 nadroparin.mp. (699)
158 ardeparin.mp. (45)
159 bemiparin.mp. (88)
160 certoparin.mp. (128)
161 parnaparin.mp. (60)
162 reviparin.mp. (174)
163 tinzaparin.mp. (434)
164 danaparoid.mp. (373)
165 fondaparinux.mp. (1341)
166 idraparinux.mp. (153)
167 rivaroxaban.mp. (722)
168 hirudins/ (2991)
169 desirudin.mp. (177)
170 argatroban.mp. (1117)
171 bivalirudin.mp. (1058)
172 lepirudin.mp. (546)
173 dabigatran.mp. (889)
174 warfarin/ (14015)
175 4-Hydroxycoumarins/ (678)
176 warfarin.mp. (20105)
177 acenocoumarol.mp. (1348)
178 dicoumarol.mp. (640)
179 dextran sulfate/ (2794)
180 dextran sulfate.mp. (4402)
181 or/142-180 (189892)
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184 compression stockings.mp. (1102)
185 compression boot.mp. (11)
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187 graduated compression stockings.mp. (317)
188 elastic stocking.mp. (80)
189 elastic stockings.mp. (382)
190 GCS.mp. (7101)
191 venous foot pump.mp. (13)
192 intermittent pneumatic compression devices/ (377)
193 intermittent pneumatic compression.mp. (822)

194 pneumatic compression stocking.mp. (6)
195 pneumatic compression stockings.mp. (29)
196 pneumatic hose.mp. (1)
197 pneumatic compression hose.mp. (2)
198 IPC.mp. (2102)
199 or/182-198 (11695)
200 181 or 199 (200663)
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205 ("annals of internal medicine" or "annals internal medicine").jn. (28791)
206 (bmj or bmj british medical journal or bmj clinical research ed).jn. (76041)
207 (british medical journal or british medical journal 1857 or british medical journal clinical research or british medical journal clinical research ed or british medical journal clinical research edition).jn. (111715)
208 ("new england journal of medicine" or "new england journal of medicine the" or new engljmed).jn. (66331)
209 "the new england journal of medicine".jn. (68829)
210 "journal of bone & joint surgery american volume".jn. (15288)
211 ("the journal of bone and joint surgery" or "the journal of bone and joint surgery american volume").jn. (420)
212 (clinical orthopaedic related research or clinical orthopaedics or clinical orthopaedics & related research or "clinical orthopaedics and related research" or clinical orthopaedics related research or clinical orthopeadics related research).jn. (20824)
213 ("journal of thrombosis & haemostasis" or "journal of thrombosis and haemostasis" or "journal of thrombosis and haemostasis jth").jn. (4807)
214 "journal of arthroplasty".jn. (4778)
215 "the journal of arthroplasty".jn. (5003)
216 ("archives of internal medicine" or "archives of internal medicne" or "archives internal medicine").jn. (20360)
217 or/202-216 (555294)
218 201 and 217 (24)
219 limit 218 to yr="2010-current" (4)
220 219 use cctr (0)
221 108 or 220 (2)
222 remove duplicates from 221 (1)
223 221 not 222 (1)
224 223 use prmz (1)
225 223 use cctr (0)

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>, EBM Reviews - Cochrane Central Register of Controlled Trials <September 2012>

Search Strategy:

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1 arthroplasty, replacement, knee/ (11708)

2 knee.mp. and arthroplasty/ (1212)
3 total knee replacement.mp. (3783)
4 knee arthroplasty.mp. (10499)
5 TKR.mp. (1118)
6 knee prosthesis/ (8586)
7 knee prosthesis.mp. (9091)
8 knee joint.mp. (43752)
9 arthroplasty, replacement, hip/ (16040)
10 hip.mp. and arthroplasty/ (1946)
11 total hip replacement.mp. (7076)
12 hip arthroplasty.mp. (12084)
13 THR.mp. (20355)
14 hip prosthesis/ (19072)
15 hip prosthesis.mp. (19848)
16 hip fracture surgery.mp. (487)
17 HFS.mp. (1568)
18 hip.mp. and fracture fixation, internal/ (2924)
19 or/1-18 (110995)
20 pulmonary embolism/ (30203)
21 pulmonary embol*.mp. (39705)
22 pulmonary thromboembol*.mp. (2648)
23 PE.mp. (23132)
24 deep vein thrombos*.mp. (11611)
25 deep venous thrombos*.mp. (8621)
26 deep venous thromboembol*.mp. (74)
27 deep vein thromboembol*.mp. (20)
28 DVT.mp. (6629)
29 venous thromboembolism/ (3262)
30 venous thromboembol*.mp. (12519)
31 VTE.mp. (4248)
32 venous thrombosis/ (16753)
33 venous thrombos*.mp. (31180)
34 clot.mp. (14299)
35 or/20-34 (106154)
36 anticoagulants/ (51481)
37 aspirin/ (40170)
38 aspirin.mp. (56927)
39 clopidogrel.mp. (8541)
40 ticlopidine.mp. (8457)
41 prasugrel.mp. (751)
42 heparin/ (49919)
43 heparinoids/ (779)
44 heparin.mp. (85546)
45 UFH.mp. (1761)
46 heparin, low-molecular weight/ (7099)
47 [or/36-74] (0)
48 [or/76-93] (0)
49 [or/95-98] (0)
50 [or/102-111] (0)
51 [or/117-134] (0)
52 [or/136-150] (0)
53 [or/152-190] (0)
54 [or/192-209] (0)
55 [or/211-214] (0)
56 [or/218-232] (0)
57 [limit 234 to yr="2010-current"] (0)

58 [remove duplicates from 237] (0)
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61 total knee replacement.mp. (3783)
62 knee arthroplasty.mp. (10499)
63 TKR.mp. (1118)
64 knee prosthesis/ (8586)
65 knee prosthesis.mp. (9091)
66 knee joint.mp. (43752)
67 arthroplasty, replacement, hip/ (16040)
68 hip.mp. and arthroplasty/ (1946)
69 total hip replacement.mp. (7076)
70 hip arthroplasty.mp. (12084)
71 THR.mp. (20355)
72 hip prosthesis/ (19072)
73 hip prosthesis.mp. (19848)
74 hip fracture surgery.mp. (487)
75 HFS.mp. (1568)
76 hip.mp. and fracture fixation, internal/ (2924)
77 or/59-76 (110995)
78 pulmonary embolism/ (30203)
79 pulmonary embol*.mp. (39705)
80 pulmonary thromboembol*.mp. (2648)
81 PE.mp. (23132)
82 deep vein thrombos*.mp. (11611)
83 deep venous thrombos*.mp. (8621)
84 deep venous thromboembol*.mp. (74)
85 deep vein thromboembol*.mp. (20)
86 DVT.mp. (6629)
87 venous thromboembolism/ (3262)
88 venous thromboembol*.mp. (12519)
89 VTE.mp. (4248)
90 venous thrombosis/ (16753)
91 venous thrombos*.mp. (31180)
92 clot.mp. (14299)
93 or/78-92 (106154)
94 anticoagulants/ (51481)
95 aspirin/ (40170)
96 aspirin.mp. (56927)
97 clopidogrel.mp. (8541)
98 ticlopidine.mp. (8457)
99 prasugrel.mp. (751)
100 heparin/ (49919)
101 heparinoids/ (779)
102 heparin.mp. (85546)
103 UFH.mp. (1761)
104 heparin, low-molecular weight/ (7099)
105 low molecular weight heparin.mp. (8487)
106 LMWH.mp. (3621)
107 enoxaparin.mp. (4217)
108 dalteparin.mp. (1294)
109 nadroparin.mp. (699)
110 ardeparin.mp. (45)
111 bemiparin.mp. (88)
112 certoparin.mp. (128)
113 parnaparin.mp. (60)

114 reviparin.mp. (174)
115 tinzaparin.mp. (434)
116 danaparoid.mp. (373)
117 fondaparinux.mp. (1340)
118 idraparinux.mp. (153)
119 rivaroxaban.mp. (721)
120 hirudins/ (2991)
121 desirudin.mp. (177)
122 argatroban.mp. (1116)
123 bivalirudin.mp. (1056)
124 lepirudin.mp. (546)
125 dabigatran.mp. (886)
126 warfarin/ (14015)
127 4-Hydroxycoumarins/ (678)
128 warfarin.mp. (20096)
129 acenocoumarol.mp. (1348)
130 dicoumarol.mp. (639)
131 dextran sulfate/ (2794)
132 dextran sulfate.mp. (4402)
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136 compression stockings.mp. (1102)
137 compression boot.mp. (11)
138 graduated compression stocking.mp. (28)
139 graduated compression stockings.mp. (317)
140 elastic stocking.mp. (80)
141 elastic stockings.mp. (382)
142 GCS.mp. (7096)
143 venous foot pump.mp. (13)
144 VFP.mp. (139)
145 intermittent pneumatic compression devices/ (377)
146 intermittent pneumatic compression.mp. (822)
147 pneumatic compression stocking.mp. (6)
148 pneumatic compression stockings.mp. (29)
149 pneumatic hose.mp. (1)
150 pneumatic compression hose.mp. (2)
151 IPC.mp. (2102)
152 or/134-151 (11828)
153 vena cava filters/ (2032)
154 vena cava filter.mp. (906)
155 vena cava filters.mp. (2184)
156 IVC.mp. (4195)
157 or/153-156 (6058)
158 133 or 152 or 157 (206003)
159 77 and 93 and 158 (1914)
160 lancet.jn. (129318)
161 jama.jn. (62989)
162 "annals of internal medicine".jn. (28788)
163 bmj.jn. (74589)
164 "new england journal of medicine".jn. (66322)
165 "journal of bone & joint surgery american volume".jn. (15288)
166 "clinical orthopaedics & related research".jn. (20096)
167 "journal of thrombosis & haemostasis".jn. (4636)
168 "journal of arthroplasty".jn. (4778)
169 "archives of internal medicine".jn. (20357)

170 or/160-169 (427161)
171 159 and 170 (420)
172 (201011* or 201012* or 2011* or 2012*).ed. (1791047)
173 171 and 172 (28)
174 173 use prmz (28)
175 arthroplasty, replacement, knee/ (11708)
176 knee.mp. and arthroplasty/ (1212)
177 total knee replacement.mp. (3783)
178 knee arthroplasty.mp. (10499)
179 TKR.mp. (1118)
180 knee prosthesis/ (8586)
181 knee prosthesis.mp. (9091)
182 knee joint.mp. (43752)
183 arthroplasty, replacement, hip/ (16040)
184 hip.mp. and arthroplasty/ (1946)
185 total hip replacement.mp. (7076)
186 hip arthroplasty.mp. (12084)
187 THR.mp. (20355)
188 hip prosthesis/ (19072)
189 hip prosthesis.mp. (19848)
190 hip fracture surgery.mp. (487)
191 HFS.mp. (1568)
192 hip.mp. and fracture fixation, internal/ (2924)
193 or/175-192 (110995)
194 pulmonary embolism/ (30203)
195 pulmonary embol*.mp. (39705)
196 pulmonary thromboembol*.mp. (2648)
197 PE.mp. (23132)
198 deep vein thrombos*.mp. (11611)
199 deep venous thrombos*.mp. (8621)
200 deep venous thromboembol*.mp. (74)
201 deep vein thromboembol*.mp. (20)
202 DVT.mp. (6629)
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204 venous thromboembol*.mp. (12519)
205 VTE.mp. (4248)
206 venous thrombosis/ (16753)
207 venous thrombos*.mp. (31180)
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217 heparinoids/ (779)
218 heparin.mp. (85546)
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259 venous foot pump.mp. (13)
260 VFP.mp. (139)
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266 pneumatic compression hose.mp. (2)
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302 knee prosthesis/ (8586)
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308 hip arthroplasty.mp. (12084)
309 THR.mp. (20355)
310 hip prosthesis/ (19072)
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313 HFS.mp. (1568)
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321 deep venous thrombos*.mp. (8621)
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323 deep vein thromboembol*.mp. (20)
324 DVT.mp. (6629)
325 venous thromboembolism/ (3262)
326 venous thromboembol*.mp. (12519)
327 VTE.mp. (4248)

328 venous thrombosis/ (16753)
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337 prasugrel.mp. (751)
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348 ardeparin.mp. (45)
349 bemiparin.mp. (88)
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351 parnaparin.mp. (60)
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356 idraparinux.mp. (153)
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360 argatroban.mp. (1116)
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382 VFP.mp. (139)
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384 intermittent pneumatic compression.mp. (822)
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417 TKR.mp. (1118)
418 knee prosthesis/ (8586)
419 knee prosthesis.mp. (9091)
420 knee joint.mp. (43752)
421 arthroplasty, replacement, hip/ (16040)
422 hip.mp. and arthroplasty/ (1946)
423 total hip replacement.mp. (7076)
424 hip arthroplasty.mp. (12084)
425 THR.mp. (20355)
426 hip prosthesis/ (19072)
427 hip prosthesis.mp. (19848)
428 hip fracture surgery.mp. (487)
429 HFS.mp. (1568)
430 hip.mp. and fracture fixation, internal/ (2924)
431 or/413-430 (110995)
432 pulmonary embolism/ (30203)
433 pulmonary embol*.mp. (39705)
434 pulmonary thromboembol*.mp. (2648)
435 PE.mp. (23132)
436 deep vein thrombos*.mp. (11611)
437 deep venous thrombos*.mp. (8621)
438 deep venous thromboembol*.mp. (74)
439 deep vein thromboembol*.mp. (20)

440 DVT.mp. (6629)
441 venous thromboembolism/ (3262)
442 venous thromboembol*.mp. (12519)
443 VTE.mp. (4248)
444 venous thrombosis/ (16753)
445 venous thrombos*.mp. (31180)
446 clot.mp. (14299)
447 or/432-446 (106154)
448 anticoagulants/ (51481)
449 aspirin/ (40170)
450 aspirin.mp. (56927)
451 clopidogrel.mp. (8541)
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481 4-Hydroxycoumarins/ (678)
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489 compression stocking.mp. (164)
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496 GCS.mp. (7096)
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500 intermittent pneumatic compression.mp. (822)
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503 pneumatic hose.mp. (1)
504 pneumatic compression hose.mp. (2)
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506 or/488-505 (11828)
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509 vena cava filters.mp. (2184)
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513 431 and 447 and 512 (1914)
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523 ("the journal of bone and joint surgery" or "the journal of bone and joint surgery american volume").jn. (420)
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526 "journal of arthroplasty".jn. (4778)
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529 or/514-528 (555263)
530 513 and 529 (518)
531 limit 530 to yr="2010-current" (53)
532 531 use cctr (8)
533 412 or 532 (36)
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Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>, EBM Reviews - Cochrane Central Register of Controlled Trials <September 2012>

Search Strategy:

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4 (synovectomy adj arthroscop*).mp. (11)
5 (cruciate ligament and (arthroscop* or repair)).mp. (4675)
6 casts, surgical/ or casts, surgical.mp. (7963)
7 plaster cast.mp. (1355)
8 splint*.mp. or splints/ (15918)
9 (Achilles adj tendon).mp. (7130)
10 tibial plateau fracture.mp. (189)
11 (distal adj femur fracture).mp. (46)
12 (lumbar adj laminectomy).mp. (416)
13 (lumbar adj diskectomy).mp. (91)
14 (lumbar adj spinal fusion).mp. (329)
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17 or/1-16 (57853)
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20 pulmonary thromboembol*.mp. (2648)
21 PE.mp. (23132)
22 deep vein thrombos*.mp. (11611)
23 deep venous thrombos*.mp. (8621)
24 deep venous thromboembol*.mp. (74)
25 deep vein thromboembol*.mp. (20)
26 DVT.mp. (6629)
27 venous thromboembolism/ (3262)
28 venous thromboembol*.mp. (12519)
29 VTE.mp. (4248)
30 venous thrombosis/ (16753)
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53 parnaparin.mp. (60)

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55 tinzaparin.mp. (434)
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67 4-Hydroxycoumarins/ (678)
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115 plaster cast.mp. (1355)
116 splint*.mp. or splints/ (15918)
117 (Achilles adj tendon).mp. (7130)
118 tibial plateau fracture.mp. (189)
119 (distal adj femur fracture).mp. (46)
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121 (lumbar adj diskectomy).mp. (91)
122 (lumbar adj spinal fusion).mp. (329)
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131 deep venous thrombos*.mp. (8621)
132 deep venous thromboembol*.mp. (74)
133 deep vein thromboembol*.mp. (20)
134 DVT.mp. (6629)
135 venous thromboembolism/ (3262)
136 venous thromboembol*.mp. (12519)
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138 venous thrombosis/ (16753)
139 venous thrombos*.mp. (31180)
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141 or/126-140 (106154)
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147 prasugrel.mp. (751)
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152 heparin, low-molecular weight/ (7099)
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155 enoxaparin.mp. (4217)
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158 ardeparin.mp. (45)
159 bemiparin.mp. (88)
160 certoparin.mp. (128)
161 parnaparin.mp. (60)
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163 tinzaparin.mp. (434)
164 danaparoid.mp. (373)

165 fondaparinux.mp. (1340)
166 idraparinux.mp. (153)
167 rivaroxaban.mp. (721)
168 hirudins/ (2991)
169 desirudin.mp. (177)
170 argatroban.mp. (1116)
171 bivalirudin.mp. (1056)
172 lepirudin.mp. (546)
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174 warfarin/ (14015)
175 4-Hydroxycoumarins/ (678)
176 warfarin.mp. (20096)
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192 intermittent pneumatic compression devices/ (377)
193 intermittent pneumatic compression.mp. (822)
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210 "journal of bone & joint surgery american volume".jn. (15288)
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218 201 and 217 (24)
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221 108 or 220 (2)
222 remove duplicates from 221 (1)
223 221 not 222 (1)
224 223 use prmz (1)
225 223 use cctr (0)

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SCOPUS: Major

Line: 4

(ALL(anticoagulants OR aspirin OR clopidogrel OR ticlopidine OR prasugrel OR heparin OR heparinoids OR ufh OR low-molecular weight heparin OR low molecular weight heparin OR lmwh OR enoxaparin OR dalteparin OR nadroparin OR ardeparin OR bemiparin OR certoparin) OR ALL(parnaparin OR reviparin OR tinzaparin OR danaparoid OR fondaparinux OR idraparinux OR rivaroxaban OR hirudin OR desirudin OR argatroban OR bivalirudin) OR ALL(lepirudin OR dabigatran OR warfarin OR 4-hydroxycoumarin OR acenocoumarol OR dicoumarol OR dextran sulfate) OR ALL(vena cava filters OR vena cava filter OR ivc) OR ALL(compression stocking$) OR ALL(graduated compression stocking$) OR ALL(elastic stocking$) OR ALL(venous foot pump) OR ALL(intermittent pneumatic compression) OR ALL(pneumatic compression)) AND (ALL(deep vein thrombos* OR deep venous thrombos* OR venous thromboembol* OR pulmonary thromboembol* OR pulmonary embol* OR venous thrombos*) AND ALL(knee replacement OR knee arthroplasty OR hip arthroplasty OR hip replacement OR hip fracture surgery) AND (SRCTITLE(lancet)) OR ((SRCTITLE(jama) OR SRCTITLE("journal of the american medical association"))) OR (SRCTITLE("annals of internal medicine")) OR ((SRCTITLE("british medical journal") OR SRCTITLE(bmj))) OR (SRCTITLE("new england journal of medicine")) OR (SRCTITLE("journal of bone and joint surgery")) OR (SRCTITLE("clinical orthopaedics and related research")) OR (SRCTITLE("journal of thrombosis and haemostasis")) OR (SRCTITLE("journal of arthroplasty")) OR (SRCTITLE("archives of internal medicine")))

AND (LIMIT-TO(PUBYEAR, 2013) OR LIMIT-TO(PUBYEAR, 2012) OR LIMIT-TO(PUBYEAR, 2011))

Total: 13

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Line: 1

ALL(anticoagulants OR aspirin OR clopidogrel OR ticlopidine OR prasugrel OR heparin OR heparinoids OR ufh OR low-molecular weight heparin OR low molecular weight heparin OR lmwh OR enoxaparin OR dalteparin OR nadroparin OR ardeparin OR bemiparin OR certoparin) OR ALL(parnaparin OR reviparin OR tinzaparin OR danaparoid OR fondaparinux OR idraparinux OR rivaroxaban OR hirudin OR desirudin OR argatroban OR bivalirudin) OR ALL(lepirudin OR dabigatran OR warfarin OR 4-hydroxycoumarin OR acenocoumarol OR

dicoumarol OR dextran sulfate) OR ALL(vena cava filters OR vena cava filter OR ivc) OR ALL(compression stocking$) OR ALL(graduated compression stocking$) OR ALL(elastic stocking$) OR ALL(venous foot pump) OR ALL(intermittent pneumatic compression) OR ALL(pneumatic compression)

Total: 110,032

AND (LIMIT-TO(PUBYEAR, 2013) OR LIMIT-TO(PUBYEAR, 2012) OR LIMIT-TO(PUBYEAR, 2011))

Total: 15,025

ALL(deep vein thrombos* OR deep venous thrombos* OR venous thromboembol* OR pulmonary thromboembol* OR pulmonary embol* OR venous thrombos*) AND ALL(knee replacement OR knee arthroplasty OR hip arthroplasty OR hip replacement OR hip fracture surgery) AND (SRCTITLE(lancet)) OR ((SRCTITLE(jama) OR SRCTITLE("journal of the american medical association"))) OR (SRCTITLE("annals of internal medicine")) OR ((SRCTITLE("british medical journal") OR SRCTITLE(bmj))) OR (SRCTITLE("new england journal of medicine")) OR (SRCTITLE("journal of bone and joint surgery")) OR (SRCTITLE("clinical orthopaedics and related research")) OR (SRCTITLE("journal of thrombosis and haemostasis")) OR (SRCTITLE("journal of arthroplasty")) OR (SRCTITLE("archives of internal medicine"))

Total: 189

15025 set AND 189 Set

Total:13

19 (((ALL(anticoagulants OR aspirin OR clopidogrel OR ticlopidine OR prasugrel OR heparin OR heparinoids OR ufh OR low-molecular weight heparin OR low molecular weight heparin OR lmwh OR enoxaparin OR dalteparin OR nadroparin OR ardeparin OR bemiparin OR certoparin)) OR (ALL(parnaparin OR reviparin OR tinzaparin OR danaparoid OR fondaparinux OR idraparinux OR rivaroxaban OR hirudin OR desirudin OR argatroban OR bivalirudin)) OR (ALL(lepirudin OR dabigatran OR warfarin OR 4-hydroxycoumarin OR acenocoumarol OR dicoumarol OR dextran sulfate)) OR (ALL(vena cava filters OR vena cava filter OR ivc)) OR (ALL(compression stocking$))) OR ((ALL(graduated compression stocking$)) OR (ALL(elastic stocking$)) OR (ALL(venous foot pump)) OR (ALL(intermittent pneumatic compression)) OR (ALL(pneumatic compression)))) AND ((ALL(deep vein thrombos* OR deep venous thrombos* OR venous thromboembol* OR pulmonary thromboembol* OR pulmonary embol* OR venous thrombos*)) AND (ALL(knee replacement OR knee arthroplasty OR hip arthroplasty OR hip replacement OR hip fracture surgery)) AND ((SRCTITLE(lancet)) OR ((SRCTITLE(jama) OR SRCTITLE("journal of the american medical association"))) OR (SRCTITLE("annals of internal medicine")) OR ((SRCTITLE("british medical journal") OR SRCTITLE(bmj))) OR (SRCTITLE("new england journal of medicine")) OR (SRCTITLE("journal of bone and joint surgery")) OR (SRCTITLE("clinical orthopaedics and related research")) OR (SRCTITLE("journal of thrombosis and haemostasis")) OR (SRCTITLE("journal of arthroplasty")) OR (SRCTITLE("archives of internal medicine")))) AND (LIMIT-TO(PUBYEAR, 2012) OR LIMIT-TO(PUBYEAR, 2011) OR LIMIT-TO(PUBYEAR, 2010)) 23

18 (((ALL(anticoagulants OR aspirin OR clopidogrel OR ticlopidine OR prasugrel OR heparin OR heparinoids OR ufh OR low-molecular weight heparin OR low molecular weight heparin OR lmwh OR enoxaparin OR dalteparin OR nadroparin OR ardeparin OR bemiparin OR certoparin)) OR (ALL(parnaparin OR reviparin OR tinzaparin OR danaparoid OR fondaparinux OR idraparinux OR rivaroxaban OR hirudin OR desirudin OR argatroban OR bivalirudin)) OR (ALL(lepirudin OR dabigatran OR warfarin OR 4-hydroxycoumarin OR acenocoumarol OR dicoumarol OR dextran sulfate)) OR (ALL(vena cava filters OR vena cava filter OR ivc)) OR (ALL(compression stocking$))) OR ((ALL(graduated compression stocking$)) OR (ALL(elastic stocking$)) OR (ALL(venous foot pump)) OR (ALL(intermittent pneumatic compression)) OR (ALL(pneumatic compression))))

AND ((ALL(deep vein thrombos* OR deep venous thrombos* OR venous thromboembol* OR pulmonary thromboembol* OR pulmonary embol* OR venous thrombos*)) AND (ALL(knee replacement OR knee arthroplasty OR hip arthroplasty OR hip replacement OR hip fracture surgery)) AND ((SRCTITLE(lancet)) OR ((SRCTITLE(jama) OR SRCTITLE("journal of the american medical association"))) OR (SRCTITLE("annals of internal medicine")) OR ((SRCTITLE("british medical journal") OR SRCTITLE(bmj))) OR (SRCTITLE("new england journal of medicine")) OR (SRCTITLE("journal of bone and joint surgery")) OR (SRCTITLE("clinical orthopaedics and related research")) OR (SRCTITLE("journal of thrombosis and haemostasis")) OR (SRCTITLE("journal of arthroplasty")) OR (SRCTITLE("archives of internal medicine")))) 150

17 (ALL(deep vein thrombos* OR deep venous thrombos* OR venous thromboembol* OR pulmonary thromboembol* OR pulmonary embol* OR venous thrombos*)) AND (ALL(knee replacement OR knee arthroplasty OR hip arthroplasty OR hip replacement OR hip fracture surgery)) AND ((SRCTITLE(lancet)) OR ((SRCTITLE(jama) OR SRCTITLE("journal of the american medical association"))) OR (SRCTITLE("annals of internal medicine")) OR ((SRCTITLE("british medical journal") OR SRCTITLE(bmj))) OR (SRCTITLE("new england journal of medicine")) OR (SRCTITLE("journal of bone and joint surgery")) OR (SRCTITLE("clinical orthopaedics and related research")) OR (SRCTITLE("journal of thrombosis and haemostasis")) OR (SRCTITLE("journal of arthroplasty")) OR (SRCTITLE("archives of internal medicine"))) 189

16 (SRCTITLE(lancet)) OR ((SRCTITLE(jama) OR SRCTITLE("journal of the american medical association"))) OR (SRCTITLE("annals of internal medicine")) OR ((SRCTITLE("british medical journal") OR SRCTITLE(bmj))) OR (SRCTITLE("new england journal of medicine")) OR (SRCTITLE("journal of bone and joint surgery")) OR (SRCTITLE("clinical orthopaedics and related research")) OR (SRCTITLE("journal of thrombosis and haemostasis")) OR (SRCTITLE("journal of arthroplasty")) OR (SRCTITLE("archives of internal medicine")) 792,030

15 ALL(knee replacement OR knee arthroplasty OR hip arthroplasty OR hip replacement OR hip fracture surgery) 14,701

14 ALL(deep vein thrombos* OR deep venous thrombos* OR venous thromboembol* OR pulmonary thromboembol* OR pulmonary embol* OR venous thrombos*) 28,650

13 ((ALL(anticoagulants OR aspirin OR clopidogrel OR ticlopidine OR prasugrel OR heparin OR heparinoids OR ufh OR low-molecular weight heparin OR low molecular weight heparin OR lmwh OR enoxaparin OR dalteparin OR nadroparin OR ardeparin OR bemiparin OR certoparin)) OR (ALL(parnaparin OR reviparin OR tinzaparin OR danaparoid OR fondaparinux OR idraparinux OR rivaroxaban OR hirudin OR desirudin OR argatroban OR bivalirudin)) OR (ALL(lepirudin OR dabigatran OR warfarin OR 4-hydroxycoumarin OR acenocoumarol OR dicoumarol OR dextran sulfate)) OR (ALL(vena cava filters OR vena cava filter OR ivc)) OR (ALL(compression stocking$))) OR ((ALL(graduated compression stocking$)) OR (ALL(elastic stocking$)) OR (ALL(venous foot pump)) OR (ALL(intermittent pneumatic compression)) OR (ALL(pneumatic compression))) 110,032

12 (ALL(graduated compression stocking$)) OR (ALL(elastic stocking$)) OR (ALL(venous foot pump)) OR (ALL(intermittent pneumatic compression)) OR (ALL(pneumatic compression)) 8,267

11 (ALL(anticoagulants OR aspirin OR clopidogrel OR ticlopidine OR prasugrel OR heparin OR heparinoids OR ufh OR low-molecular weight heparin OR low molecular weight heparin OR lmwh OR enoxaparin OR dalteparin OR nadroparin OR ardeparin OR bemiparin OR certoparin)) OR (ALL(parnaparin OR reviparin OR tinzaparin OR danaparoid OR fondaparinux OR idraparinux OR rivaroxaban OR hirudin OR desirudin OR argatroban OR bivalirudin)) OR (ALL(lepirudin OR dabigatran OR warfarin OR 4-hydroxycoumarin OR

acenocoumarol OR dicoumarol OR dextran sulfate)) OR (ALL(vena cava filters OR vena cava filter OR ivc)) OR (ALL(compression stocking$)) 105,608

10 ALL(pneumatic compression) 5,591
9 ALL(intermittent pneumatic compression) 2,660
8 ALL(venous foot pump) 1,025
7 ALL(elastic stocking$) 2,226
6 ALL(graduated compression stocking$) 1,321
5 ALL(compression stocking$) 4,794
4 ALL(vena cava filters OR vena cava filter OR ivc) 7,987
3 ALL(lepirudin OR dabigatran OR warfarin OR 4-hydroxycoumarin OR acenocoumarol OR dicoumarol OR dextran sulfate) 27,000

2 ALL(parnaparin OR reviparin OR tinzaparin OR danaparoid OR fondaparinux OR idraparinux OR rivaroxaban OR hirudin OR desirudin OR argatroban OR bivalirudin) 26,557

1 ALL(anticoagulants OR aspirin OR clopidogrel OR ticlopidine OR prasugrel OR heparin OR heparinoids OR ufh OR low-molecular weight heparin OR low molecular weight heparin OR lmwh OR enoxaparin OR dalteparin OR nadroparin OR ardeparin OR bemiparin OR certoparin) 56,598

Appendix B: Updating Signals

Qualitative signals*

Potentially invalidating change in evidence

This category of signals (A1-A3) denotes findings from a pivotal trial**, meta-analysis (with at least one new trial), practice guideline (from major specialty organization or published in peer-reviewed journal), or recent textbook (e.g., *UpToDate*):

- Opposing findings (e.g., effective vs. ineffective) – **A1**
- Substantial harm (e.g., the risk of harm outweighs the benefits) – **A2**
- A superior new treatment (e.g., new treatment that is significantly superior to the one assessed in the original CER) – **A3**

Major change in evidence

This category of signals (A4-A7) refers to situations in which there is a clear potential for the new evidence to affect the clinical decision making. These signals, except for one (A7), specify findings from a pivotal trial, meta-analysis (with at least one new trial), practice guideline (from major specialty organization or published in peer-reviewed journal), or recent textbook (e.g., *UpToDate*):

- Important changes in effectiveness short of "opposing findings" – **A4**
- Clinically important expansion of treatment (e.g., to new subgroups of subjects) – **A5**
- Clinically important caveat – **A6**
- Opposing findings from meta-analysis (in relation to a meta-analysis in the original CER) or non-pivotal trial – **A7**

* Please, see Shojania et al. 2007 for further definitions and details

**A pivotal trial is defined as: 1) a trial published in top 5 general medical journals such as: Lancet, JAMA, Annals of Intern Med, BMJ, and NEJM. Or 2) a trial not published in the above top 5 journals but have a sample size of at least triple the size of the previous largest trial in the original CER.

Appendix B - continued

Quantitative signals (B1-B2)*

Change in statistical significance (B1)

Refers to a situation in which a statistically significant result in the original CER is now NOT statistically significant or vice versa- that is a previously non-significant result become statistically significant. For the 'borderline' changes in statistical significance, at least one of the reports (the original CER or new updated meta-analysis) must have a p-value outside the range of border line (0.04 to 0.06) to be considered as a quantitative signal for updating.

Change in effect size of at least 50% (B2)

Refers to a situation in which the new result indicates a relative change in effect size of at least 50%. For example, if relative risk reduction (RRR) new / RRR old <=0.5 or RRR new / RRR old >=1.5. Thus, if the original review has found RR=0.70 for mortality, this implies RRR of 0.3. If the updated meta-analytic result for mortality were 0.90, then the updated RRR would be 0.10, which is less than 50% of the previous RRR. In other words the reduction in the risk of death has moved from 30% to 10%. The same criterion applied for odds ratios (e.g., if previous OR=0.70 and updated result were OR=0.90, then the new reduction in odds of death (0.10) would be less 50% of the magnitude of the previous reduction in odds (0.30). For risk differences and weighted mean differences, we applied the criterion directly to the previous and updated results (e.g., RD new / RD old <=0.5 or RD new / RD old >=1.5).

* Please, see Shojania et al. 2007 for further definitions and details

Appendix C: Evidence Table

Author year Study name (if applicable)	Study design	Subjects	Treatment groups (n; dose)	Treatment duration/ study duration	Outcome	Findings
Key Question # 1: : In patients undergoing major orthopedic surgery (total hip or knee replacement or hip fracture surgery) what is the baseline postoperative risk of VTE and bleeding outcomes in contemporary practice?						
No new study was identified.						
Key Question # 2: In patients undergoing major orthopedic surgery (total hip or knee replacement or hip fracture surgery) what is the baseline postoperative risk of VTE and bleeding outcomes in contemporary practice?						
No new study was identified.						
Key Question # 3: In patients undergoing major orthopedic surgery (total hip or knee replacement or hip fracture surgery), in the absence of final health outcomes, can the risk for such outcomes reliably be estimated by measuring intermediate outcomes, such as DVT (asymptomatic or symptomatic, proximal or distal) as detected by venography or ultrasound?						
No new study was identified.						
Key Question # 4: In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery), what is the relative impact of thromboprophylaxis compared with no thromboprophylaxis on symptomatic objectively confirmed VTE, major VTE, PE, fatal PE, nonfatal PE, post thrombotic syndrome (PTS), mortality, mortality due to bleeding, DVT (asymptomatic or symptomatic, proximal or distal DVT), asymptomatic DVT, symptomatic DVT, proximal DVT, distal DVT, major bleeding, major bleeding leading to reoperation, minor bleeding, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, heparin-induced thrombocytopenia (HIT), discomfort, readmission, and reoperation? Thromboprophylaxis includes any pharmacologic agent within the defined classes (oral antiplatelet agents, injectable low molecular weight heparins [LMWHs], injectable unfractionated heparin [UFH], injectable or oral factor Xa inhibitors, injectable or oral direct thrombin inhibitors [DTIs], oral vitamin K antagonists [VKAs]) or any external mechanical intervention within the defined classes (graduated compression, intermittent pneumatic compression, or venous foot pump).						
FUJI,2010 [6]	RCT	523 pts undergone total arthroplasty; Mean age: ; Male:	Edoxaban (n=418; dose: 5, 15, 30, 60 mg.day) vs. placebo (n=102;NA)	11-14 days	primary efficacy outcome was the incidence of VTE (lower-extremity deep vein thrombosis, symptomatic pulmonary embolism or symptomatic deep vein thrombosis). The primary safety outcome was the incidence of major and clinically relevant non-major bleeding.	**Placebo vs. Edoxaban (5, 15, 30, 60)mg** VTE incidence [# of pts with events(%); 95% CI]: 43 (48.3); (37. 9, 58.7) versus { 5mg: [26 (29.5); (20.0, 39.1)]; 15mg: [24 (26.1); (17.1, 35.1)]; 30mg:[11 (12.5); (5.6, 19.4)]; 60mg:[8 (9.1); (3.1, 15.1)]} VTE incidence difference from placebo [(%); 95% CI; p-value vs. placebo]: 5mg: 18.8; (4.7, 32.9); 0.01

Author year Study name (if applicable)	Study design	Subjects	Treatment groups (n; dose)	Treatment duration/ study duration	Outcome	Findings
						15mg: 22.2; (8.5, 35.9); 0.002 30mg: 35.8; (23.3, 48.3); < 0.001 60mg: 39.2; (27.2, 51.2); < 0.001 Symptomatic PE [# of pts with events (%)] 0(0) vs. 0(0) in all groups Symptomatic PE difference from placebo (%)] 0.0 vs. 0.0 in all groups Symptomatic DVT[# of pts with events (%)] 0(0.0) vs.[5mg: 1(1) 15mg: 0(0.0) 30mg: 0(0.0) 60mg: 0(0.0)] Symptomatic DVT difference from placebo (%): 5mg: -1.1 15mg: 0.0 30mg: 0.0 60mg: 0.0 DVT total [# of pts with events (%)] 43 (48.3) vs.[5mg: 25(28.7) 15mg: 24(26.1) 30mg: 11(12.5) 60mg: 8(9.1)] DVT total; difference from placebo (%): 5mg: 19.6 15mg: 22.2 30mg: 35.8 60mg: 39.2

Author year Study name (if applicable)	Study design	Subjects	Treatment groups (n; dose)	Treatment duration/ study duration	Outcome	Findings
						DVT Proximal [# of pts with events (%)] 4 (4.5) vs.[5mg: 0(0.0) 15mg: 0(0.0) 30mg: 1(1.1) 60mg: 1(1.1)] DVT Proximal; difference from placebo (%): 5mg: 4.5 15mg: 4.5 30mg: 3.4 60mg: 3.4 DVT Distal [# of pts with events (%)] 43 (48.3) vs.[5mg: 25 (28.7) 15mg: 24 (26.1) 30mg: 11(12.5) 60mg: 7(8.0)] DVT Distal; difference from placebo (%): 5mg: 19.6 15mg: 22.2 30mg: 35.8 60mg: 40.4 Major Bleeding, n (%) Placebo: 0 (0.0) vs. [5mg: 0 (0.0) 15mg: 0 (0.0) 30mg: 0 (0.0) 60mg: 1.(0.9)] Major or clinically relevant non-major, n (%); p-value vs. placebo Placebo: 4 (3.9) vs. [

Author year Study name (if applicable)	Study design	Subjects	Treatment groups (n; dose)	Treatment duration/ study duration	Outcome	Findings
						5mg: 2 (1.9) ; 0.445 15mg: 4 (3.8); 1.000 30mg: 4 (3.9); 1.000 60mg: 5.(4.1);1.000]
Key Question # 5: In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery), what is the comparative efficacy between classes of agents on outcomes: symptomatic objectively confirmed VTE, major VTE, PE, fatal PE, nonfatal PE, PTS, mortality, mortality due to bleeding, DVT (asymptomatic or symptomatic, proximal or distal DVT), asymptomatic DVT, symptomatic DVT, proximal DVT, distal DVT, major bleeding, major bleeding leading to reoperation, minor bleeding, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, HIT, discomfort, readmission, and reoperation? Classes include oral antiplatelet agents, injectable LMWHs, injectable UFH, injectable or oral factor Xa inhibitors, injectable or oral DTIs, oral VKAs, and mechanical interventions.						
Eriksson, 2011[7]	RCT	2013 pts undergone hip arthroplasty; Mean age: 62±11.5 yrs , Male: 48.2%	Oral dabigartan (n=1010 ; 220mg/day) vs. subcutaneous enoxaparin (n=1003; 40mg/day)	28- 35 days treatment/ March 2008 and May 2009	Primary: composite of total venous thromoemblism (venographic or symptomatic), and all cause death. Secondary: composite major VTE (paroxysmal deep-vein thrombosis or non-fatal pulmonary emblism) plus VTE relate death. Safety outcome: major bleeding	**Dabigatran vs. Enoxaparin** *During Treatment Period:* Primary efficacy outcome [# of pts with event/total # (%, 95% CI)]: 61/792 (7.7%, 5.8 to 9.6%) versus 69/785 (8.8%, 6.8 to 10.8%) Absolute risk difference; 95% CI.; p-value: – 1.1% (-3.8 to 1.6%); 0.43 Total DVT[# of pts with event/total # (%)]: 60/791 (7.6%) versus 67/783 (8.6%) Absolute risk difference; 95% CI.; p-value: – 1.0% (-3.7 to 1.7%); 0.48 Proximal DVT[# of pts with event/total # (%)]: 17/804 (2.1%) versus 31/792 (3.9%) Absolute risk difference; 95% CI.; p-value: – 1.8% (-3.5 to –0.1%); 0.04 Distal DVT[# of pts with event/total # (%)]:

Author year Study name (if applicable)	Study design	Subjects	Treatment groups (n; dose)	Treatment duration/ study duration	Outcome	Findings
						43/792 (5.4%) versus 35/785 (4.5%) Symptomatic VTE [# of pts with event/total # (%)]: 1/1,001 (0.1%) versus 6/992 (0.6%) Symptomatic DVT[# of pts with event/total # (%); p-value]: 0/1,001 (0.0%) versus 4/992 (0.4%); 0.06 Symptomatic non-fatal PE[# of pts with event/total # (%); p-value]: 1/1,001 (0.1%) versus 2/992 (0.2%); p=0.62 Death [# of pts with event/total # (%); p-value]: 0/1,001 (0.0%) versus 1/992 (0.1%); p=0.50 Major VTE and VTE-related mortality[# of pts with event/total # (%, 95% CI)]: 18/805 (2.2%, 1.2 to 3.3%) versus 33/794 (4.2%, 2.8 to 5.5%) Absolute risk difference; 95% CI.; p-value: – 1.9% (-3.6 to –0.2%); p=0.03 *During Follow-up Period:* Total VTE and all-cause mortality[# of pts with event/total # (%); p-value]: 2/942 (0.2%) versus 4/951 (0.4%); p= 0.69 Symptomatic VTE[# of pts with event/total # (%)]:

Author year Study name (if applicable)	Study design	Subjects	Treatment groups (n; dose)	Treatment duration/ study duration	Outcome	Findings
						2/942 (0.2%) versus 2/951 (0.2%) Death [# of pts with event/total # (%)]: 0/942 (0.0%) versus 1/951 (0.1%) *Total study period (treatment + follow-up)* Symptomatic VTE + all-cause mortality[# of pts with event/total # (%)]: 3/942 (0.3%) versus 10/951 (1.1%) *Bleeding outcomes:* Major bleeding, No. patients (%, 95% CI);p-value: 14 (1.4%; 0.8 to 2.3%) vs. 9 (0.9%; 0.4 to 1.7%); 0.40 Clinically overt leading to transfusion of 2 units of packed cells or whole blood (# of events): 12 vs. 6 Leading to re-operation (# of events): 0 vs. 0 Minor bleeding – No. patients (%) 61 (6.0%) versus 54 (5.4%)
Key Question # 6: In patients undergoing major orthopedic surgery (total hip or knee replacement or hip fracture surgery), what is the comparative efficacy of individual agents within classes (LMWH and mechanical devices) on symptomatic objectively confirmed VTE, major VTE, PE, fatal PE, nonfatal PE, PTS, mortality, mortality due to bleeding, DVT (asymptomatic or symptomatic, proximal or distal DVT), asymptomatic DVT, symptomatic DVT, proximal DVT, distal DVT, major bleeding, major bleeding leading to reoperation, minor bleeding, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, HIT, discomfort, readmission, and reoperation?						
Laseen, 2012 [5]	1 study reports findings of 3	2326 pts undergone elective hip replacement;	Enoxaparin (n= 1155; dose: 40mg) vs.	a 7–10-day treatment	The primary efficacy endpoint was a	**Semuloparin vs. Enoxaparin**

Author year Study name (if applicable)	Study design	Subjects	Treatment groups (n; dose)	Treatment duration/ study duration	Outcome	Findings
	RCTs	Median age: 75.5; Male: NR 1003 pts undergone hip fracture surgery; Median age: 64.5 yrs; Male: NR 1150 pts undergone elective knee replacement; Median age: 59.5 yrs; Male: NR	Semuloparin (n=1153; dose: 20mg) Enoxaparin (n= 499; dose: 40mg) vs. Semuloparin (n= 488; dose: 20mg) Enoxaparin (n= 568; dose: 30mg) vs. Semuloparin (n= 573; dose: 20mg)	period, and a follow-up period with a visit between day 35 and day 42 after randomization.	composite of any deep vein thrombosis, non-fatal pulmonary embolism or all-cause death. Safety outcomes included major bleeding, clinically relevant non-major (CRNM) bleeding, and any clinically relevant bleeding (major bleeding plus CRNM)	<u>Any DVT, OR [95% CI]:</u> 0.54 [0.38–0.76] in Hip replacement RCT 0.73 [0.50–1.05] in Hip surgery RCT 0.83 [0.61–1.13] in Knee Replacement RCT <u>Any proximal DVT, OR [95% CI]</u> 0.87 [0.40–1.86] in Hip replacement RCT 0.48 [0.23–0.93]] in Hip surgery RCT 1.74 [0.79–3.99] in Knee Replacement RCT <u>Distal DVT only, OR [95% CI]</u> 0.49 [0.33–0.72] in Hip replacement RCT 0.97 [0.63–1.50]] in Hip surgery RCT 0.77 [0.55–1.06] in Knee Replacement RCT <u>Non-fatal PE, n/N (%)</u> 0/1152 (0) vs. 0/1150 (0) 0/499 (0) vs. 1/488 (0.2) 1/568 (0.2) vs. 0/573 (0) <u>All-cause death, OR [95% CI]</u> 0.50 [0.02–6.59] 2.05 [0.36–16.08] not estimable <u>Secondary outcomes</u> <u>Major VTE or all cause mortality, OR (95% CI):</u>

Author year Study name (if applicable)	Study design	Subjects	Treatment groups (n; dose)	Treatment duration/ study duration	Outcome	Findings
						0.68 (0.35–1.33) 0.71 (0.41–1.24) 1.18 (0.67–2.08) **(Hip replacement RCT)** Clinically relevant bleeding, OR (95% CI): 0.48(0.23–0.94) Major bleeding, OR (95% CI): 0.28 (0.08–0.83) **(Knee replacement RCT)** Clinically relevant bleeding, OR (95% CI): 1.5 (0.67–3.49 **(Hip surgery RCT)** Clinically relevant bleeding, OR (95% CI): 2.59, 95%CI 0.83–9.57 **Enoxaparin vs. Semuloparin** **(Knee replacement RCT)** Major bleeding incidence, n(%) 4 (0.7) vs. 3 (0.5) OR (95% CI): 0.74 (0.14–3.61) **(Hip surgery RCT)** Major bleeding incidence, n(%) 3 (0.6) vs. 5 (1.0) OR (95% CI): 1.71 (0.39–8.73)
Key Question # 7: In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery), what are the effect estimates of combined pharmacologic and mechanical modalities versus single modality on symptomatic objectively confirmed VTE, major VTE, PE, fatal PE, nonfatal PE, PTS, mortality,						

Author year Study name (if applicable)	Study design	Subjects	Treatment groups (n; dose)	Treatment duration/ study duration	Outcome	Findings
mortality due to bleeding, DVT (asymptomatic or symptomatic, proximal or distal DVT), asymptomatic DVT, symptomatic DVT, proximal DVT, distal DVT, major bleeding, major bleeding leading to reoperation, minor bleeding, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, HIT, discomfort, readmission, and reoperation?						
No new study was identified.						
Key Question # 8: In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery), regardless of thromboprophylaxis method, what are the effects of prolonging thromboprophylaxis for 28 days or longer compared with thromboprophylaxis for 7 to 10 days on symptomatic objectively confirmed VTE, major VTE, PE, fatal PE, nonfatal PE, PTS, mortality, mortality due to bleeding, DVT (asymptomatic or symptomatic, proximal or distal DVT), asymptomatic DVT, symptomatic DVT, proximal DVT, distal DVT, major bleeding, major bleeding leading to reoperation, minor bleeding, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, HIT, discomfort, readmission, and reoperation?						
No new study was identified.						
Key Question # 9: In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery) who have known contraindications to antithrombotic agents, what is the relative impact of prophylactic inferior vena cava (IVC) filter placement compared with any external mechanical intervention on symptomatic objectively confirmed VTE, major VTE, PE, fatal PE, nonfatal PE, PTS, mortality, mortality due to bleeding, DVT (asymptomatic or symptomatic, proximal or distal DVT), asymptomatic DVT, symptomatic DVT, proximal DVT, distal DVT, major bleeding, major bleeding leading to reoperation, minor bleeding, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, HIT, discomfort, readmission, reoperation, and IVC filter placement associated insertion site thrombosis?						
No new study was identified.						
Key question # 10: In patients requiring knee arthroscopy, surgical repair of a lower extremity injury distal to the hip, or elective spine surgery, what is the relative impact of thromboprophylaxis (any agent, any mechanical intervention) compared with no thromboprophylaxis intervention on symptomatic objectively confirmed VTE, major VTE, PE, fatal PE, nonfatal PE, PTS, mortality, mortality due to bleeding, DVT (asymptomatic or symptomatic, proximal or distal DVT), asymptomatic DVT, symptomatic DVT, proximal DVT, distal DVT, major bleeding, major bleeding leading to reoperation, minor bleeding, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, HIT, discomfort, readmission, and reoperation?						
No new study was identified.						
Key question 11: In patients requiring knee arthroscopy, surgical repair of a lower extremity injury distal to the hip, or elective spine surgery, what is the relative impact of injectable antithrombotic agents (LMWH vs. UFH vs. factor Xa inhibitors vs. DTIs) compared with mechanical interventions on symptomatic objectively confirmed VTE, major VTE, PE, fatal PE, nonfatal PE, PTS, mortality, mortality due to bleeding, DVT (asymptomatic or symptomatic, proximal or distal DVT), asymptomatic DVT, symptomatic DVT, proximal DVT, distal DVT, major bleeding, major bleeding leading to reoperation, minor bleeding, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, HIT, discomfort, readmission, and reoperation?						
No new study was identified.						
No new study was identified.						
Abbreviations: RCT=randomized controlled trial; pts=patients; yr(s)=years; NR=not reported; vs.= versus; OR= odds ratio; CI= confidence interval; DVT=Deep venous thrombosis; VTE: venous thromboembolism; PE= pulmonary embolism; OR= pulmonary embolism; mg= milligram; %= percentage						

Appendix D: Questionnaire Matrix

Comparative Effectiveness of Venous Thromboembolism Prophylaxis in Orthopedic Surgery

AHRQ Publication No. 12-EHC020-EF, March 2012

Access to full report: http://effectivehealthcare.ahrq.gov/index.cfm/search-for-guides-reviews-and-reports/?productid=999&pageaction=displayproduct

Clinical expert name:

Conclusions from CER (executive summary)	Is the conclusion(s) in this CER still valid? (Yes/No/Don't know)	Are you aware of any new evidence that is sufficient to invalidate the finding(s) in CER? (Yes/No/Don't know) If yes, please provide references	Comments
Key Question 1. In patients undergoing major orthopedic surgery (total hip or knee replacement or hip fracture surgery) what is the baseline postoperative risk of venous thromboembolism and bleeding outcomes in contemporary practice?			
Data were limited to placebo or control arms of trials for PE and DVT outcomes and placebo, control, or mechanical prophylaxis arms for bleeding outcomes. In contemporary surgical practice, the native postoperative incidence of DVT events was highest followed by PE and bleeding events. Followup periods were defined in most trials as the postoperative period and may imply a more immediate rather than longer term followup. The strength of evidnce is predominately low for outcomes evaluated in hip and knee replacement surgery while all outcomes in hip fracture surgery were rated with insufficient evidence. Not all three surgeries had incidence data reported in clinical trials; therefore, the symbol "--" is used when no data were reported for the given surgery and outcome. In THR, TKR, and HFS, respectively, the incidences were: DVT (39 percent, 46 percent, 47 percent), proximal DVT (32 percent, 17 percent, --), distal DVT (30 percent, 22 percent, --), PE (6 percent, 1 percent, 3 percent), major bleeding (1 percent, 3 percent, 8 percent), minor bleeding (5 percent, 5 percent, --), major bleeding leading to reoperation (0 percent, 0 percent, --), and bleeding leading to transfusion (0 percent, 0 percent, --). Statistically significant levels of publication bias were detected for major bleeding and minor bleeding in THR, suggesting an underestimation of the incidence, which directionality of publication bias for proximal DVT in THR was unclear. Although RCTs and studies that used objective diagnostic means to confirm efficacy outcomes were			

included as opposed to less rigorous criteria, a high degree of heterogeneity was present for most outcomes. This may be due to additional factors, such as different definitions of events, different ethnicities and countries in which trials were conducted, and undefined periods of postoperative followup and variation in duration of followup, potentially leading to insufficient length of followup for the outcomes being assessed. Our results are similar to that of previous pooled analyses of patients with total hip and total knee arthroplasty conducted between 1993 and 2001, in which 23 to 60 percent of patients had deep vein thrombosis, 23 to 26 percent had proximal deep vein thrombosis, 2 percent had pulmonary embolism, 1 percent had major bleeding, and 3 percent had minor bleeding.			
Key Question 2. In patients undergoing major orthopedic surgery (total hip or knee replacement or hip fracture surgery) what patient, surgical or postsurgical characteristics predict or differentiate patient risk of venous thromboembolism and bleeding outcomes in contemporary practice?			
Several RCTs identified through our literature search evaluated different surgical characteristics on outcomes of interest, including anesthetic regimen, cemented arthroplasty, tourniquet use, limb positioning, and fibrin adhesive use. However, few trials evaluated each characteristic and subsequently did not address all major orthopedic procedures. Additionally, most trials evaluated intermediate health outcomes and did not address final health outcomes, and only one trial evaluated bleeding outcomes. As such, pooling was not possible. The surgical comparison with the most identified data was general anesthesia versus regional anesthesia. The impact of general versus regional anesthesia on several measures of DVT (overall, asymptomatic, proximal) was favorable to neutral for regional anesthesia while distal and symptomatic DVT, PE, and major bleeding were neutral. In a previous meta-analysis of 21 studies, regional anesthesia was associated with nonsignificantly reduced odds of pulmonary embolism and significantly reduced odds of deep vein thrombosis with no real impact on mortality versus general anesthesia. Although one trial compared spinal versus epidural anesthesia on the risk of deep vein thrombosis, no events occurred in the groups compared. The other characteristics were too limited to make any determinations. Patient characteristics were primarily evaluated in multivariate regression analyses of observational studies. Few characteristics were evaluated in multiple studies, and oftentimes when a significant finding was observed, the magnitude or direction of the effect was not reported. Patient characteristics found to significantly increase the odds of symptomatic objectively confirmed VTE in all available studies included congestive heart failure (two studies), inactive malignancy (one study), hormone replacement therapy (one study), living at home (one study), intertrochanteric fracture (one study), subtrochanteric fracture (one study), increased hemoglobin (one study), personal or familial history of VTE, (one study), and varicose veins (one study). Patient characteristics found to increase the odds of PE (evaluated in one study each) included age and genitourinary infection while cardiovascular disease was found to decrease the odds of PE. The following characteristics showed a mixed effect on DVT: age (two studies showed a significant increase while one study showed no effect), obesity (one study showed a significant			

increase while one study showed no effect), and gender (one study showed a significant increase in females while one study showed gender had no effect). Metabolic syndrome increased the odds of symptomatic DVT while congestive heart failure increased the odds of proximal DVT in the single study that evaluated each covariate. The one study that evaluated harms (major bleeding) suggested that age, gender, risk of bleeding, specific surgical procedure (total hip, knee replacement or hip fracture surgery), and prophylaxis administered in the hospital significantly impacted the risk of major bleeding. However, the magnitude and direction of the effect was not specified.			
Key Question 3. In patients undergoing major orthopedic surgery (total hip or knee replacement or hip fracture surgery), in the absence of final health outcomes, can the risk for such outcomes reliably be estimated by measuring surrogate outcomes, such as deep vein thrombosis (asymptomatic or symptomatic, proximal or distal) as detected by venography or ultrasound?			
Pulmonary embolism was the only final health outcome with data depicting the relationship to the intermediate outcome DVT. In one observational study in TKR surgery, the overall occurrence of PE and the subset with symptomatic PE occurred more frequently in those with DVT. However, the data were not adjusted for confounders, and we cannot discern whether these variables are correlated or colinear. No trials or studies were available assessing whether DVT was correlated with or a multivariate predictor of PE. This data may be limited because the routine use of prophylaxis may have reduced the occurrence of DVT and the scheduled anticoagulant treatment for DVT, once it was detected, may have diminished the percentage that developed into PE.			
Key Question 4. In patients who had major orthopedic surgery (total hip or knee replacement, hip fracture surgery), what is the relative impact of thromboprophylaxis compared with no thromboprophylaxis on symptomatic objectively confirmed venous thromboembolism, major venous thromboembolism (proximal deep vein thrombosis, pulmonary embolism or venous thromboembolism-related mortality), pulmonary embolism, fatal pulmonary embolism, nonfatal pulmonary embolism, post thrombotic syndrome, mortality, mortality due to bleeding, deep vein thrombosis (asymptomatic or symptomatic, proximal or distal deep vein thrombosis), asymptomatic deep vein thrombosis, symptomatic deep vein thrombosis, proximal deep thrombosis, distal deep vein thrombosis, major bleeding, major bleeding leading to reoperation, minor bleeding, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, heparin-induced thrombocytopenia, discomfort, readmission, and reoperation? Thromboprophylaxis includes any pharmacologic agent within the defined classes (oral antiplatelet agents, injectable low molecular weight heparins, injectable unfractionated heparin, injectable or oral factor Xa inhibitors, injectable or oral direct thrombin inhibitors, oral vitamin K antagonists) or any external mechanical intervention within the defined classes (graduated compression stockings, intermittent pneumatic compression devices, or venous foot pumps)]?			
Providing pharmacologic prophylaxis versus no prophylaxis has a better comparative balance of benefits and harms. There is high evidence that pharmacologic prophylaxis versus no prophylaxis significantly decreased risk of proximal and distal DVT (relative risk reduction [RRR] 47 percent and 41 percent, respectively), with moderate evidence for the decrease in DVT overall and asymptomatic DVT (RRR 44 percent and 48 percent, respectively) in patients undergoing major orthopedic surgery. Higher levels of statistically heterogeneity were detected for the evaluation of DVT (I^2 =52.8 percent). Statistically significant publication bias was detected in the evaluation of proximal DVT, suggesting an underestimation of benefit. There is low evidence that pharmacologic prophylaxis versus no prophylaxis significantly decreases major VTE in patients undergoing major orthopedic surgery (RRR 79 percent). Pharmacologic prophylaxis did			

not significantly impact PE versus no prophylaxis, although it was trending in that direction, and significantly reduced the risk of PE when the analysis was limited to the most stringent trials in which background prophylaxis (such as compression stockings) was not allowed in the experimental groups. There is high evidence that pharmacologic prophylaxis versus no prophylaxis significantly increases minor bleeding (relative risk increase 67 percent), and in a single observational study, pharmacologic prophylaxis increased the risk of reoperation. Pharmacologic prophylaxis versus no prophylaxis did not significantly impact nonfatal PE, mortality, symptomatic DVT, or major bleeding in patients undergoing major orthopedic surgery. Our results are in general agreement with the six previous meta-analyses of trials comparing pharmacologic prophylaxis versus placebo/control in patients with major orthopedic surgery. We could not determine the impact of pharmacologic prophylaxis on other endpoints either due to a lack of data or because there were no events in either experimental group. Providing mechanical prophylaxis versus no prophylaxis may have a better comparative balance of benefits and harms, but more data are needed to support this assumption. One RCT found that mechanical prophylaxis versus no prophylaxis significantly decreased the occurrence of DVT in patients undergoing major orthopedic surgery. While mechanical prophylaxis versus no prophylaxis was not found to significantly impact proximal or distal DVT in patients undergoing major orthopedic surgery, the power to detect these differences was low. In the only previous meta-analysis comparing mechanical prophylaxis (intermittent pneumatic compression and venous foot pump) versus control, the risks of deep vein thrombosis (any, proximal, and distal) and pulmonary embolism were significantly reduced and the risk of fatal pulmonary embolism and mortality were nonsignificantly reduced. We could not adequately assess the other outcomes because there were either no trials or the available trials had no events in either group. Given the mechanism of action for these devices, bleeding should not result from their use, so benefits would likely overwhelm the risk of harms.			
Key Question 5. In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery), what is the comparative efficacy between classes of agents on outcomes: symptomatic objectively confirmed venous thromboembolism, major venous thromboembolism, pulmonary embolism, fatal pulmonary embolism, nonfatal pulmonary embolism, post thrombotic syndrome, mortality, mortality due to bleeding, deep vein thrombosis (asymptomatic or symptomatic, proximal or distal deep vein thrombosis), asymptomatic deep 3 vein thrombosis, symptomatic deep vein thrombosis, proximal deep thrombosis, distal deep vein thrombosis, major bleeding, major bleeding leading to reoperation, minor bleeding, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, heparin-induced thrombocytopenia, discomfort, readmission, and reoperation? Classes include oral antiplatelet agents, injectable low molecular weight heparins, injectable unfractionated heparin, injectable or oral factor Xa inhibitors, injectable or oral direct thrombin inhibitors, oral vitamin K antagonists, and mechanical interventions.			
While we sought to determine the impact of therapy on numerous outcomes, we were only able to discern significant differences between classes for relatively few outcomes. For the other outcomes, either there was a lack of evaluable data or no significant differences were found. Variable levels of statistical heterogeneity were detected in the base case analyses, and in a few cases, heterogeneity improved when each surgery was			

evaluated separately in subgroup analysis while other times the heterogeneity increased. However, in the majority of cases, the number of trials in a subgroup analysis was too low to evaluate statistical heterogeneity. We could not determine if this means that there is a lack of effect versus a lack of power to show that it is significant. The results of previous meta-analyses are in general agreement with the findings of our comparative effectiveness review. When compared directly with UFH, LMWH agents, as a class, have a better comparative balance of benefits and harms with significantly fewer PEs, DVTs, proximal DVTs, major bleeding, and HIT events. A higher level of statistical heterogeneity was detected in the evaluation of PE. The comparative balance of benefits and harms for LMWHs with other classes could not be readily determined. LMWH agents were also superior to VKAs at reducing measures of DVT (any, asymptomatic, proximal, and distal) but increased major, minor, and surgical site bleeding. A higher level of statistical heterogeneity was detected in the evaluation of DVT as was the presence of publication bias, which suggested an underestimation of the benefit of LMWH. Since no significant differences were found in important final health outcomes, the relevance of these reductions in DVT needs to be considered. LMWHs may be inferior to factor Xa inhibitors in terms of any, proximal, and distal DVTs but have a lower risk of major and minor bleeding. A higher level of statistical heterogeneity was detected in the evaluation of proximal DVT and major bleeding. Observational data suggested LMWH agents had decreased mortality, although this was not supported by data pooled from RCTs, which showed no significant difference. Comparing LMWH agents with DTIs is difficult because the occurrence of DVT was greater, but the occurrence of distal DVT was less with LMWHs, and while surgical site bleeding is higher LMWH therapy, the overall risk of serious bleeding was not significantly altered. Finally, when LMWH agents were compared versus mechanical prophylaxis, the only significant difference is the lower occurrence for patient discomfort in the group receiving LMWHs. It is difficult to discern the comparative balance of benefits and harms for oral antiplatelet therapy versus mechanical prophylaxis or VKAs. Oral antiplatelet therapy had significantly greater occurrence of any and distal DVT versus mechanical prophylaxis. In a controlled observational study, oral VKAs had significantly fewer fatal PE events versus oral antiplatelet agents. In the only available RCT comparing VKAs to oral antiplatelet agents, the same direction of effect was found, suggesting VKA superiority, but this was not significant. Mortality was higher in patients receiving aspirin versus warfarin in one observational study and was nonsignificantly trending in that direction in another observational study, but showed no difference in a clinical trial. UFH, which was found to be inferior to LMWH agents in the balance of benefits and harms, had a greater occurrence of death and major bleeding versus factor Xa inhibitors in an observational study (with no clinical trial data to support or refute the findings), had a greater occurrence of any and proximal DVT versus DTIs, and had a greater occurrence			

of DVT versus mechanical prophylaxis. As such, it is likely inferior to factor Xa inhibitors in the balance of benefits and harms as well. Patients receiving VKAs had less occurrence of proximal DVT versus mechanical prophylaxis, but with no other differences in other health outcomes or bleeding, it is hard to discern a difference in the balance of efficacy to harms between them.			
Key Question 6. In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery), what is the comparative efficacy of individual agents within classes (injectable low molecular weight heparin or mechanical) on symptomatic objectively confirmed venous thromboembolism, major venous thromboembolism (proximal deep vein thrombosis, pulmonary embolism or venous thromboembolism related mortality), pulmonary embolism, fatal pulmonary embolism, nonfatal pulmonary embolism, post thrombotic syndrome, mortality, mortality due to bleeding, deep vein thrombosis (asymptomatic or symptomatic, proximal or distal deep vein thrombosis), asymptomatic deep vein thrombosis, symptomatic deep vein thrombosis, proximal deep thrombosis, distal deep vein thrombosis, major bleeding, major bleeding leading to reoperation, minor bleeding, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, heparin-induced thrombocytopenia, discomfort, readmission, and reoperation?			
For both LMWHs and mechanical devices, there were no significant differences in PE (any, fatal, and nonfatal), mortality, and mortality due to bleeding between modalities within a class, but these evaluations were based on one or two trials with either no events or a very low number of events. The balance of benefits and harms from using enoxaparin versus another low molecular weight heparin within the class (dalteparin or tinzaparin) is similar. No difference in the occurrence of DVT or proximal DVT occurred between LMWHs (enoxaparin versus either tinzaparin or dalteparin). No significant difference was seen in asymptomatic DVT between enoxaparin and dalteparin, symptomatic DVT between enoxaparin and tinzaparin, or distal DVT between enoxaparin and tinzaparin. For major bleeding, two trials compared LMWHs and found no differences between enoxaparin and either dalteparin or tinzaparin. For minor bleeding, one trial found no significant difference between enoxaparin and tinzaparin for this outcome. For surgical site bleeding, two trials compared LMWHs and found no differences between enoxaparin and either dalteparin or tinzaparin. For HIT, one trial found no significant difference between enoxaparin and tinzaparin for this outcome. The balance of benefits and harms for different mechanical modalities within a class could not be determined with the current literature base. The Venaflow pneumatic compression device significantly reduced the occurrence of DVT or distal DVT versus the Kendall pneumatic compression device in the only trial but did not significantly reduce proximal DVT. Intermittent compression stockings significantly reduced the occurrence of DVT or distal DVT versus graduated compression stockings but did not significantly reduce proximal DVT. In the only observational study, two intermittent compression devices were compared (ActiveCare system vs. Flowtron excel pump) and found to have a similar occurrence of DVT. Harms were not assessed in these trials or observational studies.			
Key Question 7. In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery), what are the effect estimates of combined			

pharmacologic and mechanical modalities versus single modality on symptomatic objectively confirmed venous thromboembolism, major venous thromboembolism (proximal deep vein thrombosis, pulmonary embolism or venous thromboembolism related mortality), pulmonary embolism, fatal pulmonary embolism, nonfatal pulmonary embolism, post thrombotic syndrome, mortality, mortality due to bleeding, deep vein thrombosis (asymptomatic or symptomatic, proximal or distal deep vein thrombosis), asymptomatic deep vein thrombosis, symptomatic deep vein thrombosis, proximal deep thrombosis, distal deep vein thrombosis, major bleeding, major bleeding leading to reoperation, minor bleeding, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, heparin-induced thrombocytopenia, discomfort, readmission, and reoperation?			
The balance of benefits and harms for combining a pharmacologic and mechanical strategy versus using either strategy alone in patients undergoing major orthopedic surgery could not be determined. The use of a pharmacologic plus mechanical strategy versus either pharmacologic or mechanical prophylaxis did not significantly impact nonfatal PE, mortality, or DVT subsets (asymptomatic, symptomatic, proximal, or distal). The comparative impact of pharmacologic plus mechanical prophylaxis versus pharmacologic or mechanical prophylaxis on major or minor bleeding could not be determined. There was moderate evidence that the use of pharmacologic plus mechanical prophylaxis significantly decreases the occurrence of DVT versus pharmacologic prophylaxis alone. The impact of dual prophylaxis versus single modality on other outcomes could not be determined.			
Key Question 8. In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery), regardless of thromboprophylaxis method, what are the effects of prolonging thromboprophylaxis for 28 days or longer compared with thromboprophylaxis for 7 to 10 days on symptomatic objectively confirmed venous thromboembolism, major venous thromboembolism (proximal deep vein thrombosis, pulmonary embolism or venous thromboembolism related mortality), pulmonary embolism, fatal pulmonary embolism, nonfatal pulmonary embolism, post thrombotic syndrome, mortality, mortality due to bleeding, deep vein thrombosis (asymptomatic or symptomatic, proximal or distal deep vein thrombosis), asymptomatic deep vein thrombosis, symptomatic deep vein thrombosis, proximal deep thrombosis, distal deep vein thrombosis, major bleeding, major bleeding leading to reoperation, minor bleeding, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, heparin-induced thrombocytopenia, discomfort, readmission, and reoperation?			
Prolonged prophylaxis had a better comparative balance of benefits and harms versus short-term prophylaxis in patients undergoing major orthopedic surgery. The impact of prolonging prophylaxis for 28 days or longer on events was compared with prophylaxis for 7 to 10 days in patients who had major orthopedic surgery. Prolonged prophylaxis reduced the occurrence of symptomatic objectively confirmed VTE, PE (overall and nonfatal), and DVT (overall, symptomatic, asymptomatic, and proximal) versus shorter term prophylaxis. Statistically significant publication bias was detected in the evaluation of distal DVT and nonfatal PE although the directionality was unclear. While higher heterogeneity was found for symptomatic VTE and DVT, the direction of effect was consistent among all of the trials. In base case analyses, prolonged prophylaxis increases the occurrence of minor bleeding and surgical site bleeding versus shorter term prophylaxis. Four previous meta-analyses compared the impact of longer versus shorter duration pharmacologic prophylaxis and are in general agreement with our present comparative effectiveness review.			
Key Question 9. In patients undergoing major orthopedic surgery (total hip or knee replacement, hip fracture surgery) who have known contraindications to antithrombotic agents, what is the relative impact of prophylactic inferior vena cava filter placement compared with any external mechanical intervention on symptomatic			

objectively confirmed venous thromboembolism, major venous thromboembolism (proximal deep vein thrombosis, pulmonary embolism or venous thromboembolism related mortality), pulmonary embolism, fatal pulmonary embolism, nonfatal pulmonary embolism, post thrombotic syndrome, mortality, mortality due to bleeding, deep vein thrombosis (asymptomatic or symptomatic, proximal or distal deep vein thrombosis), asymptomatic deep vein thrombosis, symptomatic deep vein thrombosis, proximal deep thrombosis, distal deep vein thrombosis, major bleeding, major bleeding leading to reoperation, minor bleeding, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, heparin-induced thrombocytopenia, discomfort, readmission, reoperation or IVC filter placement-associated insertion site thrombosis?			
There were no trials or studies that met our inclusion criteria.			
Key Question 10. In patients requiring knee arthroscopy, surgical repair of a lower extremity injury distal to the hip, or elective spine surgery what is the relative impact of thromboprophylaxis (any agent, any mechanical intervention) compared with no thromboprophylaxis intervention on symptomatic objectively confirmed venous thromboembolism, major venous thromboembolism (proximal deep vein thrombosis, pulmonary embolism or venous thromboembolism related mortality), pulmonary embolism, fatal pulmonary embolism, nonfatal pulmonary embolism, post thrombotic syndrome, mortality, mortality due to bleeding, deep vein thrombosis (asymptomatic or symptomatic, proximal or distal deep vein thrombosis), asymptomatic deep vein thrombosis, symptomatic deep vein thrombosis, proximal deep thrombosis, distal deep vein thrombosis, major bleeding, major bleeding leading to reoperation, minor bleeding, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, heparin-induced thrombocytopenia, discomfort, readmission, and reoperation?			
One trial was available for Achilles tendon rupture and for knee arthroscopy, but no literature met inclusion criteria for elective spine surgery. Both of the available trials were small in size leading to limited power to detect differences between the groups compared. The comparative balance of benefits and harms for dalteparin therapy versus placebo or control was difficult to discern based on the scant data. In patients who had surgical repair of Achilles tendon rupture, the use of dalteparin versus placebo for 6 weeks did not significantly impact the incidence of total or proximal DVT. No patients developed a PE or major bleeding. In patients who had arthroscopic knee surgery, the use of dalteparin versus control led to significantly fewer patients with total or distal DVT. One patient in the dalteparin group developed a PE and also had a DVT. No patients had major bleeding, and the occurrence of minor bleeding was not significantly different between the two groups.			
Key Question 11. In patients requiring knee arthroscopy, surgical repair of a lower extremity injury distal to the hip, or elective spine surgery what is the relative impact of injectable antithrombotic agents (low molecular weight heparin agents, injectable unfractionated heparin, injectable factor Xa inhibitors, injectable direct thrombin inhibitors) compared with mechanical interventions on symptomatic objectively confirmed venous thromboembolism, major venous thromboembolism (proximal deep vein thrombosis, pulmonary embolism or venous thromboembolism related mortality), pulmonary embolism, fatal pulmonary embolism, nonfatal pulmonary embolism, post thrombotic syndrome, mortality, mortality due to bleeding, deep vein thrombosis (asymptomatic or symptomatic, proximal or distal deep vein thrombosis), asymptomatic deep vein thrombosis, symptomatic deep vein thrombosis, proximal deep thrombosis, distal deep vein thrombosis, major bleeding, major bleeding leading to reoperation, minor bleeding, surgical site bleeding, bleeding leading to infection, bleeding leading to transfusion, heparin-induced thrombocytopenia, discomfort, readmission, and reoperation?			
There were no trials or studies that met our inclusion criteria.			
CER=comparative effectiveness review; RCT=randomized controlled trial; pts=patients; yr(s)=years; NR=not reported; vs.= versus; OR= odds ratio; CI= confidence interval; DVT=Deep venous thrombosis; VTE: venous thromboembolism; PE= pulmonary embolism; OR= pulmonary embolism; mg= milligram; %= percentage			