APPENDIX A. SEARCH STRATEGIES

Table A-1. Search strategy for RCTs (PubMed, February 2012)

Step	Category	Terms	Result
1	Newer anticoagulants	dabigatran OR desirudin OR ximelagatran 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" OR "newer anticoagulants" OR "newer anticoagulant" **AND**	3289
2	Disorders of interest	"Venous Thrombosis"[Mesh:noexp] OR "Venous Thromboembolism"[Mesh] OR "Pulmonary Embolism"[Mesh] OR "Atrial Fibrillation"[Mesh] OR "Heart Valve Prosthesis"[Mesh] OR "Aortic Valve"[Mesh] OR "Mitral Valve"[Mesh] OR deep vein thrombosis OR AF OR dvt OR PE OR pulmonary embolism OR mechanical heart valve OR mechanical heart valves OR "mechanical valve" OR "mechanical valves" OR "mechanical mitral" OR "mechanical aortic" OR thromboembolism AND	217463
3	Study designs	randomized controlled trial[Publication Type] OR random*	711597
4	Combine results and apply limits	#1 AND #2 AND #3 English, Publication Date from 2001 to 2011	320

Table A-2. Search strategy for observational studies (February 2012)

Step	Category	Terms	Results
1	Newer anticoagulants	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] **AND**	1112
2	Disorders of interest	"Venous Thrombosis"[Mesh:noexp] OR "Venous Thromboembolism"[Mesh] OR "Pulmonary Embolism"[Mesh] OR "Atrial Fibrillation"[Mesh] OR "Heart Valve Prosthesis"[Mesh] OR "Aortic Valve"[Mesh] OR "Mitral Valve"[Mesh] OR "deep vein thrombosis"[tiab] OR "atrial fibrillation"[tiab] OR dvt[tiab] OR "pulmonary embolism"[tiab] OR "mechanical heart valve"[tiab] OR "mechanical heart valves"[tiab] OR "mechanical valve"[tiab] OR "mechanical valves"[tiab] OR "mechanical aortic"[tiab] OR thromboembolism[tiab] **AND**	145374
3	Study designs	("evaluation studies"[Publication Type] OR "evaluation studies as topic"[MeSH Terms] OR "evaluation study"[tiab] OR evaluation studies[tiab] OR "intervention studies"[MeSH Terms] OR "intervention study"[tiab] OR "intervention studies"[tiab] OR "case-control studies"[MeSH Terms] OR "case-control"[tiab] OR "cohort studies"[MeSH Terms] OR cohort[tiab] OR "longitudinal studies"[MeSH Terms] OR "longitudinal"[tiab] OR longitudinally[tiab] OR "prospective"[tiab] OR prospectively[tiab] OR "retrospective studies"[MeSH Terms] OR "retrospective"[tiab] OR "follow up"[tiab] OR "comparative study"[Publication Type] OR "comparative study"[tiab] OR "Case Reports"[Publication Type] OR "case report"[tiab] OR "case series"[tiab] OR observational[tiab]) NOT (Editorial[ptyp] OR Letter[ptyp] OR Comment[ptyp])	4927238

Step	Category	Terms	Results
3	Combine results and apply limits	#1 AND #2 AND #3 Publication Date from 2001 to 2012	278
4	Additional study designs	"Case Reports"[Publication Type] OR "Case-Control Studies"[Mesh]) OR "Cohort Studies"[Mesh] OR "case report"[tiab] OR cohort[tiab] OR case-control[tiab] OR "case series"[tiab]	2841521
5	Combine results and apply limits	#1 AND #2 AND #4 Publication Date from 2001 to 2012	47

Table A-3. Search strategy for systematic reviews (PubMed, February 2012)

Step	Category	Terms	Results
1	New oral anticoagulants	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]	1121
2	Disorders of interest	"Venous Thrombosis"[Mesh:noexp] OR "Venous Thromboembolism"[Mesh] OR "Pulmonary Embolism"[Mesh] OR "Atrial Fibrillation"[Mesh] OR "Heart Valve Prosthesis"[Mesh] OR "Aortic Valve"[Mesh] OR "Mitral Valve"[Mesh] OR "deep vein thrombosis"[tiab] OR "atrial fibrillation"[tiab] OR dvt[tiab] OR "pulmonary embolism"[tiab] OR "mechanical heart valve"[tiab] OR "mechanical heart valves"[tiab] OR "mechanical valve"[tiab] OR "mechanical valves"[tiab] OR "mechanical aortic"[tiab] OR thromboembolism[tiab]	145502
3	Study designs	Systematic[sb]	170174
3	Combine results and apply limits	Search #1 AND #2 AND #3 Publication Date from 2001 to 2012	64

APPENDIX B. STUDY SELECTION FORM

Criteria for Inclusion and Exclusion of RCTs

Inclusion criteria:

- An RCT or a secondary data analysis from an RCT comparing a newer anticoagulant to an eligible comparator (warfarin and LMWH are the two comparators we are accepting for the various key questions)
- Sample population with history of chronic nonvalvular AF, deep venous thromboembolism, or mechanical valve replacement. Atrial fibrillation may be assessed by any accepted threshold on any valid diagnostic tool (e.g., electrocardiogram and/or echocardiogram).
- Sample population ≥18 years of age
- Outpatient setting (community clinic, medical clinic or office, or transitioning from inpatient for acute treatment to long-term outpatient management)
- Random allocation to the intervention groups
- Reports at least one of the included outcomes:
    - **KQs 1–3:** The main outcome is a thromboembolic event. Thromboembolic events must be documented radiologically and produce clinical symptoms. Asymptomatic thromboembolism (e.g., detected on surveillance imaging) will not be included.
    - **KQs 1–3**: Other outcomes are mortality, health-related quality of life, and patient treatment experience—the latter two measured by a validated instrument.
    - **KQ 4:** Adverse effects will be specific to the interventions examined and will include bleeding complications, myocardial infarction, and gastrointestinal adverse effects.
- Study duration of at least 6 months (KQ 2 acute treatment) or at least 12 months (KQ 1, KQ 2 chronic treatment, KQ 3, KQ 4)
- Peer-reviewed publication

Exclusion criteria:

- Non-English language publication
- Cross-sectional studies
- Pregnant population
- Studies with sample size <50
- Studies with <6 months postrandomization outcomes

Eligibility Criteria for Observational Studies

- **Patients**: chronic atrial fibrillation or VTE treated with an oral DTI or FXa inhibitor
- **Comparator**: none or adjusted-dose warfarin
- **Outcomes**: adverse events
- **Timing**: ≥ 3months use
- **Setting**: any outpatient
- **Study designs**:
    - Comparative: secondary analyses from RCTs (including patient level meta-analysis), cohort studies (prospective or retrospective-including analyses of claims databases), case control, cross-sectional.
    - Noncomparative: case-reports, case-series.

APPENDIX C. EXCLUDED STUDIES

All citations listed in Tables C-1 and C-2 were reviewed in their full-text version and excluded for the reason indicated. An alphabetical reference list follows each table.

Table C-1. Excluded RCTs with reasons

Reference	Not full publication, peer-reviewed, or primary data	Not study population of interest	New drug or comparator not of interest	No relevant outcomes reported at ≥6 months
Adams 2005	X			
Ageno 2005	X			
Agnelli 2009		X		
Amadeus Investigators 2008			X	
Anonymous 2004	X			
Anonymous 2009	X			
Berry 2005	X			
Botticelli Investigators 2008				X
Buller 2007			X	
Buller 2007			X	
Buller 2007			X	
Camm 2009	X			
Chung 2011				X
Cohen 2006		X		
Connolly 2011			X	
Connolly 2010	X			
Dahl 2010	X			
Deitcher 2006			X	
EAFT Study Group 1993			X	
Eriksson 2005			X	
Eriksson 2003				X
Fiessinger 1996			X	
Halperin 2005	X			
Halperin 2005	X			
Hankey 2004	X			
Hankey 2009	X			
Hankey 2011	X			
Harenberg 2002	X			
Hart 1999			X	
Heidbuchel 2010	X			
Hull 2006			X	
Kaul 2005	X			
Kubitza 2006	X			
Kwok 2004	X			
Lee 2003			X	
Lip 2009				X
Lopez-Beret 2001			X	
Meyer 2002			X	
Olsson 2010				X
Paikin 2011	X			
Party 2010			X	
Persist Investigators 2004				X
Petersen 2003				X
Prandoni 2010	X			
Prins 2009			X	
Rother 2010	X			

Reference	Not full publication, peer-reviewed, or primary data	Not study population of interest	New drug or comparator not of interest	No relevant outcomes reported at ≥6 months
Salam 2004	X			
Schulman 2005			X	
Segal 2001			X	
SPIAF Investigators 1996			X	
SPIAF Investigators 1991			X	
Taylor 2001			X	
Wahlander 2006			X	
Wallentin 2010	X			
Weitz 2010				X
Weitz 2010				X

Abbreviations: EAFT = European Atrial Fibrillation Trial; SPIAF = Stroke Prevention in Atrial Fibrillation

LIST OF EXCLUDED RCTs

Adams HP. Prevention of embolism among patients with atrial fibrillation. *Curr Neurol Neurosci Rep*. 2005;5(1):9-12.

Ageno W, Turpie AG. Clinical trials of deep vein thrombosis prophylaxis in medical patients. *Clin Cornerstone*. 2005;7(4):16-22.

Agnelli G, Eriksson BI, Cohen AT, et al. Safety assessment of new antithrombotic agents: lessons from the EXTEND study on ximelagatran. *Thromb Res*. 2009;123(3):488-97.

Amadeus Investigators. Comparison of idraparinux with vitamin K antagonists for prevention of thromboembolism in patients with atrial fibrillation: a randomised, open-label, non-inferiority trial. *The Lancet*. 2008;371(9609):315-321.

Anonymous. Results of THRIVE treatent study show that ximelagatran is safe and effective against throbosis. *J Support Oncol*. 2004;2(1):56.

Anonymous. Dabigatran: safer, more effective and easier to use than warfarin. *Cardiovasc J Afr*. 2009;20(5):311-2.

Berry C, Norrie J, McMurray JJ. Ximelagatran compared with warfarin for the prevention of systemic embolism and stroke. An imputed placebo analysis. *Cardiovasc Drugs Ther*. 2005;19(2):149-51.

Botticelli Investigators. Efficacy and safety of the oral direct factor Xa inhibitor apixaban for symptomatic deep vein thrombosis. The Botticelli DVT dose-ranging study. *Journal of thrombosis and haemostasis : JTH*; 2008:1313-8.

Buller HR, Cohen AT, Davidson B, et al. Idraparinux versus standard therapy for venous thromboembolic disease. *New England Journal of Medicine*. 2007;357(11):1094-1104.

Buller HR, Cohen AT, Davidson B, et al. Extended prophylaxis of venous thromboembolism with idraparinux. *New England Journal of Medicine*. 2007;357(11):1105-1112.

Buller HR, Cohen AT, Davidson B, et al. Idraparinux versus standard therapy for venous thromboembolic disease. *N Engl J Med*. 2007;357(11):1094-104.

Camm AJ. The RE-LY study: Randomized Evaluation of Long-term anticoagulant therapY: Dabigatran vs. warfarin. *European Heart Journal*. 2009;30(21):2554-2555.

Chung N, Jeon HK, Lien LM, et al. Safety of edoxaban, an oral factor Xa inhibitor, in Asian patients with non-valvular atrial fibrillation. *Thromb Haemost*. 2011;105(3):535-44.

Cohen AT, Davidson BL, Gallus AS, et al. Efficacy and safety of fondaparinux for the prevention of venous thromboembolism in older acute medical patients: randomised placebo controlled trial. *BMJ*. 2006;332(7537):325-327.

Connolly SJ, Eikelboom J, Joyner C, et al. Apixaban in patients with atrial fibrillation. *N Engl J Med*. 2011;364(9):806-17.

Connolly SJ, Ezekowitz MD, Yusuf S, et al. Newly identified events in the RE-LY trial. *N Engl J Med*. 2010;363(19):1875-6.

Dahl OE, Huisman MV. Dabigatran etexilate: advances in anticoagulation therapy. *Expert Rev Cardiovasc Ther*. 2010;8(6):771-4.

Deitcher SR, Kessler CM, Merli G, et al. Secondary prevention of venous thromboembolic events in patients with active cancer: enoxaparin alone versus initial enoxaparin followed by warfarin for a 180-day period. *Clin Appl Thromb Hemost*. 2006;12(4):389-96.

EAFT (European Atrial Fibrillation Trial) Study Group. Secondary prevention in non-rheumatic atrial fibrillation after transient ischaemic attack or minor stroke. *Lancet*. 1993;342(8882):1255-62.

Eriksson H, Lundstrom T, Wahlander K, et al. Prognostic factors for recurrence of venous thromboembolism (VTE) or bleeding during long-term secondary prevention of VTE with ximelagatran. *Thromb Haemost*. 2005;94(3):522-7.

Eriksson H, Wahlander K, Gustafsson D, et al. A randomized, controlled, dose-guiding study of the oral direct thrombin inhibitor ximelagatran compared with standard therapy for the treatment of acute deep vein thrombosis: THRIVE I. *J Thromb Haemost*. 2003;1(1):41-7.

Fiessinger JN, Lopez-Fernandez M, Gatterer E, et al. Once-daily subcutaneous dalteparin, a low molecular weight heparin, for the initial treatment of acute deep vein thrombosis. *Thromb Haemost*. 1996;76(2):195-9.

Halperin JL. Anticoagulation for atrial fibrillation in the elderly. *Am J Geriatr Cardiol*. 2005;14(2):81-6.

Halperin JL. Ximelagatran: oral direct thrombin inhibition as anticoagulant therapy in atrial fibrillation. *J Am Coll Cardiol*. 2005;45(1):1-9.

Hankey GJ. At last, a RE-LYable alternative to warfarin for atrial fibrillation. *Int J Stroke*. 2009;4(6):454-5.

Hankey GJ, Eikelboom JW. Dabigatran etexilate: a new oral thrombin inhibitor. *Circulation*. 2011;123(13):1436-50.

Hankey GJ, Klijn CJ, Eikelboom JW. Ximelagatran or warfarin for stroke prevention in patients with atrial fibrillation? *Stroke*. 2004;35(2):389-91.

Harenberg J, Ingrid J, Tivadar F. Treatment of venous thromboembolism with the oral thrombin inhibitor, ximelagatran. *Isr Med Assoc J*. 2002;4(11):1003-5.

Hart RG, Benavente O, McBride R, et al. Antithrombotic therapy to prevent stroke in patients with atrial fibrillation: a meta-analysis. *Ann Intern Med*. 1999;131(7):492-501.

Heidbuchel H, Verhamme P. Dabigatran for stroke prevention in atrial fibrillation: from RE-LY to daily clinical practice. *Acta Cardiol*. 2010;65(5):491-7.

Hull RD, Pineo GF, Brant RF, et al. Long-term low-molecular-weight heparin versus usual care in proximal-vein thrombosis patients with cancer. *Am J Med*. 2006;119(12):1062-72.

Kaul S, Diamond GA, Weintraub WS. Trials and tribulations of non-inferiority: the ximelagatran experience. *J Am Coll Cardiol*. 2005;46(11):1986-95.

Kubitza D, Haas S. Novel factor Xa inhibitors for prevention and treatment of thromboembolic diseases. *Expert Opin Investig Drugs*. 2006;15(8):843-55.

Kwok L, Boucher M. Ximelagatran for prevention and treatment of venous thromboembolism. *Issues Emerg Health Technol*. 2004(57):1-4.

Lee AY, Levine MN, Baker RI, et al. Low-molecular-weight heparin versus a coumarin for the prevention of recurrent venous thromboembolism in patients with cancer. *N Engl J Med*. 2003;349(2):146-53.

Lip GY, Rasmussen LH, Olsson SB, et al. Oral direct thrombin inhibitor AZD0837 for the prevention of stroke and systemic embolism in patients with non-valvular atrial fibrillation: a randomized dose-guiding, safety, and tolerability study of four doses of AZD0837 vs. vitamin K antagonists. *Eur Heart J*. 2009;30(23):2897-907.

Lopez-Beret P, Orgaz A, Fontcuberta J, et al. Low molecular weight heparin versus oral anticoagulants in the long-term treatment of deep venous thrombosis. *J Vasc Surg*. 2001;33(1):77-90.

Meyer G, Marjanovic Z, Valcke J, et al. Comparison of low-molecular-weight heparin and warfarin for the secondary prevention of venous thromboembolism in patients with cancer: a randomized controlled study. *Arch Intern Med*. 2002;162(15):1729-35.

Olsson SB, Rasmussen LH, Tveit A, et al. Safety and tolerability of an immediate-release formulation of theoral direct thrombin inhibitor AZD0837 in the prevention of stroke and systemic embolism in patients with atrial fibrillation. *Thromb Haemost*. 2010;103(3):604-12.

Paikin JS, Haroun MJ, Eikelboom JW. Dabigatran for stroke prevention in atrial fibrillation: the RE-LY trial. *Expert Rev Cardiovasc Ther*. 2011;9(3):279-86.

Paty I, Trellu M, Destors JM, et al. Reversibility of the anti-FXa activity of idrabiotaparinux (biotinylated idraparinux) by intravenous avidin infusion. *J Thromb Haemost*. 2010;8(4):722-9.

Persist Investigators. A novel long-acting synthetic factor Xa inhibitor (SanOrg34006) to replace warfarin for secondary prevention in deep vein thrombosis. A Phase II evaluation. *J Thromb Haemost*. 2004;2(1):47-53.

Petersen P, Grind M, Adler J. Ximelagatran versus warfarin for stroke prevention in patients with nonvalvular atrial fibrillation. SPORTIF II: a dose-guiding, tolerability, and safety study. *J Am Coll Cardiol*. 2003;41(9):1445-51.

Prandoni P, Taher A. Insights from the dabigatran versus warfarin trial in patients with venous thromboembolism (the RE-COVER trial). *Expert Opin Pharmacother*. 2010;11(6):1035-7.

Prins MH, Guillemin I, Gilet H, et al. Scoring and psychometric validation of the Perception of Anticoagulant Treatment Questionnaire (PACT-Q(copyright)). *Health and Quality of Life Outcomes*. 2009;7.

Rother J, Crijns H. Prevention of stroke in patients with atrial fibrillation: the role of new antiarrhythmic and antithrombotic drugs. *Cerebrovasc Dis*. 2010;30(3):314-22.

Salam AM. Ximelagatran for stroke prevention in atrial fibrillation. *Therapy*; 2004:49-52.

Schulman S, Lundstrom T, Walander K, et al. Ximelagatran for the secondary prevention of venous thromboembolism: a complementary follow-up analysis of the THRIVE III study. *Thromb Haemost*. 2005;94(4):820-4.

Segal JB, McNamara RL, Miller MR, et al. Anticoagulants or antiplatelet therapy for non-rheumatic atrial fibrillation and flutter. *Cochrane Database of Systematic Reviews*. 2001(1).

Stroke Prevention in Atrial Fibrillation Investigators. Stroke Prevention in Atrial Fibrillation Study Final Results. *Circulation*. 1991;84(2):527-39.

Stroke Prevention in Atrial Fibrillation Investigators. Bleeding During Antithrombotic Therapy in Patients With Atrial Fibrillation. *Arch Intern Med*. 1996;156(4):409-16.

Taylor FC, Cohen H, Ebrahim S. Systematic review of long term anticoagulation or antiplatelet treatment in patients with non-rheumatic atrial fibrillation. *BMJ*. 2001;322(7282):321-6.

Wahlander K, Eriksson H, Lundstrom T, et al. Risk of recurrent venous thromboembolism or bleeding in relation to thrombophilic risk factors in patients receiving ximelagatran or placebo for long-term secondary prevention of venous thromboembolism. *British Journal of Haematology*; 2006:68-77.

Wallentin L, Ezekowitz MD, Eikelboom J, et al. Efficacy and safety of dabigatran compared to warfarin at different levels of INR control for stroke prevention in 18,113 patients with atrial fibrillation in the RE-LY trial. *Circulation*. 2010;120(21):2158.

Weitz JI, Cao C, Eriksson BI, et al. A dose-finding study with TAK-442, an oral factor Xa inhibitor, in patients undergoing elective total knee replacement surgery. *Thromb Haemost*. 2010;104(6):1150-7.

Weitz JI, Connolly SJ, Patel I, et al. Randomised, parallel-group, multicentre, multinational phase 2 study comparing edoxaban, an oral factor Xa inhibitor, with warfarin for stroke prevention in patients with atrial fibrillation. *Thromb Haemost*. 2010;104(3):633-41.

Table C-2. Excluded observational studies

Reference	Background only	Not full publication	Not study population of interest	No relevant outcomes (adverse effects) reported at >2 weeks from drug initiation	Not good quality
Aalbers 2010	X				
Anonymous 2011		X			
Baruch 2011			X		
Beyer-Westendorf 2011	X				
Bovio 2011	X				
Camm 2009		X			
Coleman 2012					X
Cotton 2011	X				
Eerenberg 2011	X				
Gerotziafas 2005				X	
Jacobs 2012	X				
Kaeberich 2011			X		
Lip 2010					
Loke 2011	X				
McKellar 2011			X		
Poultside 2012			X		
Roskell 2010					X
Tzeis 2011	X				
Watanabe 2012		X			

LIST OF EXCLUDED OBSERVATIONAL STUDIES

Aalbers J. Rivaroxaban equals warfarin treatment in atrial fibrillation patients at high risk of stroke. *Cardiovasc J Afr*. 2010;21(6):342-3.

Anonymous. New insights and results from the RE-LY trial. *Cardiovasc J Afr*. 2011;22(5):284-6.

Baruch L, Sherman O. Potential inaccuracy of point-of-care INR in dabigatran-treated patients. *Ann Pharmacother*. 2011;45(7-8):e40.

Beyer-Westendorf J, Buller H. External and internal validity of open label or double-blind trials in oral anticoagulation: better, worse or just different? *J Thromb Haemost*. 2011;9(11):2153-8.

Bovio JA, Smith SM, Gums JG. Dabigatran etexilate: a novel oral thrombin inhibitor for thromboembolic disease. *Ann Pharmacother*. 2011;45(5):603-14.

Camm. Dabigatran: safer, more effective and easier to use than warfarin. *Cardiovasc J Afr*. 2009;20(5):311-2.

Coleman CI, Sobieraj DM, Winkler S, et al. Effect of pharmacological therapies for stroke prevention on major gastrointestinal bleeding in patients with atrial fibrillation. *Int J Clin Pract*. 2012;66(1):53-63.

Cotton BA, McCarthy JJ, Holcomb JB. Acutely injured patients on dabigatran. *N Engl J Med*. 2011;365(21):2039-40.

Eerenberg ES, Kamphuisen PW, Sijpkens MK, et al. Reversal of rivaroxaban and dabigatran by prothrombin complex concentrate: a randomized, placebo-controlled, crossover study in healthy subjects. *Circulation*. 2011;124(14):1573-9.

Gerotziafas GT, Samama MM. Heterogeneity of synthetic factor Xa inhibitors. *Curr Pharm Des*. 2005;11(30):3855-76.

Jacobs JM, Stessman J. Dabigatran: Do We Have Sufficient Data?: Comment on "Dabigatran Association With Higher Risk of Acute Coronary Events". *Arch Intern Med*. 2012.

Kaeberich A, Reindl I, Raaz U, et al. Comparison of unfractionated heparin, low-molecular-weight heparin, low-dose and high-dose rivaroxaban in preventing thrombus formation on mechanical heart valves: results of an in vitro study. *J Thromb Thrombolysis*. 2011;32(4):417-25.

Lip GY, Lane DA. Does warfarin for stroke thromboprophylaxis protect against MI in atrial fibrillation patients? *Am J Med*. 2010;123(9):785-9.

Loke YK, Kwok CS. Dabigatran and rivaroxaban for prevention of venous thromboembolism--systematic review and adjusted indirect comparison. *J Clin Pharm Ther*. 2011;36(1):111-24.

McKellar SH, Abel S, Camp CL, et al. Effectiveness of dabigatran etexilate for thromboprophylaxis of mechanical heart valves. *J Thorac Cardiovasc Surg*. 2011;141(6):1410-6.

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.

Roskell NS, Lip GY, Noack H, et al. Treatments for stroke prevention in atrial fibrillation: a network meta-analysis and indirect comparisons versus dabigatran etexilate. *Thromb Haemost*. 2010;104(6):1106-15.

Tzeis S, Andrikopoulos G. Novel Anticoagulants for Atrial Fibrillation: A Critical Appraisal. *Angiology*. 2011.

Watanabe M, Siddiqui FM, Qureshi AI. Incidence and management of ischemic stroke and intracerebral hemorrhage in patients on dabigatran etexilate treatment. *Neurocrit Care*. 2012;16(1):203-9.

APPENDIX D. SAMPLE DATA EXTRACTION FORMS

Elements abstracted from RCTs

Study abstracted (Author, year, ID#)

Companion Study Ref IDs (Author, Year)

Form 1

Study Sites

☐ Single Center ☐ Multicenter ☐ Not reported/unclear

Geographical Location

Single Center: ☐

Enter City and State (if U.S.); Country (If outside the U.S.).

☐

Multicenter: ☐

Enter number of sites. Enter NR, if not reported.

Select all applicable geographical locations.

☐ U.S. ☐ Canada ☐ UK ☐ Europe ☐ S. America ☐ C. America ☐ Asia

☐ Africa ☐ Australia/NZ. ☐ Middle East ☐ Not reported/Unclear ☐ Other ☐

Funding Source

Check all that apply:

☐ Government ☐ Private Foundation ☐ Industry ☐ Not Reported ☐ Other ☐

Study Design

☐ 1. Patient Level RCT

☐ 2. Other

Comparator Setting (check all that apply):

☐ Specialized anticoagulation clinic

☐ Other

☐ Not Reported/unclear

Enrollment Approach
Check all that apply:

☐ Consecutive patients

☐ Convenience sample

☐ Other

☐ Not Reported/unclear

Study Inclusion and Exclusion Criteria

1) Age range (years)

2) Diagnosis

☐ DVT/PE

Symptomatic?

☐ Yes ☐ No

Objectively confirmed?

☐ Yes ☐ No

☐ Afib

EKG?

☐ Yes ☐ No

3) Intended duration of Anticoagulation therapy? (check one choice)

Choose an item.

Check all exclusion criteria used in the study (check all that apply)

☐ Asymptomatic

☐ Yes ☐ No

☐ Alcohol or Drug Abuse

☐ Upper age limit Age

☐ Medical instability Type

☐ Anemia (give cut-off)

☐ Antiplatelet treatment

☐ ASA (give dosage)

☐ Clopidogrel

☐ NSAIDS

☐ Dipyridamole/ASA

☐ Clinically significant liver disease

☐ transaminase study threshold

☐ High risk of bleeding

Define:

☐ Clinically significant kidney disease

☐ eGFR (ml/min) study threshold ☐

☐ Platelet count (threshold) ☐

Study Enrollment/Study Completion

Note: Patients who are eligible, but refuse participation should be counted in the "eligible" number.

Assessed for eligibility (N): ☐

Eligible (N): ☐

Randomized (N): ☐

Completed follow-up (N): ☐

Comments:

ANTICOAGULATION TREATMENT

Acute Treatment ☐ Yes ☐ No

☐ Heparin (unfractionated)

☐ LMWH

"Duration of acute treatment" # days

☐

Newer Anticoagulant Drug and Standard dosing

a) Drug Name: **Choose an item.**

b) Dose ☐ mg

c) Frequency **Choose an item.**

d) Were there dose modifications for sub-populations ☐ Yes ☐ No

Newer Anticoagulant intended duration of treatment.

Choose an item.

If others: [ ]

Comparator Anticoagulant Drug and Dosing

a) Comparator Drug Name Choose an item.

b) If a=adjusted dose Warfarin, then INR range low [ ]
high [ ]

If a= any other answer, then Dose [ ] mg

c) Frequency **Choose an item.**

Comparator Anticoagulant intended duration of treatment.

Choose an item.

Visit frequency monitoring

On average at least monthly?

☐ Yes ☐ No

Form 2

Baseline Characteristics

Dichotomous variables

		Primary AC Intervention Choose an item. **N=**	**Comparator 1** Choose an item. **N=**	**Comparator 2** Choose an item. **N=**
GENDER	**Female** ☐ Not reported	N= %=	N= %=	N= %=
	Male ☐ Not reported	N= %=	N= %=	N= %=
RACE	**White** ☐ Not reported	N= %=	N= %=	N= %=
	Blacks ☐ Not reported	N= %=	N= %=	N= %=

RACE	**Latino/Hispanic** ☐ Not reported	N= %=	N= %=	N= %=
	Asian ☐ Not reported	N= %=	N= %=	N= %=
RACE	**Other *** ☐ Not reported **(includes Native American, Pacific Islander, etc.)**	N= %=	N= %=	N= %=
Antiplatelet drug use	**ASA (>80 mg daily)** ☐ Not reported	N= %=	N= %=	N= %=
	Clopidogrel ☐ Not reported	N= %=	N= %=	N= %=

Antiplatelet drug use	**NSAIDS** ☐ Not reported	N= %=	N= %=	N= %=
	Aggrenox ☐ Not reported	N= %=	N= %=	N= %=
	Dipyridamole ☐ Not reported	N= %=	N= %=	N= %=
History of heart disease	**History of Ischemic heart disease** **Define:** ischemic OR angina OR acute coronary syndrome (ACS) ☐ Not reported	N= %=	N= %=	N= %=

Impaired Renal Function	**Define:** Moderate **Define:** Severe ☐ Not reported	N= %= N= %=	N= %= N= %=	N= %= N= %=

Comments:

Continuous variables

	Primary AC Intervention Choose an item. **N=**	**Comparator 1** Choose an item. **N=**	**Comparator 2** Choose an item. **N=**
Age (years) ☐ Not reported	Choose an item. Choose an item.	Choose an item. Choose an item.	Choose an item. Choose an item.
eGFR/ Creatinine Clearance (mL/min) ☐ Not reported	Choose an item. Choose an item.	Choose an item. Choose an item.	Choose an item. Choose an item.
Obesity? Choose an item. ☐ Not reported	Choose an item. Choose an item.	Choose an item. Choose an item.	Choose an item. Choose an item.

Time from index event ☐ Not reported	Choose an item. Choose an item.	Choose an item. Choose an item.	Choose an item. Choose an item.

Comments:

Do these key questions apply to this article, yes/no?

KQ 1:
For patients with chronic nonvalvular AF, what is the comparative effectiveness of long-term anticoagulation using newer anticoagulants versus warfarin on stroke incidence, mortality, health-related quality of life (HRQOL), and patient treatment experience?

☐ Yes ☐ No

KQ 2:
For patients with venous thromboembolism, are there differential effects of newer anticoagulants versus warfarin or low molecular weight heparins (LMWHs) on recurrent thromboembolism, mortality, HRQOL, and patient treatment experience?

☐ Yes ☐ No

KQ3 does not appear because no studies of mechanical heart valves.

KQ 4:
When used for long-term anticoagulation treatment, what is the nature and frequency of adverse effects for newer anticoagulants versus warfarin?

☐ Yes ☐ No

Considering all baseline characteristics, are there significant baseline imbalances between the groups?

☐ Yes ☐ No

Comments:

Form 3a: Atrial Fibrillation

Risk factor screen type

☐ CHADS 2 ☐ CHADS 2 VASC ☐ No CHADS ☐

Comparative Analysis Choose an item.	**Primary AC Intervention** Choose an item. **N=**	**Comparator 1** Choose an item. **N=**	**Comparator 2** Choose an item. **N=**	**Comparative analysis** ☐ **New vs Comp** ☐ **Comp vs New**
CHADS total score ☐ Not reported	Mean / SD	Mean / SD	Mean / SD	Choose an item. Choose an item.
CHADS score=1 ☐ Not reported	N / %	N / %	N / %	Choose an item. Choose an item.
CHADS score=2 ☐ Not reported	N / %	N / %	N / %	Choose an item. Choose an item.
CHADS score=3 ☐ Not reported	N / %	N / %	N / %	Choose an item. Choose an item.
CHADS score >=4 ☐ Not reported	N / %	N / %	N / %	Choose an item. Choose an item.

Prior TE ☐ Not reported	N %	N %	N %	Choose an item. Choose an item.
Cancer ☐ Not reported	N %	N %	N %	Choose an item. Choose an item.
Known Thrombophilic condition ☐ Not reported	N %	N %	N %	Choose an item. Choose an item.
Pregnancy, post-partum or OBGYN complications ☐ Not reported	N %	N %	N %	Choose an item. Choose an item.
Recent surgery/trauma ☐ Not reported	N %	N %	N %	Choose an item. Choose an item.
Immobilization ☐ Not reported	N %	N %	N %	Choose an item. Choose an item.
Estrogen therapy ☐ Not reported	N %	N %	N %	Choose an item. Choose an item.

Others condition ☐ Not reported	N %	N %	N %	Choose an item. Choose an item.

If No CHADS, please record the following:

Age >75 years ☐ Not reported	Mean SD	Mean SD	Mean SD	Choose an item. Choose an item.
Diabetes Mellitus ☐ Not reported	Mean SD	Mean SD	Mean SD	Choose an item. Choose an item.
HF ☐ Not reported	Mean SD	Mean SD	Mean SD	Choose an item. Choose an item.
HTN ☐ Not reported	Mean SD	Mean SD	Mean SD	Choose an item. Choose an item.

Comments:

Form 3b: VTE

If DVT/PE, risk factors-Indication for anticoagulation

	Total	**Primary AC Intervention** Choose an item. **N=**	**Comparator 1** Choose an item. **N=**	**Comparative analysis** ☐ **New vs Comp** ☐ **Comp vs New**
DVT ☐ Not reported	N %	N %	N %	Choose an item. Choose an item.
PE ☐ Not reported	N %	N %	N %	Choose an item. Choose an item.
DVT/PE ☐ Not reported	N %	N %	N %	Choose an item. Choose an item.
Prior TE ☐ Not reported	N %	N %	N %	Choose an item. Choose an item.
Cancer ☐ Not reported	N %	N %	N %	Choose an item. Choose an item.

Known Thrombophilic condition ☐ Not reported	N %	N %	N %	Choose an item. Choose an item.
Pregnancy, post-partum or OBGYN complications ☐ Not reported	N %	N %	N %	Choose an item. Choose an item.
Recent surgery/trauma ☐ Not reported	N %	N %	N %	Choose an item. Choose an item.
Immobilization ☐ Not reported	N %	N %	N %	Choose an item. Choose an item.
Estrogen therapy ☐ Not reported	N %	N %	N %	Choose an item. Choose an item.
Others condition ☐ Not reported	N %	N %	N %	Choose an item. Choose an item.

Form 4a: Outcome Measures Reported

☐ Yes ☐ No ☐ Unclear

Central Adjudication

Timing of the outcome data reported in the table below [Repeat this table as needed]

☐ 24 months ☐ 12 months ☐ 6 months ☐ Other ☐

	Primary AC Intervention Choose an item. **N=** ☐	**Comparator 1** Choose an item. **N=** ☐	**Comparator 2** Choose an item. **N=** ☐
Adherence: newer AC, defined as 1) % above cut-off **OR** 2) Average, % of medication taken **OR** ☐ Not reported	% N %	% N %	% N %

Adherence: If comparator= Warfarin, % time in therapeutic range: ☐

Below range: ☐

Above range: ☐

☐ Not reported

	Primary AC Intervention Choose an item. **N=**	**Comparator 1** Choose an item. **N=**	**Comparative analysis** ☐ new vs comp ☐ comp vs new
Death all cause ☐ Not reported	N % Choose an item.	N % Choose an item.	Choose an item. Choose an item.
Death TE ☐ Not reported	N % Choose an item.	N % Choose an item.	Choose an item. Choose an item.
Stroke Ischemic ☐ Not reported	N % Choose an item.	N % Choose an item.	Choose an item. Choose an item.
Peripheral arterial embolism ☐ Not reported	N % Choose an item.	N % Choose an item.	Choose an item. Choose an item.
Stroke Hemorrhage ☐ Not reported	N % Choose an item.	N % Choose an item.	Choose an item. Choose an item.

Combined Stroke ☐ Not reported	N %	N %	Choose an item. Choose an item.
Quality of life ☐ Not reported	N %	N %	Choose an item. Choose an item.

Comment:

Form 4b: Outcome Measures Reported

Central Adjudication ❍ Yes ❍ No ❍ Unclear

Timing of the outcome data reported in the table below [Repeat this table as needed]

❍ 24 months ❍ 12 months ❍ 6 months Other

	Primary AC Intervention Choose an item. **N=**	**Comparator 1** Choose an item. **N=**	**Comparator 2** Choose an item. **N=**
Adherence: newer AC, defined as 1) % above cut-off **OR** 2) Average, % of medication taken **OR** ☐ Not reported	% N %	% N %	% N %

Adherence: If comparator= Warfarin, % time in therapeutic range:

% Below range:

% Above range:

☐ Not reported

	Primary AC Intervention Choose an item. **N=**	**Comparator 1** Choose an item. **N=**	**Comparator 2** Choose an item. **N=**
Death all cause ☐ Not reported	N %	N %	N %
Death TE ☐ Not reported	N %	N %	N %
Stroke Ischemic ☐ Not reported	N %	N %	N %
Peripheral arterial embolism ☐ Not reported	N %	N %	N %
Stroke Hemorrhage ☐ Not reported	N %	N %	N %
Combined Stroke ☐ Not reported	N %	N %	N %

Quality of life ☐ Not reported	N %	N %	N %

Return to Contents

Form 5

Adverse Event Outcomes

Timing of the outcome data reported in the table below [Repeat this table as needed]

☐ 24 months ☐ 12 months ☐ 6 months ☐ Other

	Primary AC Intervention Choose an item. **N=**	**Comparator 1** Choose an item. **N=**	**Comparative analysis** ☐ new vs comp ☐ comp vs new
Any adverse events ☐ Not reported	N %	N %	Choose an item. Choose an item.
Serious adverse events ☐ Not reported	N %	N %	Choose an item. Choose an item.
Adverse event-drug discontinuation ☐ Not reported	N %	N %	Choose an item. Choose an item.

Major bleeding-total ☐ Not reported	N %	N %	Choose an item. Choose an item.
Major bleeding-fatal ☐ Not reported	N %	N %	Choose an item. Choose an item.
Major bleeding-require transfusion ☐ Not reported	N %	N %	Choose an item. Choose an item.
Myocardial infarction ☐ Not reported	N %	N %	Choose an item. Choose an item.
LFT >3X ULN Choose an item. ☐ Not reported	N %	N %	Choose an item. Choose an item.
Intracranial bleeding ☐ Not reported	N %	N %	Choose an item. Choose an item.

Elements Abstracted From Observational Studies

- Study design
- Setting/study sites
- Geographic location
- Patient demographics
  - Age
  - Race/ethnicity
  - Gender
  - Diagnosis
  - Important medical history (e.g., CHADS score, EGR)
  - Comorbidities
- Types of adverse effects reported
- Suspected agent
- Degree of certainty that agent was causative
- Duration of illness
- Was patient hospitalized?
- Was episode fatal?
- Did episode resolve?
- Other necessary description of episode

APPENDIX E. PEER REVIEW COMMENTS

Reviewer	Comment	Response
Question 1: Are the objectives, scope, and methods for this review clearly described?		
1	Yes, and no comments from reviewer 1.	Thank you.
2	Yes, and no comments from reviewer 2.	Thank you.
3	Yes, and comment was "Methods, scope, and objectives are sufficiently described."	Thank you.
4	Yes, and comment was "Very clear, comprehensive report of the current literature."	Thank you.
Question 2: Is there any indication of bias in our synthesis of the evidence?		
1	No, and no comments from reviewer 1.	Thank you.
2	No, and no comments from reviewer 2.	Thank you.
3	Search methods identified all relevant studies (published and unpublished), the identified studies are of good quality, and author's analysis of the data does not appear to be influenced by any obvious source of bias. However, the analysis is potentially misleading by combining together the findings from clinical trials for all new anticoagulants - thus obfuscating any differences (in efficacy or safety) that might exist between these new agents (for example – figure 14 suggests there are significant differences in medication discontinuation rates)... or diminishing the effect a medication or class of medication may have had on outcomes relative to warfarin. At the very least, the reader should be alerted to this potential flaw in the analytical methods (e.g. the analysis, as constructed, assumes that "new anticoagulants" are substantially similar and were treated as a single class of medications).	We conducted additional analyses and presented results by drug class. However, these analyses consist of indirect comparisons (across studies that may differ in other ways, such as differences in the patient population or quality of adjusted-dose warfarin) and should be considered hypothesis generating. We added statements in the Discussion section and both the global Summary and Strengths and Limitations sections.
4	While the report is a comprehensive review of the current literature with sound results, the text is currently written in a biased manner favoring the newer anticoagulants without equally balancing the disadvantages and unknowns. Recommend revising to be more balanced in describing the findings and including disadvantages and unknowns. Examples provided below: Exec Summary, p. 1: potential benefits of newer anticoagulants are over-stated, and clinical limitations are not included (i.e., dabigatran is associated with higher GI bleeding than warfarin; downside is that there is not a readily available means of quantifying anticoag effect of newer agents in cases of emergency such as bleeding or emergent procedure/surgery needed). There is also more recent concern raised by FDA as well as other agencies outside of US about serious bleeding events with dabigatran, particularly in the elderly and renally impaired.	We have performed a secondary search of the observational literature and the FDA Web site looking specifically for reports of adverse events. These data are included under KQ 4 and in the Executive Summary.

Reviewer	Comment	Response
4	Page 5, page 36: "In the trial of dabigatran for chronic AF, myocardial infarction was increased, but the enrolled sample had higher CHADS2 scores than other trials." First, this statement is incorrect; mean CHADS2 score for RE-LY ~2.1; mean CHADS2 score ROCKET ~3.5. Second, the "but…" phrase does not explain the increase in MI. CHADS2 score is an assessment of stroke risk in patients with AF.	Thank you for pointing out this factual error that was an artifact of editing. The ROCKET study did have a higher mean CHADS score, and this factual error has been corrected. While it is true that the CHADS2 score is an assessment of stroke risk in patients with AF, many of the risk factors used in this assessment (e.g., HTN, DM, history of vascular disease) are risk factors for myocardial infarction too. We have clarified this point in the discussion.
4	Intro and Page 10: It is misleading to state that the newer agents are free from monitoring. It is more accurate, fair and balanced to state that there is not a need for "routine anticoagulant monitoring". All patients on anticoagulants should be monitored for s/sx bleeding, stroke, AEs, medication adherence. In addition, certain newer anticoagulants require monitoring of renal function (i.e., dabigatran, rivaroxaban).	Agreed. We have modified this statement to state: "These drugs characteristically have a predictable anticoagulant effect, eliminating the need for routine monitoring. However, patients on newer anticoagulants should still be monitored for any adverse events, including bleeding. Bleeding risk is increased with concurrent use of antiplatelet medications, older age, and renal impairment since most of these drugs are eliminated through the kidneys. (Harder 2011)"
4	GI bleeding and GI related adverse events were not included in KQ4; these events were reported more often with dabigatran.	We have now addressed GI bleeding and GI-related events in KQ 4.
4	Page 39, summary of KQ1: only the favorable outcomes of the newer anticoagulants are discussed. It may be stated that there was no significant difference found in VTE related mortality and ischemic stroke.	Agreed. The following statement was added to the paragraph: "However, VTE-related mortality and ischemic stroke were not significantly lower with newer oral anticoagulants."

Reviewer	Comment	Response
4	Page 39, summary of KQ1: bleeding outcomes and INR control – "The difference in bleeding related outcomes are dependent in part upon the quality of adjusted-dose warfarin treatment; these studies reported rates of time in therapeutic range that were similar to those observed in the VHA." Statement is misleading and an oversimplification as is. First, it would be more accurate to state that it is the MEAN or AVERAGE TTR from the clinical trials. Second, VHA national data show that ~70% of INRs are between 1.8 and 3.3. The method used to calculate TTR in the clinical trials differed and therefore limits the ability to directly compare numbers. The take home message to me is that outcomes with dabigatran vs. warfarin were similar when INR control was good. Further, outcomes with dabigatran were better when INR control was poor. INR control in the rivaroxaban study was poorer than typical standard. Suggest revision of the statement to include these limitations. Also suggest adding that anticoagulation control in VHA appears to be at least as good as the mean TTR in clinical trials.	The discussion of bleeding rates has been revised to: "While anticoagulation control in the VHA appears to be at least as good as that found in clinical trials, the ROCKET-AF study had a mean TTR that was worse than typical standards. In the RE-LY study, the advantages of dabigatran were greater at sites with poor INR control than at those with good INR control for all vascular events, nonhemorrhagic events, and mortality. Warfarin and dabigatran showed comparable outcomes in centers with good mean TTR."
4	Page 39, summary of KQ1: "Except for discontinuations due to adverse effects, other outcomes also favored newer anticoagulants but were not statistically significant." The MI outcome did not favor newer anticoagulants and should be stated here.	The statement was revised to: "Except for discontinuations due to adverse effects, other outcomes also favored newer anticoagulants; however, they were not statistically significant."
4	Page 40, summary of KQ2: Agree with conclusion; however similarly as for KQ1, only the positive effects of newer anticoagulants is included. It should also be stated that rate of DC due to AEs was higher with newer anticoagulants, though not statistically significant.	We have added this text: "When the study examining ximelagatran was included, results were similar except that drug discontinuation due to adverse effects was significantly higher than rates with adjusted-dose warfarin."
4	Page 41, summary of KQ4: same incorrect statement about the dabigatran, higher CHADS2 – see comment above.	ROCKET-AF had a higher mean CHADS2, and the text has been corrected to reflect this.
4	Page 41, summary of KQ4: "Fatal bleeding was significantly lower for newer anticoagulants in the chronic AF studies, and the point estimate favored these drugs for fatal bleeding in patients with VTE and major bleeding in both groups." For the VTE AEs, these were not statistically significant. Statement currently is unbalanced, showing bias in reporting to the newer anticoagulants.	We agree and have changed the statement to: "The newer oral anticoagulants were associated with a consistent decrease in mortality (0.88; 95% CI, 0.82 to 0.95), without significant variability across studies or differences between drug classes. Similarly, rates of fatal bleeding were consistently lower with newer oral anticoagulants (Table 9). There was a non–statistically significant reduction in major bleeding, but this effect varied importantly across studies—variability that was not explained by drug class."

Reviewer	Comment	Response
4	Page 42, "It is possible that the newer agents may improve patient experience and HRQOL." Statement is biased; a more balanced statement is that it is unknown whether new agents may improve patient experience and HRQOL.	This statement has been rephrased to: "Because no studies reported effects on patient experience and HRQOL, effects on these important outcomes are unknown."
4	Page 42, it states that patients with high bleeding risk were excluded from clinical trials, yet in the next paragraph it goes on to recommend these newer agents in patients at higher than average risk of bleeding. I don't agree with this statement and it is not supported by evidence.	Agreed. We have changed the wording to: "In the RE-LY study, the advantages of dabigatran were greater at sites with poor INR control than at those with good INR control for all vascular events, nonhemorrhagic events, and mortality. Warfarin and dabigatran showed comparable outcomes in centers with good mean TTR."
4	Page 42, including only part of the recommendation from ACCP/AHA on dabigatran is biased. The update also states that: because of BID dosing and greater risk of nonhemorrhagic AEs with dabigatran, patients already taking warfarin with excellent INR control may have little to gain by switching to dabigatran.	The discussion has been updated to include the point that patients already taking warfarin and who have excellent INR control may have little to gain by switching.
4	Page 42 – Clinical and Policy Implications: It is not balanced in that this section currently omits discussion of the unknowns or disadvantages of newer anticoagulants. 1) unknown outcomes in the setting of lower adherence – Adherence in clinical trials was very high and likely to be lower in real-world setting. Given the short half-life of the newer agents and the fact that patients discontinue them more frequently, the clinical implications of lower adherence rates are unknown (but potentially important, increased stroke risk).; 2) Higher GI bleeds, GI adverse effects with dabigatran; 3) higher bleeding rates with the newer anticoagulants vs. warfarin in the elderly –this is important and extremely applicable to the VA population; 4) higher MI with dabigatran	We have added the following text: "In a prespecified subgroup analysis, Wallentin et al.99 found that the advantage of dabigatran over warfarin in terms of major bleeding rates was evident only at sites with poor-quality anticoagulation (TTR <57.1%), while rates of major bleeding were not significantly different at sites with higher quality anticoagulation. Hence, better INR control led to similar bleeding rates between both groups. In the VHA, time in treatment exceeds this threshold, but newer oral anticoagulants could have important advantages for individual patients who have difficulty maintaining a therapeutic INR. However, since newer oral anticoagulants are dosed twice daily, compared with once daily dosing of warfarin, better outcomes would not be expected if poor medication adherence were the cause of the subtherapeutic INR." *(continued)*

Reviewer	Comment	Response
4 continued		Also: "Although newer oral anticoagulants are associated with a lower risk of fatal bleeding compared with warfarin, this advantage may be tempered by the increased risk of gastrointestinal bleeding with dabigatran.70,84,91,99 The FDA is currently evaluating reports of high rates of serious bleeding. The reports of bleeding appear to be concentrated in older adults and those with impaired renal function. Another worrisome finding is elevated rates of myocardial infarction with dabigatran, although the strength of evidence for this finding is low." And: "VA should carefully consider the potential benefits and harms, along with patients at higher risk for adverse effects when establishing eligibility criteria for newer oral anticoagulants."
4	Page 42, "In a prespecified subgroup analysis, Wallentin et al.22 found that major bleeding rates with dabigatran were lower than warfarin at sites where time in therapeutic range was low (<57.1%); rates were not significantly different at sites with higher quality anticoagulation." This statement is somewhat misleading by not also including that major GI bleeding was significantly HIGHER with dabigatran vs. warfarin when INR control was good. Also, for the primary endpoint of stroke or systemic embolism, outcomes were similar with dabigatran and warfarin when INR control was good. In other words, dabigatran was not superior to warfarin when INR control was good.	Agreed. We have rephrased the statement to: "In a prespecified subgroup analysis, Wallentin et al.99 found that the advantage of dabigatran over warfarin in terms of major bleeding rates was evident only at sites with poor-quality anticoagulation (TTR <57.1%), while rates of major bleeding were not significantly different at sites with higher quality anticoagulation. Hence, better INR control led to similar bleeding rates between both groups. In the VHA, time in treatment exceeds this threshold, but newer oral anticoagulants could have important advantages for individual patients who have difficulty maintaining a therapeutic INR. However, since newer oral anticoagulants are dosed twice daily, compared with once daily dosing of warfarin, better outcomes would not be expected if poor medication adherence were the cause of the subtherapeutic INR."

Reviewer	Comment	Response
Question 3: Are there any published or unpublished studies that we may have overlooked?		
1	No, and no comments from reviewer 1.	Thank you.
2	• Hohnloser S, Hohnloser SH, Oldgren J, Yang S, et al. Myocardial ischemic events in patients with atrial fibrillation treated with dabigatran or warfarin in the RE-LY trial. Circulation 2012; DOI: 10.1161/?CIRCULATIONAHA.111.055970. Available at: http://circ.ahajournals.org. • Uchino K, Hernandez AV. Dabigatran association with higher risk of acute coronary events: meta-analysis of noninferiority randomized controlled trials. Arch Intern Med 2012; DOI: 10.1001/archinternmed.2011.1666. Available at: http://archinte.ama-assn.org/ • Jacobs JM, Stessman J. Dabigatran: Do we have sufficient data? Arch Intern Med 2012; DOI: 10.1001/archinternmed.2011.1721. Available at: http://archinte.ama-assn.org/	The cited articles were published after our draft report was submitted. However, in response to peer review, we conducted a secondary search for observational studies and recent meta-analyses that address adverse effects of the newer anticoagulants. The updated data on myocardial ischemic events (Hohnloser et al.) are included in a newly conducted sensitivity analysis. The meta-analysis by Uchino et al. is cited in the Discussion section. The article by Jacobs et al was reviewed but is an editorial and not eligible for inclusion.
3	No – none that I am aware.	Thank you.
4	No, and no comments from reviewer 4.	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	Make it clear early on that the review covers warfarin and newer oral anticoagulants.	This has been clarified throughout the document.
1	Define 'patient treatment experience.'	Patient experience is a more inclusive set of outcomes than patient satisfaction. It has been defined as: The sum of all interactions, shaped by an organization's culture that influence patient perceptions across a continuum of care.
1	KQ4: Where there differences in bleeding when stratifying data based on age or indication (e.g., age ≥ 80 vs. < 80)?	From Eikelboom et al. 2011: 18113 patients in RE-LY study randomized to 110 mg, 150 mg dabigatran BID, or warfarin for a median followup of 2 years: • Risk of major bleeding with 150 mg dabigatran was lower than warfarin in those <75 years of age (2.12% vs. 3.04%; P<0.001) and a trend toward higher risk of major bleeding in those ≥75 (4.37%; P=0.07; P for 5.10 % vs. interaction <0.001). • In patients with AF, both doses of dabigatran are associated with lower risk of major bleeding in patients <75 years of age. In those ≥75, intracranial bleeding risk is lower, but extracranial bleeding risk is the same or higher in both doses of dabigatran.

Reviewer	Comment	Response
1	KQ2: No data are presented on LMWHs. Remove this from KQ or reword to indicate heparins overlapped with warfarin. Also, how many VTEs were DVTs versus PEs? Are results applicable to DVTs and PEs?	Agreed. It may be confusing although it is common practice to overlap warfarin with LMWH or other parenteral anticoagulants. We have changed the wording of KQ 2 to: "For patients with venous thromboembolism, are there differential effects of newer oral anticoagulants versus warfarin on recurrent thromboembolism, mortality, HRQOL, and patient treatment experience?"
1	Future research: CEAs could help address uncertain effects on health care systems in addition to BIAs. CEAs involving dabigatran noted, but none involving other agents.	In the literature search performed for the Budget Impact Analysis we plan to conduct, we did not find any CEAs on new oral anticoagulants other than Dabigatran.
1	Page 10: Warfarin has significant interactions with herbal supplements in addition to drugs and foods.	Agreed. This interaction has been noted in the report.
1	Page 10: Physicians are still concerned about inability to reverse effects of newer anticoagulants in patients at higher risk of bleeding even though half-lives are shorter (e.g., patient who is 76 years old and h/o GI bleed).	Agreed. We have added the statement: "However, there are valid concerns about the lack of specific antidotes for newer oral anticoagulants that would prevent the timely reversal of their anticoagulant effect in a bleeding patient. This is especially worrisome in elderly patients and those with renal disease, where drug clearance may be longer and the anticoagulant effects prolonged."
1	Contraindications (page 13): What is the data source?	We have changed the heading to "Precautions."
1	Objective (page 15): Clarify that data on primary VTE prevention s/p surgery are not presented.	We have added a statement that a later report will summarize the data on newer anticoagulants used for primary VTE prevention.
1	Figure 1: eliminate or clarify inclusion of LMWHs	We have adjusted Figure 1 as suggested.
1	Search strategy: standard of care was usually warfarin, rather than VKAs	Warfarin is one of the vitamin K antagonists.

Reviewer	Comment	Response
1	Clinical implications: The risk of major bleeding is unclear with newer agents in patients at higher risk for a major bleed (e.g., older elderly, h/o major bleed, renal insufficiency, h/o stroke).	We have refined the discussion to state: "Gastrointestinal bleeding was significantly increased in patients treated with dabigatran and rivaroxaban compared with warfarin.(Wallentin 2010) The efflux of dabigatran by p-glycoprotein transporters into the gastrointestinal tract may be a mechanism for this finding. (Bovio 2011) The European Society of Cardiology recommends dabigatran at a dose of 150 mg be used in patients with a low risk of bleeding, while the lower dose of 110 mg is reserved for those with a high risk of bleeding.(Camm 2010) In Canada, dabigatran is approved for the prevention of stroke in AF, and dabigatran 110 mg twice daily is recommended for elderly patients 80 years of age or older or those at a high risk of bleeding.(Cairns 2011) In the United States, the FDA has only approved the 150 mg dose and recommends a dose of 75 mg twice daily for patients with CrCl of 15 to 30 mL/min. (Beasley 2011)"
2	Page 9 – Therapeutic Options for Anticoagulation, Paragraph 1, Line 6 – additional LMWH advantage includes decreased risk of HIT. Line 8 – additional LMWH disadvantage is that it is not completely reversible by protamine.	We have added the following statement: "Unfractionated heparin requires hospital admission and continuous monitoring and carries the risk of heparin-induced thrombocytopenia. The advantages of low molecular weight heparin include longer half-life, better bioavailability, a predictable dose-response that minimizes the need for laboratory monitoring, and a decreased risk of heparin-induced thrombocytopenia.(Key 2010) The disadvantages of low molecular weight heparin include the need for subcutaneous administration once or twice daily, which patients find painful and inconvenient. Further, protamine sulfate only partially reverses heparin's anticoagulant effect. (Crowther 2002)"

Reviewer	Comment	Response
2	Page 10 – Line 1 – Point of care INR testing is simple and relatively inexpensive. Paragraph 1, Line 4 and 5 – bridging also with LMWH, generally performed in an outpatient setting, which is more convenient for the patient and less costly to the health plan (compared to admission). Paragraph 2, Line 10 – Although a shorter t1/2 is beneficial compared to warfarin, a lack of antidote for DTI and Xa inhibitors is problematic in acute hemorrhage or emergent surgery, whereas the effect of warfarin may be reversed rapidly with PCC. Paragraph 4 – Line 4 – May consider additional information regarding post-marketing bleeding in Pradaxa and 12/7/2011 FDA Safety Announcement.	This FDA Safety Announcement and several others have been addressed under KQ 4.
2	Page 11 – Paragraph 1, Line 2 – Consider noting that dabigatran is susceptible to Pgp drug:drug interactions.	Thank you. This observation has been added both to the text and the appropriate table.
2	Page 12 – Column 6, Row 8 – Typo Should read Ecarin clotting time. Row 10 – PPIs not included in package insert.	The reference has been changed to a more recent one that does include PPIs.
2	Page 13 – Column 1 – May be worthwhile adding additional row listing precautions.	"Contraindications" has been changed to "Precautions."
2	Page 36 – Paragraph 2, Line 7/8 – Do the authors have a citation for the two statements that adverse events are related to # medical conditions and # medications and that duration of treatment may increase absolute rates of adverse events?	Oldgren 2011 has been added to the text in the "Meta-analyses for KQ 1" section, 2nd paragraph, 4th sentence.
2	Page 36 – Paragraph 3, Line 10 – Is this true? I thought Rocket-AF had higher average CHADS2 score?	Agreed. This text has been corrected.
2	Page 41 – Paragraph 1, Line 6 – See previous comment regarding CHADS2 score and Rocket-AF vs. RE-LY.	We have corrected this text.
2	Page 42 – Paragraph 1, Line 5 – Should also add aspirin + clopidogrel. Paragraph 2, Line 3 – For now fewer drug interactions are noted, but new information may emerge. Paragraph 3, Line 11 – The shorter t1/2 life of new anticoagulants may be problematic in patients with non-compliant behavior (ie – increase in death rates after discontinuation of treatment in Rocket-AF).	The ACTIVE-W trial of ASA plus clopidogrel was stopped early due to inferiority compared with warfarin. Other studies are ongoing. We decided not to add this detail as it may distract the reader from the main point that warfarin is superior to antiplatelet agents.
3	I am troubled by the fact that all of the new anticoagulants are considered as a group – rather than as individual agents (or, at the very least, two distinct classes of medications). Each of these new agents have unique pharmacological and pharmacokinetic properties. While the efficacy of these agents in clinical trials appears to have been similar (for both a-fib and VTE treatment indications), the adverse event and side effect profiles clearly were not (dabigatran had a relatively higher incidence of GI side effects … rivaroxaban was associated with relatively higher rate of GI bleeding … and apixaban was not associate with either of these adverse events). Thus I believe combining, analyzing, and summarizing the results of the clinical trials of these distinct classes of medications (DTIs and direct Xa inhibitors) is not appropriate.	Thank you for this comment. Our analysis assumes a class effect. Although each drug has unique pharmacological and pharmacokinetic properties, they are all developed as anticoagulants. However, we have revised our analytic approach to analyze by drug class when there were sufficient studies for meaningful analyses. Further, we have revised the results and discussion to emphasize when the results were variable across drugs or drug class and to point out that our analyses is limited because we cannot reliably detect differences between individual drugs.

Reviewer	Comment	Response
3	Not sure why the ROCKET-AF study (Patel 2011 – reference 74) is consistently listed as Patel 2010 in the tables and figures; was this a typographical error?	The report has been revised to ensure that studies are consistently listed by author/year in the tables and figures.
4	Page 9: minor correction to be complete: Though not very commonly used, UFH may be given SC for acute VTE treatment as well as IV: "unfractionated heparin administered intravenously"	The statement has been revised to state that UFH is typically given intravenously.
4	Page 10: consider adding: warfarin's interaction with certain disease states in addition to drugs, foods. (e.g., CHF, thyroid, acute infection)	Thank you for the suggestion, but we decided to omit this detail as we believe the current text makes it abundantly clear that interindividual and intraindividual variability in warfarin response, along with food and drug interactions, is a disadvantage.
4	Page 10-11: consider adding: dabigatran's advantage over warfarin in the lack of drug-food interaction. Also, while dabigatran doesn't interact with drugs via CYP enzyme system, there are fewer but significant interactions through P-gp transporter system.	Agreed. We have added the following statement: "Dabigatran acts as a substrate for the p-glycoprotein transporter system, which makes it more prone to drug-drug interactions." It is also present in the table.
4	Page 12, Table 1: ECT time is best measure of anticoagulant effect of dabigatran, although this test is not widely available outside of a research setting at this time.	Agreed. This has been added to the report.
4	Page 13, Table 1, Contraindications: Warfarin and severe renal impairment – I could not find evidence of this to be true. Reviewed the Harder reference provided where it directs you to UK product information. The link provided in the reference in the Harder article lists renal impairment as a precaution, not contraindication. Also per US PI, severe renal impairment is NOT a contraindication. These patients likely have higher risk of bleeding and need lower doses of warfarin but it is not a contraindication to use	Agreed. We have changed the heading to "Precautions."
Optional Dissemination and Implementation Questions		
Question 5: Are there any 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	No comment from reviewer 1.	NA
2	No comment from reviewer 2.	NA
3	No comment from reviewer 3.	NA
4	The implications of this report are unclear at this time.	Acknowledged
Question 6: Please provide any recommendations on how this report can be revised to more directly address or assist implementation needs.		
1	No comment from reviewer 1.	NA
2	While it may be outside of the scope and stated objective of the review, it would be helpful to include a more comprehensive discussion of the major clinical trials including criticism and clinical applicability	We feel that it is outside the scope of this review to discuss the major trials separately.

Reviewer	Comment	Response
3	No comment from reviewer 3.	NA
4	The report should be revised to read more balanced; it is biased toward the newer agents without describing the potential disadvantages and unknowns.	Agreed. We have revised the report to be more balanced, and we highlight the potential disadvantages of the newer oral anticoagulants. For example, we state: "Wallentin et al. found that the advantage of dabigatran over warfarin in terms of major bleeding rates was only evident at sites with poor-quality anticoagulation (time in therapeutic range <57.1%), while rates of major bleeding were not significantly different at sites with higher quality anticoagulation. Hence, better INR control led to similar bleeding rates between both groups. In the VHA, time in treatment exceeds this threshold, but newer anticoagulants could have important advantages for individual patients who have difficulty maintaining a therapeutic INR. However, since newer anticoagulants are dosed twice daily, compared with once daily dosing warfarin, better outcomes would not be expected if poor medication adherence were the cause of the subtherapeutic INR. A pragmatic concern related to adherence is the FDA notification that dabigatran may lose potency if placed in pill boxes and that it should only be dispensed and stored in the original bottle or blister package. Although newer anticoagulants are associated with a lower risk of fatal bleeding compared to warfarin, this advantage may be tempered by the increased risk of gastrointestinal bleeding with dabigatran. The FDA is currently, evaluating reports of high rates of serious bleeding. The reports of bleeding appear to be concentrated in older adults and those with impaired renal function. Another worrisome finding is elevated rates of myocardial infarction with dabigatran, although the strength of evidence for this finding is low." And we have added a word of caution: "VA should carefully consider the potential benefits and harms, along with patients at higher risk for adverse effects when establishing eligibility criteria for newer anticoagulants."

Reviewer	Comment	Response
Question 7: Please provide us with contact details of any additional individuals/stakeholders who should be made aware of this report.		
1	No comment from reviewer 1.	NA
2	No comment from reviewer 2.	NA
3	No comment from reviewer 3.	NA
4	No comment from reviewer 4.	NA

APPENDIX F. ONGOING CLINICAL TRIALS

Table F-1. Ongoing RCTs of atrial fibrillation interventions (KQ 1)

Study title	VA/DoD population?	Intervention	Comparator	Sponsor and ClinicalTrials.gov ID	Funding Start/Stop	Status
Long-Term Safety in Atrial Fibrillation Patients	No	AZD0837	Vitamin K antagonists (warfarin)	AstraZeneca NCT00645853	Oct 2007–May 2009	Completed
RELY-ABLE Long Term Multi-center Extension of Dabigatran Treatment in Patients With Atrial Fibrillation Who Completed RE-LY Trial	No	Dabigatran dose 1 high dose twice daily	Dabigatran dose 2 low dose twice daily	Boehringer Ingelheim Pharmaceuticals NCT00808067	Nov 2008–Apr 2013	Ongoing, not recruiting
The IMPACT of BIOTRONIK Home Monitoring Guided Anticoagulation on Stroke Risk in Patients With Implanted ICD and CRT-D Devices	No	Dabigatran etexilate, warfarin	Dabigatran etexilate, warfarin	Biotronik NCT00559988	Feb 2008–Feb 2015	Recruiting
Direct Factor Xa Inhibitor YM150 for Prevention of Stroke in Subjects With Non-Valvular Atrial Fibrillation	No	YM150	Warfarin	Astellas Pharma Inc. NCT00448214	Mar 2007–Oct 2008	Completed

Table F-2. Ongoing RCTs of venous thromboembolism interventions (KQ 2)

Study title	VA/DoD population?	Intervention	Comparator	Sponsor and ClinicalTrials.gov ID	Funding Start/Stop	Status
Phase III Study Testing Efficacy & Safety of Oral Dabigatran Etexilate vs Warfarin for 6 m Treatment for Acute Symp VTE	No	Dabigatran etexilate	Warfarin	Boehringer Ingelheim Pharmaceuticals NCT00680186	Apr 2008–May 2011	Completed, recent
Secondary Prevention of Venous Thrombo Embolism (VTE)	No	Dabigatran	Warfarin	Boehringer Ingelheim Pharmaceuticals NCT00329238	May 2006–Oct 2010	Completed, abstract presented, but no publication to date
Oral Direct Factor Xa Inhibitor Rivaroxaban In Patients With Acute Symptomatic Pulmonary Embolism With Or Without Symptomatic Deep-Vein Thrombosis: Einstein-PE Evaluation	No	Xarelto (rivaroxaban, BAY59-7939)	Enoxaparin followed by vitamin K antagonist	Bayer NCT00439777	Mar 2007–Oct 2011	Completed, recent
Comparative Investigation of Low Molecular Weight (LMW) Heparin/Edoxaban Tosylate (DU176b) vs. LMW Heparin/ Warfarin in the Treatment of Symptomatic Deep-Vein Blood Clots and/or Lung Blood Clots.	No	LMW Heparin/ Edoxaban	LMW Heparin/ Warfarin	Daiichi Sankyo Inc. NCT00986154	Oct 2009–Sep 2012	Recruiting Methods paper published

Table F-3. Ongoing RCTs of mechanical heart valve interventions (KQ 3)

Study title	VA/DoD population?	Intervention	Comparator	Sponsor and ClinicalTrials.gov ID	Funding Start/Stop	Status
Dabigatran Etexilate in Patients With Mechanical Heart Valves	No	Dabigatran etexilate	Warfarin	Boehringer Ingelheim Pharmaceuticals NCT01452347	Oct 2011–Aug 2012	Recruiting
A Safety and Efficacy Trial Evaluating the Use of Apixaban in the Treatment of Symptomatic Deep Vein Thrombosis and Pulmonary Embolism	No	Placebo for enoxaparin Placebo for warfarin Apixaban	Active comparator: Enoxaparin Warfarin Placebo for apixaban	Bristol-Myers Squibb NCT00643201	July 2008–Mar 2013	Recruiting
A Phase 3, Randomized, Double-Blind, Double-Dummy, Parallel Group, Multi-Center, Multi-National Study for Evaluation of Efficacy and Safety of DU-176b Versus Warfarin In Subjects With Atrial Fibrillation - Effective Anticoagulation With Factor Xa Next Generation in Atrial Fibrillation (ENGAGE - AF TIMI - 48)	No	DU-176b plus warfarin placebo tablets	Warfarin tablets plus DU-176b	Daiichi Sankyo Inc. NCT00781391	Nov 2008–Feb 2012	Ongoing; methods paper published
Long-term, Open-label Follow-up Treatment of Patients With A-fib Who Have Been Previously Treated with BIBR 1048	No	Dabigatran	None- open label, nonrandomized Phase II study	Boehringer Ingelheim Pharmaceutical NCT00157248	Dec 2003–Jan 2009	Terminated; has results

APPENDIX G. CRITERIA USED IN QUALITY ASSESSMENT

General Instructions:
For each risk of bias item, rate as "Yes," "No," or "Unclear." After considering each of the quality items, give the study an overall quality rating of good, fair, or poor.

Detailed Quality Items:
If an item is rated as "No," describe why in the comments column.

Randomization and allocation concealment:

a. **Randomization adequate?* Was the allocation sequence adequately generated?

❑ No ❑ Yes ❑ Not reported/Unclear

b. **Allocation concealment?* Was allocation adequately concealed?

❑ No ❑ Yes ❑ Not reported/Unclear

Outcomes:

a. **Outcome assessors blinded (hard outcomes)?* Were *Outcome assessors* blind to treatment assignment for "hard outcomes" such as mortality?

❑ No ❑ Yes ❑ Not reported/Unclear

b. **Outcome assessors blinded (soft outcomes)?* Were *Outcome assessors* blind to treatment assignment for "soft outcomes" such as symptoms?

❑ No ❑ Yes ❑ Not reported/Unclear

c. *Lack of measurement bias?* Were the measures used reliable and valid? If so, choose "Yes," indicating no important measurement bias.

❑ No ❑ Yes ❑ Not reported/Unclear

Data analysis:

a. **All outcomes reported?* Are reports of the study free of suggestion of selective outcome reporting (systematic differences between planned and reported findings)?

❑ No ❑ Yes ❑ Not reported/Unclear

b. **Incomplete outcome data adequately addressed?*

❍ Yes (no systematic differences between groups in withdrawals from study and no high overall loss to follow-up; all eligible, randomized patients are included in analysis (ITT) ❍ No

❍ Not reported/Unclear

c. *Adequate power for main effects?*

❑ No ❑ Yes ❑ Not reported/Unclear

Results:

a. *Other selection bias?* Were systematic differences observed in baseline characteristics and prognostic factors across the groups compared?

❑ No ☑ Yes ❑ Not reported/Unclear

b. **Comparable groups maintained?* (Includes crossovers, adherence, and contamination). Consider issues of crossover (e.g., from one intervention to another), adherence (major differences in adherence to the interventions being compared), contamination (e.g., some members of control group get intervention), or other systematic differences in care that was provided.

❑ No ❑ Yes ❑ Not reported/Unclear

Conflict of interest:

a. *Was there the absence of potential important conflict of interest?* The focus here is financial conflict of interest. If no financial conflict of interest (e.g., if funded by government or foundation and authors do not have financial relationships with drug/device manufacturer), then answer "Yes."

❑ No ❑ Yes ❑ Not reported/Unclear

* Items contained in Cochrane Risk of Bias Tool

Overall study rating:

Choose an item.

Please assign each study an overall quality rating of "Good," "Fair," or "Poor" based on the following definitions:

A "Good" study has the least bias, and results are considered valid. A good study has a clear description of the population, setting, interventions, and comparison groups; uses a valid approach to allocate patients to alternative treatments; has a low dropout rate; and uses appropriate means to prevent bias, measure outcomes, and analyze and report results.

A "Fair" study is susceptible to some bias but probably not enough to invalidate the results. The study may be missing information, making it difficult to assess limitations and potential problems. As the fair-quality category is broad, studies with this rating vary in their strengths and weaknesses. The results of some fair-quality studies are possibly valid, while others are probably valid.

A "Poor" rating indicates significant bias that may invalidate the results. These studies have serious errors in design, analysis, or reporting; have large amounts of missing information; or have discrepancies in reporting. The results of a poor-quality study are at least as likely to reflect flaws in the study design as to indicate true differences between the compared interventions.

Comments:

❍ Form status:

❍ Fully complete - ready for export

Not ready for export - should be discussed further/ changes reconciled with the abstractor

Table G-1 lists the rating for each risk of bias item as well as the overall rating for each of the included studies.

Table G-1. Quality assessment of the included studies

Quality Item	Albers et al., 2005	Bauersachs et al., 2010	Connolly et al., 2009	Fiessinger et al., 2005	Granger et al., 2011	Olsson et al., 2003	Patel et al., 2011	Schulman et al., 2009
Randomization adequate?	Yes	Yes	Yes	Yes	NR/unclear	Yes	Yes	Yes
Allocation concealment?	Yes	Yes	Yes	Yes	No	Yes	NR/unclear	Yes
Outcome assessors blinded? (hard outcomes)	Yes	Yes	NR/unclear	Yes	Yes	Yes	Yes	Yes
Outcome assessor blinded? (soft outcomes)	Yes	Yes	NR/unclear	Yes	Yes	Yes	Yes	Yes
Lack of measurement bias?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
All outcomes reported?	Yes	Yes	Yes	NR/unclear	Yes	Yes	Yes	Yes
Incomplete outcome data adequately addressed?	Yes	NR/unclear	Yes	Yes	Yes	Yes	No	Yes
Adequate power for main effects?	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes
Other selection bias?	No	No	No	Yes	No	No	No	No
Comparable groups maintained?	Yes	Yes	Yes	NR/unclear	Yes	Yes	Yes	Yes
Absence of potential important conflict of interest?	No	No	No	No	No	No	No	No
Overall rating	Good	Good	Good	Good	Good	Good	Good	Good

Abbreviation: NR = not reported

APPENDIX H. 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.

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.

Cytochrome P-450 (CYP) enzyme system

A family of liver enzymes that serve two major functions: (1) biosynthesis of steroids, fatty acids, and bile acids and (2) metabolism of endogenous and a wide variety of exogenous substrates, such as toxins and drugs. They are classified into CYP gene family and subfamilies; for example, CYP1, CYP2 and CYP3 are responsible for most drug metabolism.

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.

Efflux transporter p-glycoprotein
Transporters that pump out unwanted toxic substances through specific efflux pumps. P-glycoprotein is the most common efflux transporter that allows drug molecules to pass through membranes.

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.

Mitral stenosis
A heart valve disorder that involves the mitral valve, which separates the upper and lower chambers on the left side of the heart. Stenosis refers to a condition in which the valve does not open fully, restricting blood flow.

Nonvalvular atrial fibrillation (AF)
An abnormal cardiac rhythm that occurs at the absence of mitral stenosis. AF is characterized by rapid uncoordinated firing of electrical impulses in the upper chambers of the heart (atria), which prevents the blood from being effectively pumped into lower chamber of the heart (ventricles).

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.

RevMan
Review Manager, a software program used for preparing and maintaining Cochrane systematic reviews.

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 (DVT/PE)

Obstruction of a vein or veins (embolism) by a blood clot (thrombus) in the blood stream.

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.