APPENDIX A. SEARCH STRATEGIES

Table A-1. Search strategy for PubMed (5/29/2012, updated 9/28/2012)

Set #	Terms	Results
1	Dabigatran[tiab] OR desirudin[tiab] OR edoxaban[tiab] OR rivaroxaban[tiab] OR apixaban[tiab] OR betrixaban[tiab] OR YM150[tiab] OR razaxaban[tiab] OR "dabigatran etexilate"[Supplementary Concept] OR "desirudin"[Supplementary Concept] OR "edoxaban"[Supplementary Concept] OR "rivaroxaban"[Supplementary Concept] OR "apixaban"[Supplementary Concept] OR "betrixaban"[Supplementary Concept] OR "razaxaban hydrochloride"[Supplementary Concept] OR "factor Xa, Glu-Gly-Arg-"[Supplementary Concept] OR "KFA1411"[Supplementary Concept]	1319
2	(((knee[tiab] OR hip[tiab] OR elbow[ti]) AND (replacement[tiab] OR Arthroplasty[tiab]))) OR ("Orthopedic Procedures"[Mesh])	194066
3	#1 AND #2	298
4	("Review"[Publication Type] OR "Review Literature as Topic"[Mesh]) OR ("Meta-Analysis as Topic"[Mesh] OR "Meta-Analysis"[Publication Type]) OR systematic[sb]	1782948
5	#3 AND #4	117

Table A-2. Search strategy for Embase (5/30/2012, updated 9/28/2012)

Set #	Terms	Results
1	'dabigatran'/exp OR dabigatran OR 'desirudin'/exp OR desirudin OR 'edoxaban'/exp OR edoxaban OR 'rivaroxaban'/exp OR rivaroxaban OR 'apixaban'/exp OR apixaban OR'betrixaban'/exp OR betrixaban OR 'ym150'/exp OR ym150 OR 'razaxaban'/exp OR razaxaban OR 'factor xa inhibitors' OR 'factor xa inhibitor'/exp OR 'factor xa inhibitor' OR 'fxa inhibitors' OR 'fxa inhibitor' OR'direct thrombin inhibitor' OR 'direct thrombin inhibitors' OR dtis OR 'novel anticoagulants' OR 'new anticoagulants' OR 'novel anticoagulant' OR 'new anticoagulant'	10942
2	'orthopedic surgery'/exp OR (hip:ab,ti OR knee:ab,ti OR elbow:ab,ti AND (replacement:ab,ti OR arthroplasty:ab,ti))	351,364
3	#1 AND #2	1522
4	#3 limited to Systematic reviews or meta –analysis AND (embase)/lim NOT (medline)/lim	43

Table A-3. Search strategy for Cochrane Database of Systematic Reviews (5/30/2012, updated 9/28/2012)

Set #	Term	Results
1	dabigatran OR desirudin OR edoxaban OR rivaroxaban OR apixaban OR betrixaban OR YM150 OR razaxaban OR "factor Xa inhibitors" OR "factor Xa inhibitor" OR "fxa inhibitors" OR "fxa inhibitor" OR "direct thrombin inhibitor" OR "direct thrombin inhibitors" OR DTIs OR "novel anticoagulants" OR "new anticoagulants" OR "novel anticoagulant" OR "new anticoagulant"	472
2	MeSH descriptor **Orthopedic Procedures** explode all trees OR (knee):ti,ab,kw or (elbow):ti,ab,kw) AND (replacement):ti,ab,kw or (arthroplasty):ti,ab,kw	8138
3	#1 AND #2	117
4	#3 limited to Systematic reviews or meta-analysis	8

APPENDIX B. EXCLUDED STUDIES

All citations listed in Table B-1 were reviewed in their full-text version and excluded for the reason indicated. An alphabetical reference list follows the table.

Table B-1. Excluded studies with reasons

Reference	Not a systematic review	Does not address Key Questions
Cohen, 2012	X[a]	
Dahl, 2009	X	
Dahl, 2010	X	
Diamantopoulos, 2010	X	
Duggan, 2009	X	
Eriksson, 2011	X	
Eriksson, 2009	X	
Falck-Ytter, 2012	X	
Friedman, 2011	X	
Friedman, 2010	X	
Friedman, 2011	X	
Goff, 2011	X	
Gomez-Outes, 2011	X	
Gras, 2011	X	
Holmes, 2009	X	
Hull, 2010	X	
Imberti, 2009	X	
Jacobs, 2012	X	
Kwong, 2011	X	
Kwong, 2011	X	
Lazo-Langner, 2009	X	
Lee, 2012	X	
Lereun, 2011	X	
Mantha, 2011	X	
Maratea, 2011	X	
Melillo, 2010		X
Merli, 2009	X	
Miller, 2012		X
Mont, 2011	X	
Nieto, 2012	X	
Poultsides, 2012		X
Prom, 2011		X
Raskob, 2012	X	
Stevenson, 2009	X	
Trkulja, 2010	X	
Watkins, 2011	X	
Wolowacz, 2011		X
Wolowacz, 2009	X	

[a]Rated as poor-quality systematic review and excluded.

LIST OF EXCLUDED STUDIES

Cohen A, Drost P, Marchant N, et al. The efficacy and safety of pharmacological prophylaxis of venous thromboembolism following elective knee or hip replacement: systematic review and network meta-analysis. *Clin Appl Thromb Hemost.* 2012;18(6):611-627.

Dahl OE. Dabigatran etexilate for the prophylaxis of venous thromboembolism after hip or knee replacement rationale for dose regimen. *Clin Appl Thromb Hemost*. 2009;15 Suppl 1:17S-24S.

Dahl OE, Quinlan DJ, Bergqvist D, et al. A critical appraisal of bleeding events reported in venous thromboembolism prevention trials of patients undergoing hip and knee arthroplasty. *J Thromb Haemost*. 2010;8(9):1966-75.

Diamantopoulos A, Lees M, Wells PS, et al. Cost-effectiveness of rivaroxaban versus enoxaparin for the prevention of postsurgical venous thromboembolism in Canada. *Thromb Haemost*. 2010;104(4):760-70.

Duggan ST, Scott LJ, Plosker GL. Rivaroxaban: a review of its use for the prevention of venous thromboembolism after total hip or knee replacement surgery. *Drugs*. 2009;69(13):1829-51.

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;105(4):721-9.

Eriksson BI, Friedman RJ. Dabigatran etexilate: pivotal trials for venous thromboembolism prophylaxis after hip or knee arthroplasty. *Clin Appl Thromb Hemost*. 2009;15 Suppl 1:25S-31S.

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;141(2 Suppl):e278S-325S.

Friedman RJ. Novel oral anticoagulants for VTE prevention in orthopedic surgery: overview of phase 3 trials. *Orthopedics*. 2011;34(10):795-804.

Friedman RJ, Dahl OE, Rosencher N, et al. Dabigatran versus enoxaparin for prevention of venous thromboembolism after hip or knee arthroplasty: a pooled analysis of three trials. *Thromb Res*. 2010;126(3):175-82.

Friedman RJ, Sengupta N, Lees M. Economic impact of venous thromboembolism after hip and knee arthroplasty: potential impact of rivaroxaban. *Expert Rev Pharmacoecon Outcomes Res*. 2011;11(3):299-306.

Goff T, Kontakis G, Giannoudis PV. Safety and efficacy of rivaroxaban for thromboprophylaxis following lower limb surgery: an update. *Expert Opin Drug Saf*. 2011;10(5):687-96.

Gomez-Outes A, Terleira-Fernandez A, Suarez-Gea ML, et al. New oral anticoagulants for thromboprophylaxis after total hip or knee replacement: A meta-analysis and indirect treatment comparisons. *Basic and Clinical Pharmacology and Toxicology*. 2011;109:34.

Gras J. Edoxaban for the prevention of thromboembolic events after surgery. *Drugs Today (Barc)*. 2011;47(10):753-61.

Holmes M, Carroll C, Papaioannou D. Dabigatran etexilate for the prevention of venous thromboembolism in patients undergoing elective hip and knee surgery: a single technology appraisal. *Health Technol Assess*. 2009;13 Suppl 2:55-62.

Hull RD, Liang J, Brant R. Pooled analysis of trials may, in the presence of heterogeneity inadvertently lead to fragile conclusions due to the importance of clinically relevant variables being either hidden or lost when the findings are pooled. *Thromb Res*. 2010;126(3):164-5.

Imberti D, Dall'Asta C, Pierfranceschi MG. Oral factor Xa inhibitors for thromboprophylaxis in major orthopedic surgery: a review. *Intern Emerg Med*. 2009;4(6):471-7.

Jacobs JJ, Mont MA, Bozic KJ, et al. American Academy of Orthopaedic Surgeons clinical practice guideline on: preventing venous thromboembolic disease in patients undergoing elective hip and knee arthroplasty. J Bone Joint Surg Am. 2012;94(8):746-7.

Kwong LM. Therapeutic potential of rivaroxaban in the prevention of venous thromboembolism following hip and knee replacement surgery: a review of clinical trial data. *Vasc Health Risk Manag*. 2011;7:461-6.

Kwong LM. Cost-effectiveness of rivaroxaban after total hip or total knee arthroplasty. *Am J Manag Care*. 2011;17(1 Suppl):S22-6.

Lazo-Langner A, Hawell J, Kovacs MJ, et al. A systematic review and meta-analysis of proportions of thrombosis and bleeding in patients receiving venous thromboembolism (VTE) prophylaxis after orthopedic surgery (OS). an update. *Blood*. 2009;114(22).

Lee S, White CM. Upcoming oral factor Xa inhibitors for venous thromboembolism prophylaxis in patients undergoing major orthopedic surgery: rivaroxaban (Xarelto) and apixaban (Eliquis) review. *Conn Med*. 2012;76(1):39-42.

Lereun C, Wells P, Diamantopoulos A, et al. An indirect comparison, via enoxaparin, of rivaroxaban with dabigatran in the prevention of venous thromboembolism after hip or knee replacement. *J Med Econ*. 2011;14(2):238-44.

Mantha S. Oral factor Xa inhibitors vs. enoxaparin for thromboprophylaxis after joint replacement surgery: A meta-analysis. *Journal of Thrombosis and Haemostasis*. 2011;9:189.

Maratea D, Fadda V, Trippoli S, et al. Prevention of venous thromboembolism after major orthopedic surgery: indirect comparison of three new oral anticoagulants. *J Thromb Haemost*. 2011;9(9):1868-70.

Melillo SN, Scanlon JV, Exter BP, et al. Rivaroxaban for thromboprophylaxis in patients undergoing major orthopedic surgery. *Ann Pharmacother*. 2010;44(6):1061-71.

Merli G, Spyropoulos AC, Caprini JA. Use of emerging oral anticoagulants in clinical practice: translating results from clinical trials to orthopedic and general surgical patient populations. *Ann Surg*. 2009;250(2):219-28.

Miller CS, Grandi SM, Shimony A, et al. Meta-Analysis of Efficacy and Safety of New Oral Anticoagulants (Dabigatran, Rivaroxaban, Apixaban) Versus Warfarin in Patients With Atrial Fibrillation. *Am J Cardiol*. 2012.

Mont MA, Jacobs JJ, Boggio LN, et al. Preventing venous thromboembolic disease in patients undergoing elective hip and knee arthroplasty. *J Am Acad Orthop Surg*. 2011;19(12):768-76.

Nieto JA, Espada NG, Merino RG, et al. Dabigatran, Rivaroxaban and Apixaban versus Enoxaparin for thomboprophylaxis after total knee or hip arthroplasty: Pool-analysis of phase III randomized clinical trials. *Thromb Res*. 2012;130(2):183-91.

Poultsides LA, Gonzalez Della Valle A, Memtsoudis SG, et al. Meta-analysis of cause of death following total joint replacement using different thromboprophylaxis regimens. *J Bone Joint Surg Br*. 2012;94(1):113-21.

Prom R, Spinler SA. The role of apixaban for venous and arterial thromboembolic disease. *Ann Pharmacother*. 2011;45(10):1262-83.

Raskob GE, Gallus AS, Pineo GF, et al. Apixaban versus enoxaparin for thromboprophylaxis after hip or knee replacement: pooled analysis of major venous thromboembolism and bleeding in 8464 patients from the ADVANCE-2 and ADVANCE-3 trials. *J Bone Joint Surg Br*. 2012;94(2):257-64.

Stevenson M, Scope A, Holmes M, et al. Rivaroxaban for the prevention of venous thromboembolism: a single technology appraisal. *Health Technol Assess*. 2009;13 Suppl 3:43-8.

Trkulja V, Kolundzic R. Rivaroxaban vs dabigatran for thromboprophylaxis after joint-replacement surgery: exploratory indirect comparison based on meta-analysis of pivotal clinical trials. *Croat Med J*. 2010;51(2):113-23.

Watkins PB, Desai M, Berkowitz SD, et al. Evaluation of drug-induced serious hepatotoxicity (eDISH): application of this data organization approach to phase III clinical trials of rivaroxaban after total hip or knee replacement surgery. *Drug Saf*. 2011;34(3):243-52.

Wolowacz SE. Pharmacoeconomics of dabigatran etexilate for prevention of thromboembolism after joint replacement surgery. *Expert Rev Pharmacoecon Outcomes Res*. 2011;11(1):9-25.

Wolowacz SE, Roskell NS, Plumb JM, et al. Efficacy and safety of dabigatran etexilate for the prevention of venous thromboembolism following total hip or knee arthroplasty. A meta-analysis. *Thromb Haemost*. 2009;101(1):77-85.

APPENDIX C. SAMPLE DATA ABSTRACTION FORM

First author, year, Reference Library#

STATED OBJECTIVE OF PAPER: " "

METHODS:

Databases accessed for literature search: X, Y, Z… and abstracts of (meetings, Websites, etc.):

Search date:

Language limits for search:

Inclusion criteria: Cut and paste from article AND ensure the following are addressed:

- *Study design type:*
- *Patients*: Any characteristic that would include or exclude (e.g., under 18 years)
- *Intervention*: Drugs of interest
- *Comparator*: What is considered a valid comparator for the drug of interest?
- *Outcomes*: Any of the following (also provide any definitions given by the authors):
    1. All-cause mortality
    2. VTE-related mortality
    3. VTE (only if DVT and PE not given separately)
    4. Symptomatic DVT
    5. Nonfatal PE
    6. Serious AEs
    7. Fatal bleeding
    8. Major bleeding
    9. Bleeding from the surgical site
    10. Rehospitalization (includes bleeding that requires reoperation).

Exclusion criteria: Cut and paste from article

Summary of analysis approach:

- System used (RevMan, Peto, CMA, etc.)
- Report statistic (OR, RR, RD, MD, combination?)
- Special procedures (double-checking, etc.)
- Heterogeneity addressed?
- Publication bias addressed?
- Subgroup analyses?
- Sensitivity analyses?
-

Funding Source: Look carefully for pharma $

QUALITY: See separate quality rating form

RESULTS: Number of key questions: XX (if multiple KQs, complete this section for each KQ)

A. Number of studies included (if numbers vary by KQ, give total and number for each KQ):
XX met eligibility; XX analyzed (were any articles specific excluded, why?)

B. Patient characteristics (range across studies):
Type of surgery: Knee replacement (n=); hip replacement (n=); either knee or hip (n=)
Sex (female-n %): ---- to ---- (XX.X to XX.X%)
Sample size (n): YY to YY, YYY
Mean age (years): ZZ.Z to ZZ.Z
Mean BMI or weight: AA.A to AA.A
Veteran settings, if given:
Risk factors for bleeding (prior GI bleed, anemia, renal insufficiency, DM):
Intervention drugs: (generic name, number of studies, notes about dosage)

1. *KQ1* – newer oral anticoagulants (FXa or DTI)
2. *KQ2* – combined pharmacological (any type) + mechanical modalities
3. *KQ3* – new oral anticoagulant (FXa or DTI)

Comparator:

1. *KQ1* – LMWH, UFH, warfarin, aspirin
2. *KQ2* – pharmacological treatment alone
3. *KQ3* – other newer oral anticoagulant (FXa or DTI) – direct or indirect comparison

Concurrent other drug administration? (yes/no)

- Antiplatelet drugs:
- Other

C. Outcomes: (FXa vs LMWH)
Outcomes definition:
Were they objectively evaluated?
Was there missing data?
Other specifics mentioned about quality of results:

Duration of anticoagulation:

- Knee: e.g., 5–14 days (n=)
  ≥15 days (n=)
- Hip: e.g., < 28 days (n=)
  ≥ 28 days (n=)

Followup timing:

- e.g., <14 days (n=)
- 14–30 days (n=)
- > 30 days (n=)
-

Risk of bias for primary studies: Any standard ratings given? Specific issues? (e.g., blinding? adjudication? poor completion rates?)

Quantitative summaries: Give # participants, # studies, summary estimate and 95% CI, I^2, RD (per 1,000), strength of evidence (SOE) if given. [For example: 22,838 participants, 11 studies; OR 0.95 (95% CI, 0.55 to 1.63); I^2=43%; RD=0 fewer events (CI, 2 fewer to 1 more) per 1,000; SOE=High]

Provide these data for the following outcomes, if given:
Mortality:
VTE-related mortality:
Total VTE:
Symptomatic DVT:
Nonfatal PE:
Serious AEs:
Major bleeding:
Bleeding from the surgical site:
Rehospitalization: (give reason if possible)
Other outcome of significance:

Did they measure publication bias? (via funnel plots, etc.)

Subgroup analyses: If presented, give type and outcome
- Dose:
- Type of surgery:
- Within drug class:
- Multiple treatments:

Sensitivity analysis: If presented, give type and outcome

AUTHOR'S CONCLUSION: (take-home message): " "

APPENDIX D. CRITERIA USED IN QUALITY ASSESSMENT OF SYSTEMATIC REVIEWS

For reviews, first determine whether it is a systematic review. To be a systematic review, it must include a methods section that describes (1) a search strategy and (2) an a priori approach to synthesizing the data. For reviews determined to meet the systematic review criteria, assess methodological quality.*

General instructions: The purpose of this rating tool is to evaluate the scientific quality of systematic reviews. It is not intended to measure the literary quality, importance, relevance, originality, or other attributes of systematic reviews.

Step 1: Grade each criterion listed below as "Yes," "No," "Can't tell" or "Not Applicable." Factors to consider when making an assessment are listed under each criterion. Where appropriate (particularly when assigning a "No," or "Can't tell" score), please provide a brief rationale for your decision (in parentheses).

1. **Is a focused clinical question clearly stated?**
   At a minimum, the question should be developed a priori and should clearly identify population and outcomes. The study question does not have to be in PICO format (Population, Intervention, Comparisons, Outcomes.)
   [] Yes [] No [] Can't tell [] N/A

2. **Are the search methods used to identify relevant studies clearly described?**
   Search methods described in enough detail to permit replication (The report must include search date, databases used, and search terms (Key words and/or MESH terms must be stated and where feasible the search strategy should be provided.)
   [] Yes [] No [] Can't tell [] N/A

3. **Was a comprehensive literature search performed?**
   At least 2 electronic sources should be searched and electronic searches should be supplemented by consulting: reference lists from prior reviews, textbooks, or included studies; specialized registries (e.g., Cochrane registries); or queries to experts in the field.
   [] Yes [] No [] Can't tell [] N/A

4. **Was selection bias avoided?**
   Study reports the number of studies identified through searches, the numbers excluded, and gives appropriate reasons for excluding – based on explicit inclusion/exclusion criteria.
   [] Yes [] No [] Can't tell [] N/A

5. **Was there duplicate study selection and data extraction?**
   Did two or more raters make inclusion/exclusion decisions, abstract data, and assess study quality – either independently or with one rater over-reading the first raters result?
   Was an appropriate method used to resolve disagreements (e.g., a consensus procedure)?
   [] Yes [] No [] Can't tell [] N/A

6. **Were the characteristics of the included studies provided?**
   In an aggregated form such as a table, data from the original studies should be provided on the participants, interventions and outcomes. The ranges of characteristics in all the studies analyzed (e.g., age, race, sex, relevant socioeconomic data, disease status, duration, severity or other diseases) should be reported.
   [] Yes [] No [] Can't tell [] N/A

7. **Was the scientific quality of the included studies assessed and documented?**
   A priori methods of assessment should be provided and criteria used to assess study quality specified in enough detail to permit replication.
   [] Yes [] No [] Can't tell [] N/A

8. **Were the methods used to combine the findings of studies appropriate?**
   For pooled results, an accepted quantitative method of pooling should be used (i.e., more than simple addition; e.g., random-effects or fixed-effect model). For pooled results, a qualitative and quantitative assessment of homogeneity (Cochran's Q and/or I^2) should be performed. If only qualitative analyses are completed, the study should describe the reasons that quantitative analyses were not completed.
   [] Yes [] No [] Can't tell [] N/A

9. **Was the scientific quality of the included studies used appropriately in formulating conclusions?**
   The results of the methodological rigor and scientific quality should be considered in the analysis (e.g. subgroup analyses) and the conclusions of the review, and explicitly stated in formulating recommendations.
   [] Yes [] No [] Can't tell [] N/A

10. **Was publication bias assessed?**
    Publication bias tested using funnel plots, test statistics (e.g., Egger's regression test), and/or search of trials registry for unpublished studies.
    [] Yes [] No [] Can't tell [] N/A

11. **Was the conflict of interest stated?**
    Potential sources of support should be clearly acknowledged in both the systematic review and the included studies.
    [] Yes [] No [] Can't tell [] N/A

12. **Are the stated conclusions supported by the data presented?**
    Were the conclusions made by the author(s) supported by the data and/or analyses reported in the systematic review?
    [] Yes [] No [] Can't tell [] N/A

Step 2: Rate the overall quality of the SR as "Good," "Fair," or "Poor" using the guidance below.

Good = After considering items 1-12, item 12 is rated "Yes" with no important limitations. This means that few of the items 1-12 are rated "No," and none of the limitations are thought to decrease the validity of the conclusions. If items 3, 4, 7, or 8 are rated "No," then the review is likely to have major flaws

Fair = After considering items 1-12, item 12 is rated "Yes," but with at least some important limitations. This means that enough of the items 1-12 are rated "No" to introduce some uncertainty about the validity of the conclusions.

Poor = After considering items 1-12, item 12 is rated "No." This means that several of items 1-12 are rated "No," introducing serious uncertainty about the validity of the conclusions.

*Adapted from:

1. Shea BJ, Grimshaw JM, Wells GA, et al. Development of AMSTAR: a measurement tool to assess the methodological quality of systematic reviews. BMC Med Res Methodol. 2007;7:10.
2. Moher D, Cook DJ, Eastwood S, et al. Improving the quality of reports of meta-analyses of randomised controlled trials: the QUOROM statement. Quality of Reporting of Meta-analyses. Lancet. 1999;354(9193):1896-900.
3. Marinopoulos SS, Dorman T, Ratanawongsa N, et al. Effectiveness of continuing medical education. Evid Rep Technol Assess (Full Rep). 2007(149):1-69.

Table D-1 shows the quality ratings for the systematic reviews included in this evidence report.

Table D-1. Quality assessment for included systematic reviews

Criteria for grading the quality of a systematic review (SR)	Neumann, 2012	Sobieraj, 2012	Gomez-Outes, 2012	Loke, 2011	Ringerike, 2011	Alves, 2011
Q1. Is a focused clinical question clearly stated?	Yes	Yes	Yes	Yes	Yes	Yes
Q2. Are the search methods used to identify relevant studies clearly described?	Yes	Yes	Yes	Yes	Yes	Yes
Q3. Was a comprehensive literature search performed?	Yes	Yes	Yes	Yes	Yes	Yes
Q4. Was selection bias avoided?	Yes	Yes	Yes	Yes	Yes	Yes
Q5. Was there duplicate study selection and data extraction?	Yes	Yes	Yes	Yes	Yes	Yes
Q6. Were the characteristics of the included studies provided?	Yes	Yes	Yes	Yes	No	Yes
Q7. Was the scientific quality of the included studies assessed and documented?	Yes	Yes	Yes	Yes	Yes	Can't tell
Q8. Were the methods used to combine the findings of studies appropriate?	Yes	Yes	Yes	Yes	Yes	Yes
Q9. Was the scientific quality of the included studies used appropriate in formulating conclusions?	Yes	Yes	Yes	Yes	Yes	Yes
Q10. Was publication bias assessed?	Yes	Yes	Yes	Yes	Yes	Yes
Q11. Was the conflict of interest stated?	Yes	Yes	Yes	Yes	Can't tell	Yes
Q12. Are the stated conclusions supported by the data presented?	Yes	Yes	Yes	Yes	Yes	Yes
Overall quality	Good	Good	Good	Good	Good	Good

APPENDIX E. PEER REVIEW COMMENTS

Reviewer	Comment	Response
Question 1: Are the objectives, scope, and methods for this review clearly described?		
1	Yes. Objectives are clear and KQs relevant to current clinical practice in VA. Scope as defined by KQs is appropriate and clinically relevant. Methods are rigorous, transparent, and accomplished according to latest accepted principles of evidence based medicine.	Thank you for your confidence in our process.
2	Yes, and no comments from reviewer 2.	Thank you.
3	Yes, and no comments from reviewer 3.	Thank you.
Question 2: Is there any indication of bias in our synthesis of the evidence?		
1	No. No bias detected. Transparency of methods allows for an open assessment of bias and allows reader to assess validity and accept results as valid for use in informing clinical practice.	Thank you again for your confidence in our process.
2	No, and no comments from reviewer 2.	Thank you.
3	No. No bias detected.	Thank you.
Question 3: Are there any published or unpublished studies that we may have overlooked?		
1	No. No additional references to suggest.	Thank you.
2	No, and no comments from reviewer 2.	Thank you.
3	No – Not that I am aware of	Thank you.
Question 4: Please write additional suggestions or comments below. If applicable, please indicate the page and line numbers from the draft report.		
1	1) Could improve transparency regarding conflict of interest if: a. Drugs in this report made by manufacturers Dr Ortel has potential conflicts of interest with are identified and b. The sections Dr Ortel worked on were listed. Reader would be better able to assess bias.	We added a description of Dr. Ortel's role in the project.
1	2) Page 1 executive summary, 3rd paragraph, last sentence discussing 'Disadvantages of newer oral anticoagulants…' From a clinical standpoint we are most concerned with veteran safety and the lack of specific antidote is a primary concern. Would edit that sentence to place this concern first.	The recommended change has been made.
1	3) The contemporary 35-day rate of symptomatic VTE w/o prophylaxis of 4.3% (page 1); Baseline risk estimates for LMWH of 9 per 1000 symptomatic DVT, nonfatal PE 3 per 1000, mortality 3 per 1000 and major bleeding of 7 per 1000 (page 2) are extremely useful numbers for the busy clinician to know for counseling patients, comparing with treatment with NOACs (pg 4) and for making treatment decisions. Would include these numbers in the conclusions section on page 9.	We added data on the rate of VTE to the conclusion section. We did not repeat the absolute risk reductions as this information is already contained in two locations: in the bullet points and in the summary of evidence table. We will be sure that this information is contained in the VA e-brief.

Reviewer	Comment	Response
1	4) Page 9 Conclusion section: a). first paragraph, as noted above in #3 would put in reduced risk or increase risk numbers and b). Last paragraph…'Based on current evidence, newer anticoagulants—particularly Xa inhibitors—are a reasonable option for thromboprophylaxis…' Agree from this evidence synthesis that Xa inhibitors are a reasonable option. Any suggested sequence of treatment? LMWH first then Xa? Or is Xa first just as reasonable as LMWH? Is there a way to assess the value of 4 per 1000 decrease in symptomatic DVT vs an increase of 2 major bleeds per 1000 treated with a Xa?	Although there are formal methods to consider multiple outcomes to develop a rank order of interventions, none of these methods are robust. The decision whether to use thromboprophylaxis, and the particular mode, is one that involves tradeoffs between potential benefits and harms. Clinicians must consider the patient's particular risks, values, and preferences when making this decision. Our data inform this decision.
1	5) 5 Page 12 3rd paragraph: 'Dabigatran etexilate is an oral reversible DTI…' Reversible seems to imply there is an antidote for reversal and there is no antidote (other than stopping the medication and letting it wear off). Recommend striking word 'reversible'.	The recommended change has been made.
1	6) Page 14 Search Strategy first paragraph: Might be more explicit as why a synthesis of high quality reviews would be more effective approach to summarizing the evidence than a perhaps a 'more standard' approach of searching the literature for RCTs and combining those in an evidence synthesis. Also, why limit the search only as far back as 1 Jan 2009. What is the rationale for the search timeframe?	We added a justification for this approach as follows: "This approach is particularly useful when different intervention options or outcomes are evaluated in multiple recent reviews and when the audience is policymakers."
1	7) Page 24 Participant Characteristics: Discussion regarding no Veterans studied in the trials and the participants were predominantly female 50-75%. Given the available evidence is there or are there any reason(s) to believe Veterans would respond differently to these treatments or wouldn't be applicable to Veterans patients? If so why? If not why not?	The applicability of the results to Veteran patients is discussion in the Applicability section of the Discussion.
1	8) Page 26 Oral Xa Inhibitors compared to LMWH: a reader might assume that all of these drugs are available in the US. While we are considering all the individual drugs, would improve transparency if drugs not available in the US were identified.	This detail has been added. Only rivaroxaban is currently available in the United States.
1	9) Page 27, paragraph 3, first sentence "In subgroup analysis, higher doses of Xa inhibitors, but not intermediate or lower doses, …' would list the doses considered high, intermediate or low in parentheses like on page 32.	The authors did not report the doses categorized as high, intermediate, or low. However, they do give the doses studied in the individual trials and we have added the dosing ranges for apixaban and rivaroxaban, drugs approved in Canada and the United States, respectively.
1	10) Page 29 Other Comparisons of Interest section, 2nd paragraph 'Low molecular weight heparin vs vitamin K antagonists, 3rd line, would put in dose regimen of enoxaparin (logiparin not available in US, so could omit dose). Same page, section immediately below 'Oral FXa inhibitors vs unfractionated heparin would list doses of fondaparinux and unfractionated heparin.	We added the dose of enoxaparin (30 mg subcutaneously every 12 hours). Fondaparinux and unfractionated heparin were evaluated in an observational study that did not report doses.

Reviewer	Comment	Response
1	11) Page 31 paragraph under 'Key Points' discussion of SRs and quality notes the industry sponsored network meta-analysis (Cohen 2012, ref 36) was rated **fair** quality. Then notes "The latter review did not provide an adequate description or quality assessment of the included trials and did not test the assumption of a constant treatment effect across different study populations---an assumption inherent to network meta-analysis." Page 32 same meta-analysis is being discussed and notes 'the composite outcomes are suspect because they combine events (composite VTE[any DVT, PE, death] and major bleeding[major, clinically relevant and minor bleeding) that have very different clinical importance'. These seem to be fatal deficiencies but the rating is **fair**. Appendix D pg 54 notes the quality rating scale and Pg 55 notes the individual trial assessments. Item 12 for the study in question (Cohen 2012, ref 36) is answered "Can't Tell" for which there is no provision in the scoring system which notes if item 12 is 'Yes' then study could be rated good or fair and if 'No' then Poor. A poor rating would have been excluded this trial from the analysis. The summary Table D-1 lists no answers for 6 of the remaining 11 items including critical items 7 and 8 which the text notes that the review is likely to have major flaws. Should the rating really be 'poor' and this analysis excluded?	We re-reviewed our quality rating for the Cohen study. We agree that it is poor quality and have excluded it from the final report.
1	12) Page 37 'Guidelines' section, First paragraph, end o paragraph notes ACCP recommends LMWH in absence of bleeding risk. Does ACCP suggest any sequence if there is an elevated bleeding risk?	We have added the ACCP recommendation for patients at increased bleeding risk: "For patients with increased bleeding risk, ACCP recommends intermittent pneumatic compression device or no prophylaxis."
1	13) Page 39 'Applicability'. End of paragraph notes private sector vs VA patients potential differences 9 (see comment #7 above). What should the reader conclude? This is a solid evidence synthesis but not applicable to VA patients? Or is applicable to VA patients?	We revised this section to state that the results likely apply to Veteran populations. We add a specific caution about higher comorbidities in Veterans, increasing the risk of bleeding.
1	14) Page 40 'Conclusion': Same comments as #4 above as this section also appears on page 9 in the Executive Summary.	As stated above, we think these data should be used to make individualized decisions with patients about the choice and mode of thromboprophylaxis.
1	15) Page 53 Appendix D, item 8, 2nd to last line '…If only qualitative analyses are completed, the study show describe…' Change 'show' to 'should'.	Thank you for noting this error. It has been corrected.
1	16) Glossary: Fantastic descriptions of confidence interval and statistical significance!	Thank you.
2	I was somewhat surprised to see the evidence that newer anticoagulants did not offer much advantage other than ease of administration and less monitoring but also troubled to see the incidence of side effects	Acknowledged

Reviewer	Comment	Response
3	Not the focus of this review, but might note that earlier this month the FDA approved rivaroxaban for treatment of deep vein thrombosis or pulmonary embolism, and to reduce the risk of recurrent DVT and PE following initial treatment. These are 2 other important clinical scenarios.	The role of newer anticoagulants for treatment of DVT and PE was reviewed in an earlier VA ESP report.
Question 5: Are there any VA clinical performance measures, programs, quality improvement measures, patient care services, or conferences that will be directly affected by this report? If so, please provide detail?		
1	There may be some inpatient performance measure for DVT prophylaxis that could be affected. Performance measure Technical Manual would need to be checked	We will ask that this report be sent to the VA clinical guideline and performance measure groups.
2	Not that I know of	Thank you.
3	No Comment???	Thank you.
Question 6: Please provide any recommendations on how this report can be revised to more directly address or assist implementation needs.		
1	See comments noted above.	Thank you.
2	N/A	Thank you.
3	It seems, at least from my perspective, that most VA providers are unaware of these reports, and fewer actually take the time to read them. However, I find that they are a valuable resource and reference tool.	Thank you.
Question 7: Please provide us with contact details of any additional individuals/stakeholders who should be made aware of this report.		
1	Lisa Longo PharmD who is PBM contact for these medications. Lisa.longo@va.gov based at VA Pittsburg	Thank you; the report has been sent to Dr. Longo, and she is one of our stakeholders in the product.
2	PBM; Chiefs of Medicine; Chief Medical Officers; Chiefs of Staff	Thank you.
3	No comments??	Thank you.

APPENDIX F. GLOSSARY

Abstract screening
The stage in a systematic review during which titles and abstracts of articles identified in the literature search are screened for inclusion or exclusion based on established criteria. Articles that pass the abstract screening stage are promoted to the full-text review stage.

Anticoagulant agents
A class of medication that prevents coagulation (blood clotting).

ClinicalTrials.gov
A registry and results database of federally and privately supported clinical trials conducted in the United States and around the world. ClinicalTrials.gov provides information about a trial's purpose, location, and participant characteristics among other details.

Cochrane Database of Systematic Reviews
A bibliographic database of peer-reviewed systematic reviews and protocols prepared by the Cochrane Review Groups in The Cochrane Collaboration.

Companion article
A publication from a trial that is not the article containing the main results of that trial. It may be a methods paper, a report of subgroup analyses, a report of combined analyses, or other auxiliary topic that adds information to the interpretation of the main publication.

Confidence interval (CI)
The range in which a particular result (such as a laboratory test) is likely to occur for everyone who has a disease. "Likely" usually means 95 percent of the time. Clinical research studies are conducted on only a certain number of people with a disease rather than all the people who have the disease. The study's results are true for the people who were in the study but not necessarily for everyone who has the disease. The CI is a statistical estimate of how much the study findings would vary if other different people participated in the study. A CI is defined by two numbers, one lower than the result found in the study and the other higher than the study's result. The size of the CI is the difference between these two numbers.

Data abstraction
The stage of a systematic review that involves a pair of trained researchers extracting reported findings specific to the research questions from the full-text articles that met the established inclusion criteria. These data form the basis of the evidence synthesis.

Deep vein thrombosis (DVT)
A blood clot that develops in the deep veins of the legs.

Direct thrombin inhibitors (DTIs)
A new class of anticoagulants that bind directly to thrombin and block its interaction with its substrates.

DistillerSR
An online application designed specifically for the screening and data extraction phases of a systematic review.

Embase
The Excerpta Medica database (EMBASE) produced by Elsevier, a major biomedical and pharmaceutical database indexing over 3500 international journals in the following fields: drug research, pharmacology, pharmaceutics, toxicology, clinical and experimental human medicine, health policy and management, public health, occupational health, environmental health, drug dependence and abuse, psychiatry, forensic medicine, and biomedical engineering or instrumentation. There is selective coverage for nursing, dentistry, veterinary medicine, psychology, and alternative medicine.

Exclusion criteria
The criteria, or standards, set out before a study or review. Exclusion criteria are used to determine whether a person should participate in a research study or whether an individual study should be excluded in a systematic review. Exclusion criteria may include age, previous treatments, and other medical conditions.

Factor Xa (FXa) inhibitor
A new class of anticoagulants that bind directly to factor Xa and block its interaction with other substrates.

Full-text review
The stage of a systematic review in which a pair of trained researches evaluates the full-text of study articles for potential inclusion in the review.

GRADE
Grading of Recommendations Assessment, Development, and Evaluation (GRADE), a system of assessing the quality of medical evidence and evaluating the strength of recommendations based on the evidence.

Inclusion criteria
The criteria, or standards, set out before the systematic review. Inclusion criteria are used to determine whether an individual study can be included in a systematic review. Inclusion criteria may include population, study design, sex, age, type of disease being treated, previous treatments, and other medical conditions.

Low molecular weight heparin
A class of medication used to treat thrombosis or for prophylaxis in situations that lead to a high risk of thrombosis. These medications have a more predictable anticoagulant response than naturally occurring unfractionated heparin.

Optimal information size
The number of patients that need to be included in a pooled analysis (meta-analysis) to provide sufficient power to detect the smallest clinically important difference in treatment effect.

PRISMA
Preferred Reporting Items for Systematic Reviews and Meta-Analyses, an evidence-based minimum set of items for reporting in systematic reviews and meta-analyses.

Publication bias
The tendency of researchers to publish experimental findings that have a positive result, while not publishing the findings when the results are negative or inconclusive. The effect of publication bias is that published studies may be misleading. When information that differs from that of the published study is not known, people are able to draw conclusions using only information from the published studies.

PubMed®
A database of citations for biomedical literature from MEDLINE®, life science journals, and online books in the fields of medicine, nursing, dentistry, veterinary medicine, the health care system, and preclinical sciences.

Pulmonary embolism (PE)
Blocking of the pulmonary artery (lungs) or one of its branches by a clot.

Randomized controlled trial
A prospective, analytical, experimental study using primary data generated in the clinical environment. Individuals similar at the beginning of the trial are randomly allocated to two or more treatment groups and the outcomes the groups are compared after sufficient followup time. Properly executed, the RCT is the strongest evidence of the clinical efficacy of preventive and therapeutic procedures in the clinical setting.

Risk
A way of expressing the chance that something will happen. It is a measure of the association between exposure to something and what happens (the outcome). Risk is the same as probability, but it usually is used to describe the probability of an adverse event. It is the rate of events (such as breast cancer) in the total population of people who could have the event (such as women of a certain age).

Statistical significance
A mathematical technique to measure whether the results of a study are likely to be true. Statistical significance is calculated as the probability that an effect observed in a research study is occurring because of chance. Statistical significance is usually expressed as a P-value. The smaller the P-value, the less likely it is that the results are due to chance (and more likely that the results are true). Researchers generally believe the results are probably true if the statistical significance is a P-value less than 0.05 ($p<.05$).

Strength of evidence (SOE)
A measure of how confident reviewers are about decisions that may be made based on a body of evidence. SOE is evaluated using one of four grades: (1) *High* confidence that the evidence reflects the true effect; further research is very unlikely to change reviewer confidence in the estimate of effect; (2) *moderate* confidence that the evidence reflects the true effect; further research may change the confidence in the estimate of effect and may change the estimate; (3) *low* confidence that the evidence reflects the true effect; further research is likely to change the confidence in the estimate of effect and is likely to change the estimate; and (4) *insufficient*; the evidence either is unavailable or does not permit a conclusion.

Systematic review
A summary of the clinical literature. A systematic review is a critical assessment and evaluation of all research studies that address a particular clinical issue. The researchers use an organized method of locating, assembling, and evaluating a body of literature on a particular topic using a set of specific criteria. A systematic review typically includes a description of the findings of the collection of research studies. The systematic review may also include a quantitative pooling of data, called a meta-analysis.

Venous thromboembolism (VTE)
Obstruction of a vein or veins (embolism) by a blood clot (thrombus) in the blood stream; includes deep vein thrombosis (DVT) and pulmonary embolism (PE).

Vitamin K antagonist (warfarin)
An anticoagulant that acts by inhibiting the synthesis of vitamin K-dependent coagulation factors; i.e., I, VII, IX and X.