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[DIRECT ORAL ANTICOAGULANTS FOR THE TREATMENT OF VENOUS THROMBOEMBOLIC EVENTS: A SYSTEMATIC REVIEW AND NETWORK META-ANALYSIS]

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PROTOCOL

This review is registered with the PROSPERO international prospective register of systematic reviews: CRD42015015010.

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EXECUTIVE SUMMARY

OBJECTIVES

The objective of this study was to evaluate the efficacy and harms of direct oral anticoagulants (DOACs) compared to current standard therapy (heparin product followed by oral vitamin k antagonists [VKA]) for treatment of acute venous thromboembolism (VTE) and the efficacy and harms of DOACs compared to oral VKAs for extended therapy for secondary prevention of VTE.

There were 2 primary research questions:

1. What are the efficacy and harms of DOACs compared to current standard therapy for 3 or 6 months treatment of VTE (including pulmonary embolism [PE] and deep vein thrombosis [DVT])?

2. For extended therapy for the secondary prevention of VTE (including PE and DVT), what are the efficacy and harms of DOACs compared to oral VKA?

METHODS

The strategy for building and analyzing the evidence base for DOACs in the treatment of VTEs consisted of two fundamental steps:

1. A broad systematic review of the available randomized evidence in the published and grey literature, conducted following the methods and procedures outlined in the Cochrane Handbook for Systematic Reviews of Interventions.

2. A pair-wise meta-analysis and Bayesian network meta-analysis of randomized evidence conducted relating DOACs to other DOACs in a network, for each of the efficacy and safety outcomes specified a priori. The methods and procedures followed are those developed by the Canadian Collaboration for Drug Safety, Effectiveness and Network Meta-Analysis (ccNMA), funded by the Drug Safety and Effectiveness Network (DSEN) of the Canadian Institute of Health Research.

A protocol was developed using guidance from the PRISMA Statement and following the methods and procedures outlined in the Cochrane Handbook for Systematic Reviews of Interventions. It was peer-reviewed by experts in venous thromboembolic disease, pharmacology, statistics, and systematic review methodology. This review has been registered in the PROSPERO database (PROSPERO CRD42015015010).

Studies were eligible for inclusion in the systematic review if they satisfied the population, intervention, comparator, and study design criteria. Studies were not included or excluded based on the presence or absence of outcomes of interest.

PICO statement	
Population	Adults with acute or prior VTE (DVT, PE)
Interventions	• Apixaban • Dabigatran • Rivaroxaban • Edoxaban
Comparisons	ACUTE treatment: standard therapy (LMWH followed by VKA) EXTENDED therapy: Placebo, treatment discontinuation or ASA
Outcomes: Efficacy	• Recurrent VTE • Recurrent DVT • Recurrent PE (fatal and non-fatal)
Outcomes: Safety	• Major bleeds • Acute coronary syndrome • Major adverse cardiovascular events • Stroke • Cardiovascular death • All-cause death • Intracranial bleeding
Study Types	Randomized controlled trials
Exclusions	Phase I or II clinical trials.

Note: ASA = acetylsalicylic acid, DVT = deep vein thrombosis, LMWH = low-molecular-weight heparin, PE = pulmonary embolism,
VKA = vitamin k antagonist, VTE = venous thromboembolism.

REVIEW FINDINGS

COMPARISON TO STANDARD THERAPY

The mean differences between DOACs and standard therapy (acute) or discontinuation or placebo (extended) for the pre-specified outcomes are shown below. No studies reported the occurrence of major adverse cardiovascular events (MACE).

In the acute treatment of VTEs, there were no significant differences between any of the DOACs and standard therapy for the prevention of recurrent VTE or any of the other outcomes.

In the extended treatment analysis, patients taking VKAs had a lower risk of recurrent VTE, recurrent DVT, and recurrent PE, and a higher risk of major bleeds compared to patients taking placebo or who discontinued treatment. Dabigatran, but not apixaban (2.5 or 5 mg), rivaroxaban or ASA, was better than discontinuation or placebo for prevention of recurrent VTE, and PE. Dabigatran, but not rivaroxaban, was better than placebo or discontinuation for prevention of recurrent DVT (no evidence for ASA or apixaban). The risk of major bleeding was significantly increased among patients taking rivaroxaban, but not dabigatran, ASA or apixaban (2.5 and 5 mg), relative to among patients taking placebo or who discontinued therapy; however, there was a wide credible interval.

Treatment effects relative to placebo: ACUTE studies

Treatment	Hazard ratio (95% CrI)										
	Recurrent VTE	Recurrent DVT	Recurrent PE (total)	Recurrent PE (fatal)	Recurrent PE (non-fatal)	Major bleed	ICH	All-cause death	CV death	Stroke	ACS
DBG 150 mg bid	1.10 (0.42, 2.94)	1.14 (0.31, 4.13)	1.23 (0.33, 4.93)	3.17 (0.73, 11.32)	1.08 (0.25, 4.89)	0.75 (0.28, 1.96)	0.26 (0.01, 2.68)	1.05 (0.39, 2.98)	—	3.10 (0.72, 44.31)	1.70 (0.26,11.69)
RVX 20 mg qd	0.98 (0.37, 2.52)	0.91 (0.25, 3.28)	1.18 (0.34, 4.35)	4.55 (0.26, 249.70)	1.10 (0.28, 4.80)	0.54 (0.22, 1.39)	0.34 (0.04, 3.66)	0.96 (0.36, 2.61)	1.55 (0.17, 14.16)	0.53 (0.15, 1.50)	—
EDX 60 mg qd	0.89 (0.23, 3.53)	0.90 (0.15, 5.61)	0.86 (0.14, 5.03)	1.31 (0.24, 7.19)	0.82 (0.11, 6.32)	0.85 (0.23, 3.07)	0.26 (0.02, 4.03)	1.06 (0.27, 4.24)	1.25 (0.06, 25.01)	—	—
APX 5 mg bid	0.85 (0.21, 3.15)	0.61 (0.09, 3.73)	1.13 (0.18, 7.02)	0.80 (0.08, 4.10)	1.18 (0.16, 8.76)	0.31 (0.08, 1.18)	0.48 (0.02, 8.02)	0.80 (0.19, 3.20)	0.38 (0.02, 9.40)	1.47 (0.59, 4.03)	—

Note: ACS = acute coronary syndrome, CV = cardiovascular, DVT = deep vein thrombosis, ICH = intracranial hemorrhage, VTE = venous thromboembolism.
*Statistically significant ($p < 0.05$).

Treatment effects relative to placebo: EXTENDED therapy

Treatment	Hazard ratio (95% CrI)									
	Recurrent VTE	Recurrent DVT	Recurrent PE (total)	Recurrent PE (non-fatal)	Recurrent PE (fatal)	Major bleed	All-cause death	CV death	Stroke	ACS
VKA	**0.09 (0.03, 0.36)***	**0.03 (0.00, 0.17)***	**0.05 (0.00, 0.63)***	**0.06 (0.00, 0.75)***	0.43 (0.09, 1.49)	**4.49 (1.30, 31.25)***	0.23 (0.01, 2.79)	0.22 (0.01, 1.08)	—	5.70 (0.08, 272.10)
DBG 150 mg bid	**0.10 (0.02, 0.52)***	**0.05 (0.00, 0.24)***	**0.08 (0.00, 0.82)***	**0.09 (0.01, 0.91)***	0.90 (0.30, 3.23)	2.91 (0.57, 19.13)	0.21 (0.01, 2.97)	—	0.21 (0.00, 11.62)	4.41 (0.84, 35.46)
ASA 100 mg qd	0.64 (0.17, 2.38)	—	0.74 (0.06, 9.13)	0.75 (0.06, 8.97)	0.44 (0.12, 3.72)	1.47 (0.19, 28.93)	—	—	—	—
RVX 20 mg qd	0.19 (0.03, 1.31)	0.28 (0.07, 1.07)	0.23 (0.02, 3.06)	0.12 (0.01, 1.86)	0.62 (0.04, 4.37)	**40.13* (4.20, 395.30)**	1.73 (0.02, 200.60)	2.21 (0.04, 21.91)	—	—
APX 2.5 mg bid	0.19 (0.03, 1.23)	—	0.52 (0.04, 6.38)	0.51 (0.04, 6.26)	9.08 (0.10, 132.90)	0.86 (0.34, 3.90)	2.02 (0.06, 118.50)	0.16 (0.05, 0.80)	—	—
APX 5 mg bid	0.19 (0.03, 1.31)	—	0.26 (0.02, 3.25)	0.25 (0.02, 3.43)	1.07 (0.04, 13.02)	0.43 (0.09, 1.54)	1.12 (0.03, 66.89)	0.35 (0.10, 0.80)	—	—

Note: ACS = acute coronary syndrome, CV = cardiovascular, DVT = deep vein thrombosis, VTE = venous thromboembolism.
*Statistically significant ($p < 0.05$).

COMPARISON AMONG THE DOACS

ACUTE TREATMENT

There were no significant differences between any of the DOACs for recurrent VTE, recurrent DVT, recurrent PE, major bleeds, intracranial bleeds, all-cause or cardiovascular death, stroke, or acute coronary syndrome (ACS).

Subgroup data were available only for recurrent VTE (age, weight, renal function, initial PE or DVT) and major bleeds (initial PE or DVT). Data were not sufficient for pooling for time in therapeutic range, and no studies reported the pre-specified outcomes among patients with diabetes or with cardiovascular disease taking antiplatelet agents. There were no significant differences in recurrent VTE by age, weight, renal function, or qualifying event. There were no significant differences in major bleeds by qualifying event (DVT or PE).

EXTENDED TREATMENT

Compared with VKA, ASA was associated with an increased risk of recurrent VTE; however, there was no difference in risk of major bleeding between the two treatments. Patients taking rivaroxaban were at increased risk of recurrent DVT and major bleeding relative to those taking VKA. Patients taking rivaroxaban were also at increased risk of major bleeds compared with dabigatran and ASA. Apixaban (2.5 and 5 mg) was associated with a lower risk of major bleed compared to VKA and rivaroxaban. Apixaban 5 mg was associated with a lower risk of major bleed compared to dabigatran. There were no differences in recurrent VTE between apixaban (2.5 and 5 mg) and VKA, dabigatran, ASA, or rivaroxaban.

There were no differences among the DOACs for recurrent PE, all-cause death, cardiovascular death, and acute coronary syndrome. The risk of major bleeding was increased among patients taking rivaroxaban relative to those taking VKA, ASA, dabigatran, and apixaban (2.5 and 5 mg); however, some of these estimates are based on limited data and should be interpreted with caution.

Subgroup data were available for recurrent VTE by age, weight, renal function, and qualifying event. There were no data for time in therapeutic range or comorbidities (diabetes, patients with cardiovascular disease taking antiplatelet agents).

There was no significant difference in the risk of recurrent VTE among the DOACs by age group or qualifying event.

Compared with discontinuation or placebo, the risk of recurrent VTE was lower among patients who weigh more than 60 kg taking VKA, dabigatran, rivaroxaban, or apixaban. Among patients who weigh less than 60 kg, the risk was lower among patients taking rivaroxaban or apixaban. Compared to VKA, the risk of recurrent VTE was higher among patients who weigh more than 60 kg taking apixaban (2.5 or 5 mg bid); there was no difference in risk among patients who weigh less than 60 kg.

Compared with VKA or dabigatran, the risk of recurrent VTE was increased among patients taking rivaroxaban among patients with creatinine clearance above 80 ml/min but not less than 80 ml/min. The risk of recurrent VTE was lower among patients taking apixaban (2.5 and 5 mg) compared with rivaroxaban among patients with creatinine clearance above 80 ml/min but not less than 80 ml/min.

Comparative HR (95% credible interval) of treatments based on network meta-analyses — Extended treatment

Outcome	Comparison	VKA	DBG 150 mg bid	ASA 100 mg qd	RVX 20 mg qd	APX 2.5 mg bid	APX 5 mg bid
Recurrent VTE	DBG 150 mg bid v.	1.19 (0.22, 4.80)					
Recurrent DVT		1.56 (0.46, 7.14)					
Recurrent PE (total)		1.49 (0.15, 12.37)					
Major bleeds		0.58 (0.19, 1.19)					
Intracranial bleeds		—	—				
All-cause death		0.88 (0.10, 7.85)					
CV death		—					
Stroke		—					
ACS		0.81 (0.02, 46.74)					
Recurrent VTE	ASA 100 mg qd v.	**7.41 (1.00, 41.48)***	6.26 (0.76, 48.86)				
Recurrent DVT		—	—				
Recurrent PE (total)		14.48 (0.45, 541.90)	9.44 (0.34, 405.50)				
Major bleeds		0.19 (0.04, 9.63)	0.32 (0.07, 11.81)				
Intracranial bleeds		—	–	—			
All-cause death		—	—				
CV death		—	—				
Stroke		—	—				
ACS		—	—				
Recurrent VTE	RVX 20 mg qd v.	2.17 (0.17, 19.64)	1.81 (0.14, 22.76)	0.29 (0.03, 3.07)			
Recurrent DVT		**9.58 (1.001, 167.10)***	5.87 (0.70, 79.77)	—			
Recurrent PE (total)		4.58 (0.12, 185.90)	2.99 (0.09, 133.60)	0.31 (0.01, 10.79)			
Major bleeds		**7.04 (1.34, 79.20)***	**12.59 (2.96, 92.49)***	**23.76 (1.30, 706.10)***	—		
Intracranial bleeds		—	—	—			
All-cause death		1.73 (0.02, 200.60)	1.97 (0.02, 249.60)	–			
CV death		12.96 (0.16, 526.80)	—	—			
Stroke		—	—	—			
ACS		—	—	—			
Recurrent VTE	APX 2.5 mg bid v.	2.17 (0.18, 19.30)	1.84 (0.14, 21.60)	0.29 (0.03, 3.03)	0.97 (0.06, 16.01)		
Recurrent DVT		—	—	—	—		
Recurrent PE (total)		10.07 (0.29, 379.70)	6.56 (0.24, 276.00)	0.70 (0.02, 23.63)	2.19 (0.06, 81.18)		
Major bleeds		**0.23 (0.01, 0.87)***	0.39 (0.02, 1.75)	0.52 (0.02, 10.87)	**0.02 (0.00, 0.22)***	—	
Intracranial bleeds		—	—	—	—		
All-cause death		2.02 (0.06, 118.50)	2.22 (0.06, 151.70)	–	1.12 (0.02, 133.20)		
CV death		0.95 (0.07, 32.57)	—	—	0.10 (0.00, 2.56)		

Stroke		—	—	—	—		
ACS		—	—	—	—		
Recurrent VTE	**APX 5 mg bid v.**	2.19 (0.19, 19.43)	1.87 (0.15, 21.14)	0.30 (0.03, 2.92)	1.02 (0.07, 16.02)	1.03 (0.14, 7.05)	—
Recurrent DVT		—	—	—	—	—	
Recurrent PE (total)		4.92 (0.13, 211.80)	3.24 (0.10, 139.30)	0.35 (0.01, 11.90)	1.09 (0.03,43.52)	0.50 (0.03, 6.38)	
Major bleeds		**0.10 (0.00, 0.41)***	**0.19 (0.01, 0.87)***	0.18 (0.01, 4.69)	**0.01 (0.00, 0.13)***	0.45 (0.13, 2.64)	
Intracranial bleeds		—	—	—	—	—	
All-cause death		1.12 (0.03, 66.89)	1.25 (0.03, 84.84)	—	0.64 (0.01, 80.10)	0.56 (0.04, 7.23)	
CV death		1.38 (0.27, 75.44)	—	—	0.19 (0.02, 5.13)	1.87 (0.38, 8.00)	
Stroke		—	—	—	—	—	
ACS		—	—	—	—	—	

Note: ASA = acetylsalicylic acid, APX = apixaban, ACS = acute coronary syndrome, CV = cardiovascular, DBG = dabigatran, DVT = deep vein thrombosis, PE = pulmonary embolism, RVX = rivaroxaban, VKA = vitamin k antagonist, VTE = venous thromboembolism. Recurrent PE includes both fatal and non-fatal PE.
*p < 0.05

KEY MESSAGES

ACUTE TREATMENT

- There were no significant differences between any of the DOACs and standard therapy for recurrent VTE, recurrent PE, recurrent DVT, major bleeds, intracranial hemorrhage, all-cause death, cardiovascular death, stroke, or acute coronary syndrome.
- There were no differences in recurrent VTE by age, weight, renal function, or qualifying event.

EXTENDED TREATMENT

- Compared to discontinuation or placebo, patients taking VKA or dabigatran had a lower risk of recurrent VTE, recurrent PE, and recurrent DVT.
- Compared to discontinuation or placebo, patients taking VKA or rivaroxaban, but not dabigatran, apixaban or ASA, had an increased risk of major bleeding.
- There were no significant differences between any of the DOACs and placebo/discontinuation for all-cause death, cardiovascular death, stroke, or acute coronary syndrome.
- ASA was associated with an increased risk of recurrent VTE compared with VKA
- Rivaroxaban was associated with an increased risk of recurrent DVT compared to VKA
- Rivaroxaban was associated with an increased risk of major bleeds compared with VKA, dabigatran, and ASA. Apixaban (2.5 and 5 mg) was associated with a lower risk of major bleed compared to VKA and rivaroxaban. Apixaban 5 mg was associated with a lower risk of major bleed compared to VKA, dabigatran, and rivaroxaban.

- There were no differences in risk of recurrent VTE among the DOACs when the data were stratified by age (< 75 v. >75 yr).

- Compared with discontinuation or placebo, the risk of recurrent VTE was lower among patients who weigh more than 60 kg taking VKA, dabigatran, rivaroxaban, or apixaban. Among patients who weigh less than 60 kg, the risk was lower among patients taking rivaroxaban or apixaban. The risk of recurrent VTE was higher among patients who weigh more than 60 kg taking apixaban (2.5 or 5 mg bid) compared to VKA; there was no difference in risk among patients who weigh less than 60 kg.

- The risk of recurrent VTE was increased among patients taking rivaroxaban compared with VKA or dabigatran among patients with creatinine clearance above 80 ml/min but not less than 80 ml/min. The risk of recurrent VTE was lower among patients taking apixaban (2.5 and 5 mg) compared with rivaroxaban among patients with creatinine clearance above 80 ml/min but not less than 80 ml/min.

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INTRODUCTION

Deep vein thrombosis (DVT) and pulmonary embolism (PE; collectively termed venous thromboembolism (VTE)) are common, result in significant health impact, and are likely to increase with ageing of the population (1). The average annual incidence of VTE is 1 per 1,000 population (2). Based on a population of 34.5 million people in Canada (3), the projected incidence of VTE is 34,500 Canadians per year.

Traditional treatment of VTE involves the initial use of injectable heparin products (i.e., unfractionated heparin [UH] or low-molecular weight heparin [LMWH]) followed by a course of an oral vitamin K antagonist (VKA; e.g., warfarin or acenocoumarol) (4, 5). Oral therapy with VKA is effective for the long-term prevention of VTE recurrence, and the duration of therapy is usually based on the risk of recurrence (assessed on the basis of factors such as malignancy, thrombophilic defects, or previous VTE). The risk of long-term bleeding is also considered in the decision of whether or not to extend therapy beyond the acute phase (4). The risk of recurrence of VTE after completion of initial anticoagulation treatment is estimated to be 5%–10% during the first year (6).

Three direct oral anticoagulants (DOACs) are currently available in Canada (apixaban, dabigatran, rivaroxaban) and are approved for the following indications: post-orthopedic surgery prophylaxis of VTEs, prevention of stroke in patients with atrial fibrillation, treatment of VTEs (including DVT and PE) and prevention of recurrent DVT and PE (i.e., extended therapy). The clinical development program for the latter two indications was recently completed for a fourth DOAC (edoxaban), although this drug is not currently available in Canada. Rivaroxaban was the first DOAC to obtain its notice of compliance (NOC) for DVT and PE; dabigatran and apixaban were granted a NOC for VTE in June 2014 and November 2014, respectively. DOACs belong to two groups: i) direct thrombin inhibitors, ii) direct Factor Xa inhibitors (Table I).

Table I: Direct Oral Anticoagulants

Class	Drug	Manufacturer
Direct thrombin inhibitor	Dabigatran (Pradaxa™)	Boehringer Ingelheim Canada Ltd.
Direct Factor Xa inhibitor	Rivaroxaban (Xarelto®)	Bayer Inc.
	Apixaban (Eliquis®)	Pfizer Canada Inc/Bristol-Myers Squibb Canada
	Edoxaban (Lixinia®)*	Daiichi-Sankyo

** Not available in Canada*

DOACs do not require administration by injection as heparin products do and are not subject to the same laboratory monitoring requirements as oral VKAs. They are also less prone to dietary and drug interactions than VKAs. They are, however, more expensive and are associated with less clinical experience, compared with heparin products and VKAs. In particular, management of bleeding complications associated with the use of DOACs may be challenging because of the lack of an agent to reverse their anticoagulant effect.

As the scope of indications approved for DOACs and the number of these drugs increases, the amount of pharmacological treatment options available for the treatment of VTEs expands. Consequently, there is the

need to compare the clinical and cost-effectiveness of DOACs to inform reimbursement policy development activities and clinical practice. Currently, several publicly funded drug programs in Canada provide reimbursement for DOACs, though some restrictions may apply, when used for post-orthopedic surgery VTE prevention and for stroke prevention in patients with atrial fibrillation. Rivaroxaban has been reimbursed by a number of public payers for the treatment of VTE and the prevention of recurrent events for some time; some provincial drug programs now also reimburse apixaban for these indications. As more DOACs receive their NOC for this indication, additional reimbursement decisions will need to be made. In order to inform policy work and clinical decisions, a health technology assessment was undertaken. The Canadian Collaboration for Drug Safety, Effectiveness and Network Meta-Analysis (ccNMA), funded by the Drug Safety and Effectiveness Network (DSEN) of the Canadian Institute of Health Research (CIHR) collaborated with the Canadian Agency for Drugs and Technologies in Health (CADTH) for this project. This health technology assessment includes both a clinical and an economic evaluation. Whereas the first component was done by ccNMA, the economic evaluation was done by CADTH. This report provides findings from the clinical evaluation; findings from the economic evaluation are available in a different report (see: www.cadth.ca).

1.1. OBJECTIVE

The objective of this study was to evaluate the efficacy and harms of DOACs compared to current standard therapy (heparin product followed by oral VKA) for treatment of acute VTE and the efficacy and harms of DOACs compared to oral VKAs for extended therapy for secondary prevention of VTE.

1.2. PRIMARY RESEARCH QUESTIONS

1. What are the efficacy and harms of DOACs compared to current standard therapy for 3 or 6 months treatment of VTE (including PE and DVT)?
2. For extended therapy for the secondary prevention of VTE (including PE and DVT), what are the efficacy and harms of DOACS compared to oral VKA?

2. METHODS

The strategy for building and analyzing the evidence base for the use of DOACs for treatment of VTEs consisted of two fundamental steps:

A broad systematic review and pair-wise meta-analysis of the available randomized evidence in the published and grey literature conducted following the methods and procedures outlined in the Cochrane Handbook for Systematic Reviews of Interventions (7).

A Bayesian network meta-analysis of randomized evidence conducted relating DOACs in a network, for each of the benefit and safety outcomes specified a priori. The methods and procedures followed are those developed by the ccNMA, funded by the DSEN of the CIHR.

2.1. SYSTEMATIC REVIEW

The protocol was developed using guidance from the PRISMA Statement (8) and following the methods and procedures outlined in the Cochrane Handbook for Systematic Reviews of Interventions (7). It was peer-reviewed by experts in pharmacology, biostatistics, and systematic review methodology.

Using the OVID platform, we searched Ovid MEDLINE®, Ovid MEDLINE® In-Process & Other Non-Indexed Citations, and Embase Classic+Embase on November 5, 2014. We also searched CENTRAL in the Cochrane Library on Wiley on the same date. Strategies utilized a combination of controlled vocabulary (e.g., "Venous Thromboembolism", "Heparin, Low-Molecular-Weight", "Vitamin K/ai") and keywords (e.g., VTE, Dabigatran, Fondaparinux). Vocabulary and syntax were adjusted across the databases. We used a validated filter to identify randomized controlled trials.

All database searches were limited from 2008 to the current year. Search dates were conservatively limited to 2008 to restrict returned database records to a timeline consistent with the first published RCTs of the DOACs in the literature, according to expert advice. For RCTs of extended treatment of VTEs, an existing evidence synthesis deemed to be high-quality and comprehensive by the clinical review team was used to extract studies of VKA compared to placebo or discontinuation prior to 2008 (9); within this review, only studies dating back to 1995 were included. The rationale for selecting this cut-off date was the change in practice towards outpatient treatment of VTEs with LMWH as evidence started to emerge in 1996 for this treatment strategy. Individual studies were extracted from the review and put through the same full-text screening and review process as those located through the database search.

A grey literature search of relevant databases and web sites was performed using resources listed in CADTH's *Grey Matters Light* (www.cadth.ca/en/resources/finding-evidence-is/grey-matters/grey-matters-light). Specific details regarding the strategies appear in Appendix 1.This review has been registered in the PROSPERO database (CRD42015015010).

2.1.1. POPULATION, INTERVENTION, COMPARATOR, OUTCOME (PICO) STATEMENT

Studies were eligible for inclusion in the systematic review if they satisfied the population, intervention, and comparator, as well as the study designs of interest.

Study population

The study population consists of patients with acute or prior VTE, including DVT and PE.

Intervention:

- Apixaban
- Dabigatran
- Rivaroxaban
- Edoxaban

Comparator groups

Allowable comparisons include:

ACUTE studies: standard therapy (LMWH + VKA)

EXTENDED studies: placebo or treatment discontinuation, acetylsalicylic acid (ASA), VKA

Outcome(s) of interest:

Efficacy outcomes:

- Recurrent VTE
- Recurrent DVT
- Recurrent PE (fatal, non-fatal)

Safety outcomes:

- Major bleeding
- Intracranial bleeding
- All-cause death
- Cardiovascular death
- Major adverse cardiovascular events (MACE)
- Stroke
- Acute coronary syndrome (ACS)

Study designs:

ACUTE treatment studies: Randomized controlled trials (RCTs)

EXTENDED treatment studies: RCTs in which patients had received acute treatment for at least 3 months.

Crossover studies were eligible for inclusion; however, only first-period data were included in the analysis.

Conference abstracts were eligible for inclusion if they were a companion to an included RCT and if they provided additional data beyond that in the published record (e.g., subgroup analysis).

2.1.2. OUTCOME DEFINITIONS

Recurrent VTE: Non-compressible segment found on compression leg vein ultrasound imaging, intraluminal filling defect on venography, abnormal impedance plethysmography, high-probability ventilation-perfusion, or pulmonary artery filling defect on computed tomography or pulmonary angiography. This outcome includes and combines both recurrent DVT and recurrent PE, as reported in the primary studies. Both recurrent PE and recurrent DVT were also considered separately in the analyses.

Major bleeding: clinically overt bleeding associated with at least one of the following: 1) a decrease in hemoglobin levels of at least 2 g/dl; 2) transfusion of 2 or more units of packed red blood cells; 3) intracranial,

retroperitoneal or body cavity bleeding; 4) death; or 5) major bleeding episode as defined by the investigator of each individual study.

Intracranial bleeding: as defined by the investigator of each individual study.

All-cause death: death from any cause.

Cardiovascular death: death from an acute myocardial infarction, sudden cardiac death, death due to heart failure, death due to stroke, and death from other cardiovascular causes (e.g., procedure used to treat myocardial infarction or ischemia).

Stroke: As defined by the authors of each primary study.

Acute coronary syndrome: As defined by the authors of each primary study.

Major adverse cardiovascular events: composite outcome comprised of myocardial infarction, stroke, and cardiovascular death, or as defined by the authors of each primary study.

Note:

Data were extracted and analyzed for the on-treatment period only. For acute studies, this may include a 30 day follow-up period where noted in the table of characteristics. For extended studies, only events that occurred during the treatment period were included. Studies that did not report treatment period data separately were not included in the on-treatment analysis.

2.1.3. STUDY SELECTION

Eligibility criteria were applied to each title and abstract identified in the literature search by two independent review authors in a standardized manner. Any trial that was considered to be relevant by one reviewer was retrieved for review and obtained in full-text format. The full text of each potentially relevant article was independently assessed by two reviewers, and a final decision made for inclusion. Full-text records of all studies located from an existing evidence synthesis were also screened in full-text format to ensure they met the eligibility criteria. Any uncertainties were resolved by discussion and consensus with a third review author. Reviewers did not remain blind to study authors or centre of publication prior to study selection.

2.1.4. DATA EXTRACTION

One reviewer extracted data from selected trials, and a second reviewer checked the data for accuracy. All data were extracted using a standardized data abstraction form, and the following attributes of each RCT were entered into a database:

1. Characteristics of trial participants;

2. Study design characteristics;

3. Details on each study arm/pharmacologic intervention, including but not limited to dose, frequency, route of administration, duration, and co-medication; and,

4. Data for clinical efficacy/effectiveness and safety outcomes.

The original, primary publication for each unique study was included and used for data extraction, except in the case of multiple publications for a single RCT. Multiple publications (e.g. supplemental online appendices, companion publications of specific outcomes or populations from the original study, conference abstracts) were handled by extracting the most recently and detailed adjudicated data for each outcome specified a priori.

2.1.5. CRITICAL APPRAISAL OF INCLUDED STUDIES

Risk of study bias was assessed using the Cochrane Collaboration's tool for assessing risk of bias (ROB) for RCTs (7).

2.1.6. ASSESSMENT OF PUBLICATION BIAS

Reporting bias was assessed by constructing funnel plots, as well as bias indicators (e.g. Egger, Harbold-Egger) for each outcome (10) if data were sufficient.

2.1.7. ASSESSMENT OF HETEROGENEITY

Included studies were assessed for both clinical and methodological diversity. Clinical diversity was assessed by examining that the participants, interventions, and comparators were not too different from each other such that combining them was inappropriate. Methodological diversity was also assessed by checking that the studies were similar in terms of study design and risk of bias.

2.1.8. DATA ANALYSIS METHODS

Meta-analyses were undertaken using fixed- or random-effects models if data were available, sufficiently similar, and of sufficient quality. The effect sizes for the identified dichotomous outcomes were expressed in terms of hazard ratios (HRs) and 95% credible intervals (CrI). Person-years were calculated by multiplying the number of patients in each treatment time by the treatment duration.

2.1.9. SUBGROUP ANALYSIS

Subgroups were selected a priori to compare the treatment effect across variants in the population for which a plausible difference in efficacy or safety may exist. Subgroups selected were justified against the criteria

proposed by Sun and colleagues (11) (12); wherein the greater the number of criteria that are satisfied for each subgroup and outcome, the more plausible is the hypothesized subgroup effect.

Subgroups specified a priori were:

- Age
- Quality of INR control/TTR
- Patient weight
- Renal function
- Co-morbidities (diabetes, cardiovascular disease using antiplatelet therapy)

2.2. BAYESIAN NETWORK META-ANALYSIS

Bayesian mixed treatment comparison (MTC) meta-analyses were conducted for the following outcomes: recurrent VTE, recurrent DVT, recurrent PE (fatal and non-fatal), major bleeds, acute coronary syndrome, major adverse cardiovascular events, stroke, cardiovascular death, all-cause death and intracranial bleeding. WinBUGS software (MRC Biostatistics Unit, Cambridge, UK) was used to conduct Bayesian MTC meta-analysis using a binomial likelihood model which allows for the use of multi-arm trials (13, 14). Placebo or discontinuation (EXTENDED) or standard therapy (ACUTE) were chosen as the reference group or index node in the model. Both fixed- and random-effects network meta-analyses were conducted; assessment of model fit and choice of model was based on assessment of the deviance information criterion (DIC) and comparison of residual deviance to number of unconstrained data points (13, 15).

Point estimates and 95% credible intervals for HRs were derived using Markov Chain Monte Carlo (MCMC) methods. Vague priors, such as $N(0, 100^2)$, were assigned for basic parameters throughout (13), and informative priors were considered for the variance parameter were based on Turner and colleagues (16). To ensure model convergence was reached, trace plots and the Brooks-Gelman-Rubin statistic were assessed (17). Three chains were fit in WinBUGS for each analysis, with at least 20,000 iterations, and a burn-in of at least 20,000 iterations (17) (18).

2.2.1. HETEROGENEITY

Both MTC and traditional meta-analysis require studies to be sufficiently similar in order to pool their results. As a result, heterogeneity across trials in terms of patient characteristics, trial methodologies, and treatment protocols across trials was carefully assessed.

To further investigate heterogeneity, where warranted, subgroup analyses were considered, although limited data precluded many analyses considered.

2.2.2. CONSISTENCY

Inconsistency was formally assessed by comparing the deviance and DIC statistics of the consistency and inconsistency models (21). To help identify the loops in which inconsistency was present, the posterior mean deviance of the individual data points in the inconsistency model was plotted against their posterior mean deviance in the consistency model (19).

2.2.3. MODEL DIAGNOSTICS

Model diagnostics including trace plots and the Brooks-Gelman-Rubin statistic were assessed to ensure model convergence (17) (13).

3. RESULTS

The initial literature search returned 3,213 database abstracts. A total of 9 records were identified through additional searching and from an existing evidence synthesis (9). After duplicates were removed, 3,222 remained to be assessed for inclusion and 2,899 were excluded. Of the 323 full-text articles reviewed, 198 were excluded for a variety of reasons as described in the PRISMA flow diagram (Figure 1). A total of 88 conference abstracts were identified and were included if they were deemed to be a companion of an included publication (n = 26). For EXTENDED treatment of VTE, 8 studies of VKA compared to placebo or discontinuation were identified using an existing high quality evidence synthesis (9); of these, 4 were ultimately included in the analysis. A total of 6 unique RCTs reported in 18 publications of ACUTE VTE treatment were included. Eleven unique RCTs reported in 19 publications for EXTENDED VTE treatment were included.

3.1. TRIAL AND PATIENT CHARACTERISTICS

The included studies are listed in Appendix 2, and the excluded studies (at full-text screening) are listed in Appendix 3. The included RCTs were published between 1997 and 2014, and involved a total of 36,188 participants (26,860 ACUTE; 9,328 EXTENDED). All of the acute studies were funded by pharmaceutical companies, while there was a mixture of funding among the extended studies (Table 1).

Table 1: Summary of trial characteristics

Trial characteristics	Category	No. of included studies	
		ACUTE	EXTENDED
Publication status	Literature sources	18 (+ 14 abstracts)	19 (+ 12 abstracts)
	Unique RCTs	6	11
Country	Single country	0	3
	Multi-national	6	8

Trial characteristics	Category	No. of included studies	
		ACUTE	EXTENDED
Study design	Parallel	6	11
	Factorial	0	0
	Cross-over	0	0
No. of arms	2	6	10
	3	0	1
	>3	0	0
Sponsors	Pharmaceutical	6	4
	Non-Pharmaceutical	0	1
	Mixed	0	4
	Not reported	0	2
Publication year		2008 to 2014	1997 to 2013
No. randomized		258 to 8240	17 to 1435

The doses and duration of treatment are described in Table 2. For acute treatment of VTE, LMWH was the initial treatment for studies involving dabigatran or edoxaban; studies involving apixaban or rivaroxaban had no initial treatment with LMWH; however, patients were started at a higher initial dose of the DOAC (Table 2).

Although the study by Schulman and colleagues (DURACII) (20) was included based on the PICO statement, this trial reported the combined results for the acute (months 0–6) and extended therapy (up to 4 years). As such, we were unable to determine which events occurred during the acute phase and which occurred during the extended phase. Data from this study were not included in our analyses.

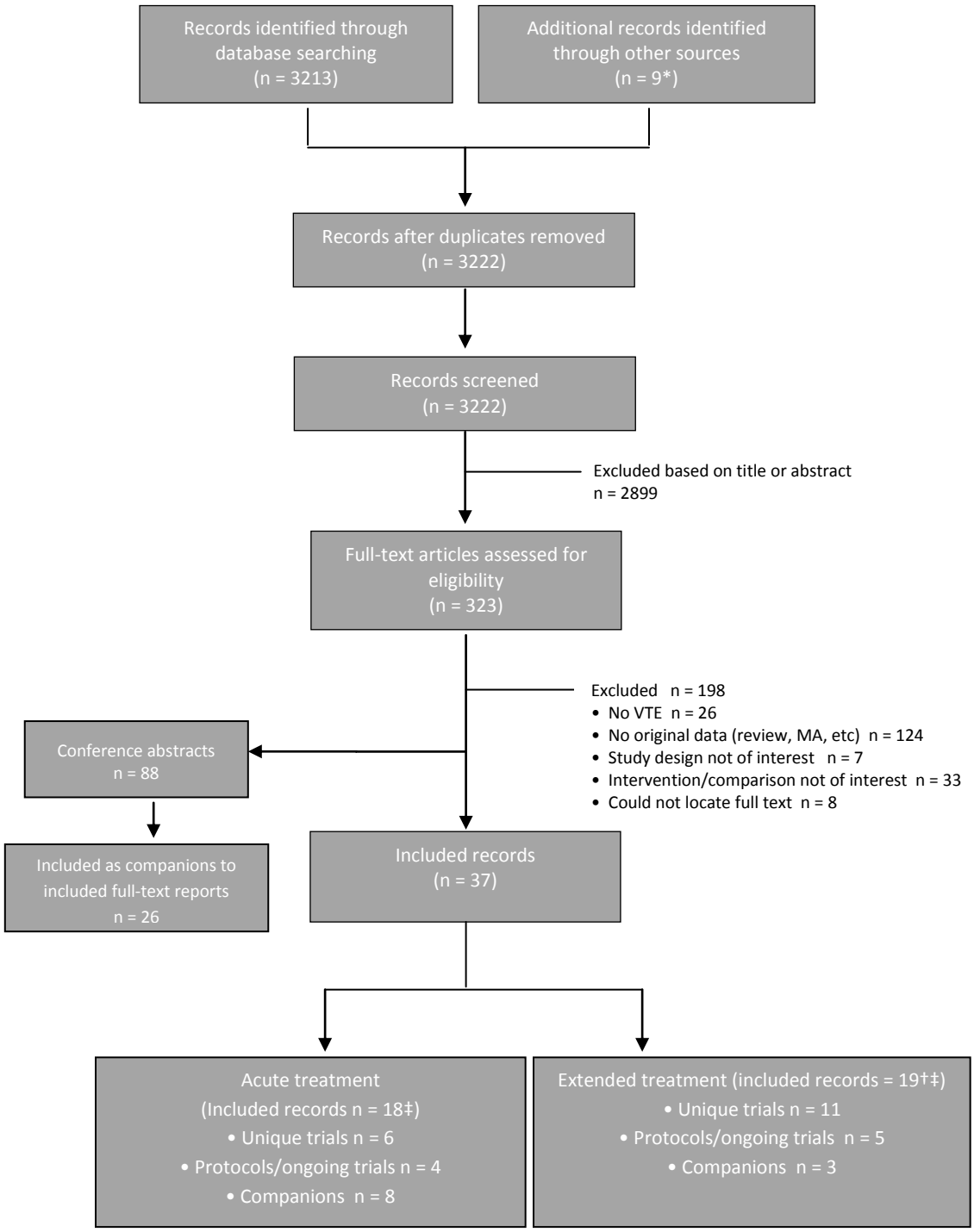
Table 2: Doses of oral anticoagulants

DOAC	Included doses	Notes
ACUTE therapy		
Apixaban	5 mg bid	Initial treatment of 10 mg bid for 7 d
Dabigatran	150 mg bid	Initial treatment with LMWH
Rivaroxaban	20 mg qd	Initial treatment of 15 mg bid for 3 wk
Edoxaban	30 mg or 60 mg qd	Initial treatment with LMWH; patients with creatinine clearance of 30–50 ml/min or weight ≤ 60 kg or receiving potent P-glycoprotein inhibitors received 30 mg qd; all others received 60 mg qd
EXTENDED therapy		

DOAC	Included doses	Notes
Apixaban	2.5 or 5 mg bid	Two apixaban arms
Dabigatran	150 mg bid	
Rivaroxaban	20 mg qd	
Acetylsalicylic acid	100 mg qd	

Note: bid = twice daily, LMWH = low-molecular-weight heparin, DOAC = new oral anticoagulant, qd = once daily.

Figure 1: PRISMA flow diagram



*Includes 8 warfarin studies and one protocol.
†Schulman 2013 reports on two unique trials, both extended treatment (RE-MEDY, RE-SONATE). This report is counted once in the list of included records, but is counted twice under "unique trials".
‡Bauersach 2010 (EINSTEIN Investigators) reports on two unique trials, one extended and one acute treatment (EINSTEIN acute, EINSTEIN extended). This publication has been counted in "included records" for the acute studies and not for extended studies. Each trial is included in the count for "unique trials" for acute and extended.

3.2. RISK OF BIAS

The risk of bias of the 17 included RCTs that reported outcome data of interest is presented in Appendix 4. The overall risk of bias was generally low for most studies, and most were well-reported.

Allocation concealment was inconsistently reported in a number of studies. In 4 of 17 studies, insufficient details were reported to allow judgment of the risk of bias, resulting in a rating of "unclear." One study was rated as being at high risk of bias for incomplete outcome data addressed for efficacy and safety outcomes (21). In this study (AMPLIFY-EXT), all randomized participants were included in the analysis except for two in each of 2.5 mg and 5 mg apixaban groups, whose verifiable source documentation was lacking. In addition, 23% (188/829), 14% (114/842), and 16% (129/815) of participants in the placebo, apixaban 2.5 mg, and 5 mg groups discontinued the study prematurely. The comparatively lower completion rate in placebo group, in addition to the handling of the missing data for primary efficacy outcomes, may have increased the number of events in the placebo group and therefore decreased the apparent risk in the apixaban 2.5 mg and 5 mg groups. This uncertainty is worsened by the fact that a large percentage participants in the placebo group (67%, 126/188) withdrew because of adverse events.

4. NETWORK META-ANALYSIS

Network meta-analyses were conducted for following outcomes: recurrent VTE, recurrent DVT, recurrent PE (total, fatal, non-fatal), major bleeding, intracranial bleeding, stroke, all-cause death, and CV death. The choice of these outcomes for network meta-analysis was based on the sufficiency of the data available to derive robust and consistent network models. No studies reported MACE.

The consistency of all networks with closed loops was assessed. The inconsistency v. consistency plots are presented in Appendix 5.

4.1. ACUTE TREATMENT

In total, 6 studies met the criteria for inclusion (Table 3). These studies all involved comparison of a DOAC with standard care, which was typically unfractionated heparin (UH) or low-molecular weight heparin (LMWH) followed by warfarin. All studies had a target INR of 2.0–3.0. Each study, except for HOKUSAI-VTE, included a 30-day observational period following the end of treatment.

Table 3: Study characteristics — ACUTE studies

Study	Population	Treatment	Treatment duration	End of study	Length of follow-up	No. randomized	
						Comparator	Intervention
Schulman 2009: **RE-COVER**	Acute symptomatic DVT or PE	• DBG, 150 mg, BID • Warfarin (initial treatment both groups:	6 mo	1 additional follow-up visit 30 days after end of treatment	7 mo	1283	1281

Study	Population	Treatment	Treatment duration	End of study	Length of follow-up	No. randomized	
						Comparator	Intervention
		UH or LMWH)					
Schulman 2014: **RE-COVER II**	Acute symptomatic DVT or PE	• DBG, 150 mg, BID • Warfarin (initial treatment both groups: UH or LMWH)	6 mo	1 additional follow-up visit 30 days after end of treatment	7 mo	1296	1293
Buller 2013: **HOKUSAI-VTE**	Acute symptomatic DVT or PE	• EDX, 60 mg, QD (30 mg QD in patients with impaired renal clearance, low body weight or receiving potent P-glycoprotein inhibitors) • Warfarin	3–12 mo	12 mo	12 mo	4149	4143
Agnelli 2013: **AMPLIFY**	Acute symptomatic DVT or PE	• APX, 10 mg bid for 7 d, followed by 5 mg BID • Enoxaparin (1.0 mg/kg) bid and warfarin or acenocoumarol	6 mo	1 additional follow-up visit 30 days after end of treatment	7 mo	2704	2691
Bauersachs 2010: **EINSTEIN**	Acute symptomatic DVT	• RVX, 15 mg bid for 3 wk, followed by 20 mg, QD • Enoxaparin (1.0 mg/kg) bid and warfarin or acenocoumarol	3, 6, or 12 mo	1 additional follow-up visit 30 days after end of treatment	4, 7, or 13 mo	3 mo: 203 6 mo: 1083 12 mo: 432	3 mo: 208 6 mo: 1083 12 mo: 440
Buller 2012: **EINSTEIN-PE**	Acute symptomatic PE with or without DVT	• RVX, 15 mg bid for 3 weeks, followed by 20 mg, QD • Enoxaparin (1.0 mg/kg) bid and warfarin or acenocoumarol	3, 6, or 12 mo	1 additional follow-up visit 30 days after end of treatment	4, 7, or 13 mo	3 mo: 122 6 mo: 1387 12 mo: 904	3 mo: 127 6 mo: 1387 12 mo: 905

Note: APX = apixaban, bid = twice daily, DBG = dabigatran, EDX = edoxaban, DVT = deep vein thrombosis, LMWH = low-molecular-weight heparin PE = pulmonary embolism,
qd = once daily, RVX = rivaroxaban, UH = unfractionated heparin, VTE = venous thromboembolism.

Most trials of acute therapy enrolled more men than women, and the mean age in each acute trial was less than 60 years (Table 4). A higher proportion of participants had a DVT as the qualifying event (v. PE). The presence of comorbidities or risk factors (surgery, immobilization, cancer, thrombophilia) was not well reported.

Table 4: Participant characteristics — ACUTE studies

Study	Comparator/ intervention	% of participants*; comparator/intervention 1/intervention 2									
		Mean age, yr	Men	DVT	PE	PE +/- DVT	Unprovoked VTE	Surgery	Immobilization	Cancer	Known thrombophilia
Schulman 2009: RE-COVER	VKA/DBG	54/55	58/59	69/69	21/21	10/10	NR	NR	NR	5/5	NR
Schulman 2014: **RE-COVER II**	VKA/DBG	55/55	60/61	68/69	23/23	9/8	NR	NR	NR	4/4	NR
Buller 2013: **HOKUSAI-VTE**	VKA/EDX	56/56	57/57	60/60	41/40	24/25	66/66	†	NR	10/9	NR
Agnelli 2013: **AMPLIFY**	VKA/APX	57/57	59/58	66/65	25/25	8/9	90/90	NR	NR	3/3	2/3
Bauersachs 2010:	VKA/RVX	56/56	56/57	99/99	0.6/0.7	NR	63/61	20/20‡	15/15	Active: 5/7	7/6

Study	Comparator/ intervention	% of participants*; comparator/intervention 1/intervention 2									
		Mean age, yr	Men	DVT	PE	PE +/- DVT	Unprovoked VTE	Surgery	Immobilization	Cancer	Known thrombophilia
EINSTEIN											
Buller 2012: **EINSTEIN-PE**	VKA/RVX	58/58	52/54	PE only	75/75	25/25	64/65	17/17‡	16/16	5/5	5/6

Note: APX = apixaban, DBG = dabigatran, DVT = deep vein thrombosis, EDX = edoxaban, PE = pulmonary embolism, RVX = rivaroxaban, VKA = vitamin k antagonist, VTE = venous thromboembolism.
*Unless otherwise stated.
†Temporary risk factor (recent surgery, trauma, immobilization, or use of estrogen: 28% of patients in each group.
‡Recent surgery or trauma.

Compared with placebo, there were no significant differences in outcomes for any of the DOACs (Table 5).

Table 5: Treatment effects relative to placebo — ACUTE studies

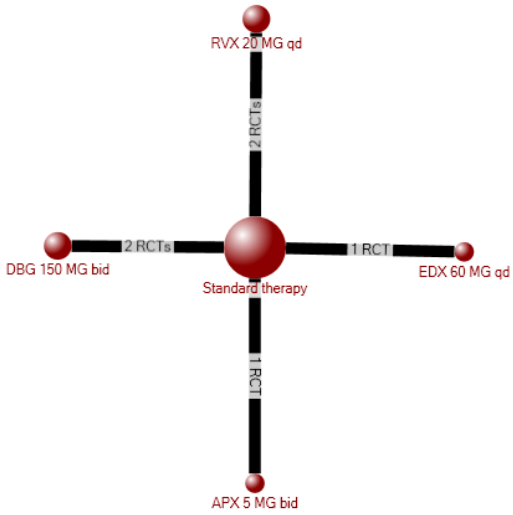
Treatment	Hazard ratio (95% CrI)										
	Recurrent VTE	Recurrent DVT	Recurrent PE (total)	Recurrent PE (fatal)	Recurrent PE (non-fatal)	Major bleed	ICH	All-cause death	CV death	Stroke	ACS
DBG 150 mg bid	1.10 (0.42, 2.94)	1.14 (0.31, 4.13)	1.23 (0.33, 4.93)	3.17 (0.73, 11.32)	1.08 (0.25, 4.89)	0.75 (0.28, 1.96)	0.26 (0.01, 2.68)	1.05 (0.39, 2.98)	—	3.10 (0.72, 44.31)	1.70 (0.26, 11.69)
RVX 20 mg qd	0.98 (0.37, 2.52)	0.91 (0.25, 3.28)	1.18 (0.34, 4.35)	4.55 (0.26, 249.70	1.10 (0.28, 4.80)	0.54 (0.22, 1.39)	0.34 (0.04, 3.66)	0.96 (0.36, 2.61)	1.55 (0.17, 14.16)	0.53 (0.15, 1.50)	—
EDX 60 mg qd	0.89 (0.23, 3.53)	0.90 (0.15, 5.61)	0.86 (0.14, 5.03)	1.31 (0.24, 7.19)	0.82 (0.11, 6.32)	0.85 (0.23, 3.07)	0.26 (0.02, 4.03)	1.06 (0.27, 4.24)	1.25 (0.06, 25.01)	—	—
APX 5 mg bid	0.85 (0.21, 3.15)	0.61 (0.09, 3.73)	1.13 (0.18, 7.02)	0.80 (0.08, 4.10)	1.18 (0.16, 8.76)	0.31 (0.08, 1.18)	0.48 (0.02, 8.02)	0.80 (0.19, 3.20)	0.38 (0.02, 9.40)	1.47 (0.59, 4.03)	—

Note: ACS = acute coronary syndrome, APX = apixaban, CV = cardiovascular, DBG = dabigatran, DVT = deep vein thrombosis, EDX = edoxaban, ICH = intracranial hemorrhage, PE = pulmonary embolism, RVX = rivaroxaban, VKA = vitamin k antagonist, VTE = venous thromboembolism.
*Statistically significant ($p < 0.05$).

4.1.1. RECURRENT VTE

The evidence network for recurrent VTE included 6 studies (6, 22-26) and a total of 27, 122 participants. Overall, 5 different treatments were considered, providing for 6 comparisons based on 6 studies designed with 2 treatment arms (Figure 2).

Figure 2: Evidence network for recurrent VTEs — ACUTE treatment



There were no significant differences in the recurrence of VTE between any of the DOACs and standard therapy, and there were no significant differences in the head-to-head comparisons of the DOACs (Table 6).

Table 6: Recurrent VTE: Hazard ratios (95% CrI) for head-to-head comparisons of DOACs — ACUTE treatment

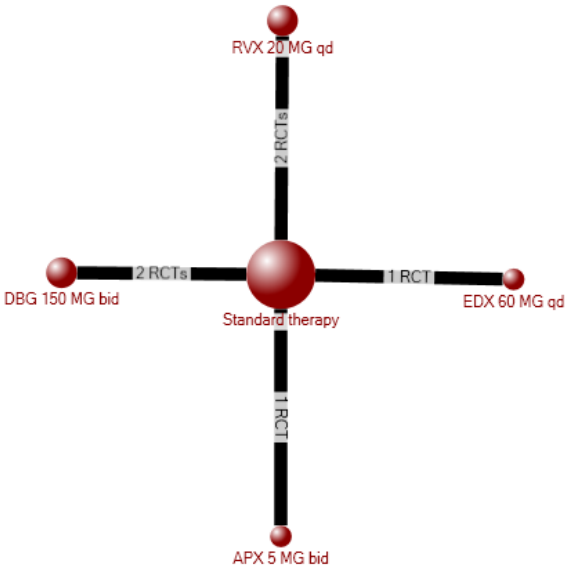
	Standard therapy	DBG 150 mg bid	RVX 20 mg qd	EDX 60 mg qd	APX 5 mg bid
DBG 150 mg bid	1.10 (0.42, 2.94)	—			
RVX 20 mg qd	0.98 (0.37, 2.52)	0.90 (0.21, 3.38)	—		
EDX 60 mg qd	0.89 (0.23, 3.53)	0.81 (0.15, 4.34)	0.90 (0.18, 5.01)	—	
APX 5 mg bid	0.85 (0.21, 3.15)	0.76 (0.14, 3.88)	0.86 (0.16, 4.42)	0.95 (0.14, 6.11)	—

Note: APX = apixaban, DBG = dabigatran, EDX = edoxaban, RVX = rivaroxaban.

4.1.2. RECURRENT DVT

The evidence network for recurrent DVT included 6 studies (6, 22-26) and a total of 27, 122 participants. Overall, 5 different treatments were considered, providing for 6 comparisons based on 6 studies each with 2 treatment arms (Figure 3).

Figure 3: Evidence network for recurrent DVT — ACUTE treatment



There were no significant differences in recurrent DVT between any of the DOACs and standard therapy, and there were no significant differences in the head-to-head comparisons of the DOACs (Table 7).

Table 7: Recurrent DVT: Hazard ratios (95% CrI) for head-to-head comparisons of DOACs — ACUTE treatment

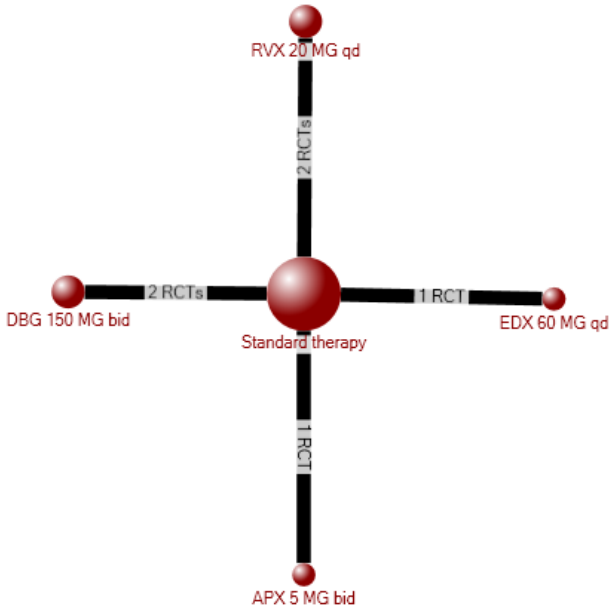
	Standard therapy	DBG 150 mg bid	RVX 20 mg qd	EDX 60 mg qd	APX 5 mg bid
DBG 150 mg bid	1.14 (0.31, 4.13)	—			
RVX 20 mg qd	0.91 (0.25, 3.28)	0.80 (0.13, 5.02)	—		
EDX 60 mg qd	0.90 (0.15, 5.61)	0.79 (0.09, 7.14)	0.99 (0.11, 8.80)	—	
APX 5 mg bid	0.61 (0.09, 3.73)	0.53 (0.06, 4.98)	0.66 (0.07, 5.99)	0.67 (0.05, 8.30)	—

Note: APX = apixaban, DBG = dabigatran, EDX = edoxaban, RVX = rivaroxaban.

4.1.3. RECURRENT PE

The evidence network for recurrent PE included 6 studies (6, 22-26) and a total of 27, 122 participants. Overall, 5 different treatments were considered, providing for 6 comparisons based on 6 studies designed with 2 treatment arms each (Figure 4).

Figure 4: Evidence network for recurrent PE (fatal and non-fatal) — ACUTE treatment



There were no significant differences in recurrent PE between any of the DOACs and standard therapy, and there were no significant differences in the head-to-head comparisons of the DOACs (Table 8). Both fatal and non-fatal PE was considered for this outcome.

Table 8: Total recurrent PE (fatal and non-fatal): Hazard ratio (95% CrI) for head-to-head comparisons of DOACs — ACUTE treatment

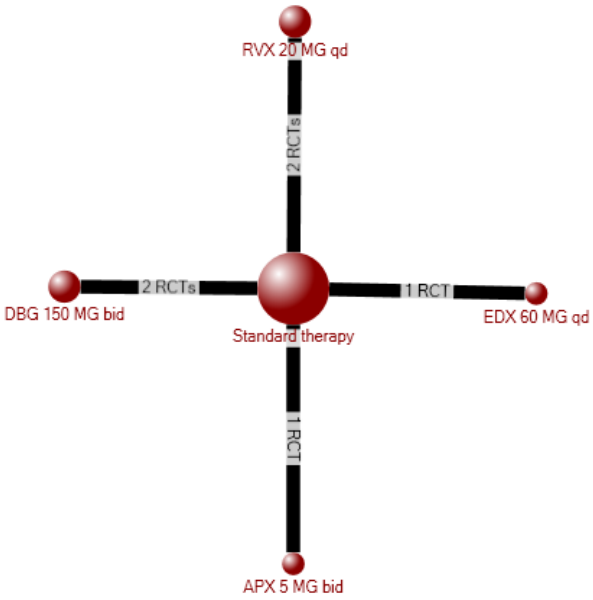
	Standard therapy	DBG 150 mg bid	RVX 20 mg qd	EDX 60 mg qd	APX 5 mg bid
DBG 150 mg bid	1.23 (0.33, 4.93)	—			
RVX 20 mg qd	1.18 (0.34, 4.35)	0.96 (0.14, 6.19)	—		
EDX 60 mg qd	0.86 (0.14, 5.03)	0.70 (0.07, 6.38)	0.72 (0.08, 6.32)	—	
APX 5 mg bid	1.13 (0.18, 7.02)	0.91 (0.09, 8.54)	0.96 (0.10, 8.46)	1.31 (0.09, 16.91)	—

Note: APX = apixaban, DBG = dabigatran, EDX = edoxaban, RVX = rivaroxaban.

4.1.4. NON-FATAL RECURRENT PE

The evidence network for non-fatal recurrent PE included 6 studies (6, 22-26) and a total of 27, 122 participants. Overall, 5 different treatments were considered, providing for 6 comparisons based on 6 studies designed with 2 treatment arms each (Figure 5).

Figure 5: Evidence network for non-fatal recurrent PE — ACUTE treatment



There were no significant differences in non-fatal recurrent PE between any of the DOACs and standard therapy, and there were no significant differences in the head-to-head comparisons of the DOACs (Table 9).

Table 9: Non-fatal recurrent PE: Hazard ratio (95% CrI) for head-to-head comparisons of DOACs — ACUTE treatment

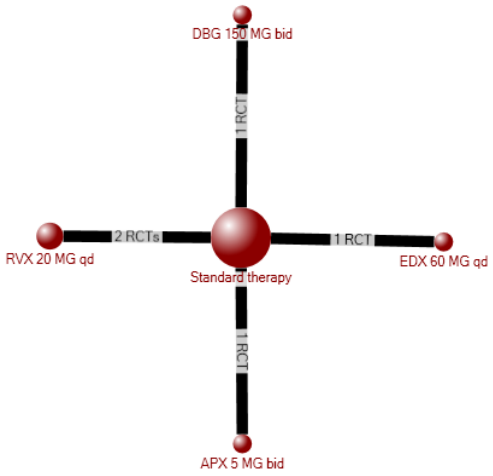
	Standard therapy	DBG 150 mg bid	RVX 20 mg qd	EDX 60 mg qd	APX 5 mg bid
DBG 150 mg bid	1.08 (0.25, 4.89)	—			
RVX 20 mg qd	1.10 (0.28, 4.80)	1.03 (0.13, 8.19)	—		
EDX 60 mg qd	0.82 (0.11, 6.32)	0.76 (0.06, 9.41)	0.75 (0.06, 8.77)	—	
APX 5 mg bid	1.18 (0.16, 8.76)	1.10 (0.09, 12.94)	1.08 (0.09, 12.10)	1.43 (0.08, 23.46)	—

Note: APX = apixaban, DBG = dabigatran, EDX = edoxaban, RVX = rivaroxaban.

4.1.5. FATAL RECURRENT PE

The evidence network for fatal recurrent PE included 5 studies (6, 23-26) and a total of 24, 558 participants. Overall, 5 different treatments were considered, providing for 6 comparisons based on 5 studies designed with 2 treatment arms each (Figure 6).

Figure 6: Evidence network for fatal recurrent PE — ACUTE treatment



There were no significant differences in recurrent non-fatal PE between any of the DOACs and standard therapy, and there were no significant differences in the head-to-head comparisons of the DOACs (Table 10). The 95% confidence interval for dabigatran compared with standard therapy was large (0.26, 249.70); one study contributed to this comparison, with zero events in the standard therapy arm and 3 events in the dabigatran arm.

Table 10: Fatal recurrent PE: Hazard ratio (95% CrI) for head-to-head comparisons of DOACs — ACUTE treatment

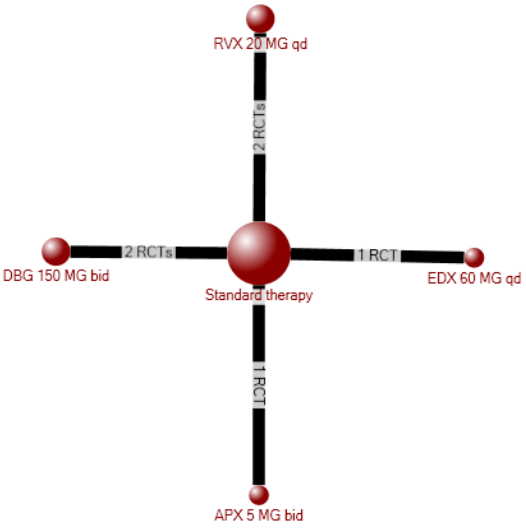
	Standard therapy	RVX 20 mg qd	DBG 150 MG bid	EDX 60 mg qd	APX 5 mg bid
RVX 20 mg qd	3.17 (0.73, 11.32)	—			
DBG 150 MG bid	4.55 (0.26, 249.70)	1.72 (0.06, 37.45)	—		
EDX 60 mg qd	1.31 (0.24, 7.19)	0.41 (0.06, 2.76)	0.32 (0.01, 4.68)	—	
APX 5 mg bid	0.80 (0.08, 4.10)	0.27 (0.02, 1.39)	0.13 (0.01, 4.86)	0.53 (0.04, 6.38)	—

Note: APX = apixaban, DBG = dabigatran, EDX = edoxaban, RVX = rivaroxaban.

4.1.6. MAJOR BLEEDS

The evidence network for major bleeds included 6 studies (6, 22-26) and a total of 27, 122 participants. Overall, 5 different treatments were considered, providing for 6 comparisons based on 6 studies designed with 2 treatment arms each (Figure 7).

Figure 7: Evidence network for major bleeds — ACUTE treatment



There were no significant differences in major bleeds between any of the DOACs and standard therapy, and there were no significant differences in the head-to-head comparisons of the DOACs (Table 11).

Table 11: Major bleeds: Hazard ratio (95% CrI) for head-to-head comparisons of DOACs — ACUTE treatment

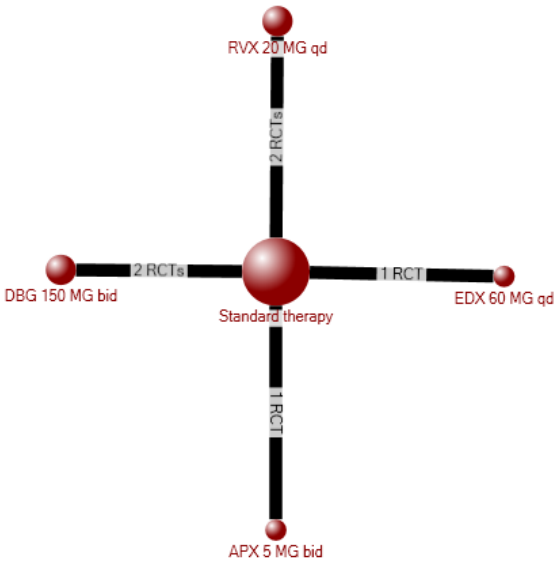
	Standard therapy	DBG 150 mg bid	RVX 20 mg qd	EDX 60 mg qd	APX 5 mg bid
DBG 150 mg bid	0.75 (0.28, 1.96)	—			
RVX 20 mg qd	0.54 (0.22, 1.39)	0.72 (0.20, 2.93)	—		
EDX 60 mg qd	0.85 (0.23, 3.07)	1.14 (0.23, 5.59)	1.57 (0.31, 7.82)	—	
APX 5 mg bid	0.31 (0.08, 1.18)	0.40 (0.08, 2.12)	0.56 (0.10, 2.80)	0.36 (0.05, 2.34)	—

Note: APX = apixaban, DBG = dabigatran, EDX = edoxaban, RVX = rivaroxaban.

4.1.7. INTRACRANIAL BLEEDS

The evidence network for major bleeds included 6 studies (6, 22-26) and a total of 27, 122 participants. Overall, 5 different treatments were considered, providing for 6 comparisons based on 6 studies designed with 2 treatment arms each (Figure 8).

Figure 8: Evidence network for intracranial bleeds — ACUTE treatment



There were no significant differences in intracranial bleeds between any of the DOACs and standard therapy, and there were no significant differences in the head-to-head comparisons of the DOACs (Table 12).

Table 12: Intracranial bleeds: Hazard ratios (95% CrI) for head-to-head comparisons of DOACs —ACUTE treatment

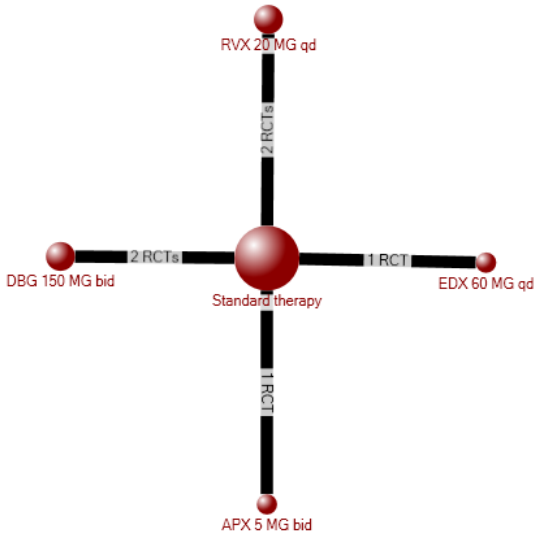
	Standard therapy	DBG 150 mg bid	RVX 20 mg qd	EDX 60 mg qd	APX 5 mg bid
DBG 150 mg bid	0.26 (0.01, 2.68)	—			
RVX 20 mg qd	0.34 (0.04, 3.66)	1.29 (0.06, 59.74)	—		
EDX 60 mg qd	0.26 (0.02, 4.03)	0.99 (0.03, 62.57)	0.79 (0.02, 24.84)	—	
APX 5 mg bid	0.48 (0.02, 8.02)	1.84 (0.05, 119.20)	1.41 (0.03, 47.85)	1.87 (0.03, 89.59)	—

Note: APX = apixaban, DBG = dabigatran, EDX = edoxaban, RVX = rivaroxaban.

4.1.8. ALL-CAUSE DEATH

The evidence network for all-cause death included 6 studies (6, 22-26) and a total of 27,122 participants. Overall, 5 different treatments were considered, providing for 6 comparisons based on 6 studies designed with 2 treatment arms each (Figure 9).

Figure 9: Evidence network for all-cause death — ACUTE treatment



There were no significant differences in all-cause deaths between any of the DOACs and standard therapy, and there were no significant differences in the head-to-head comparisons of the DOACs (Table 13).

Table 13: All-cause death: Hazard ratios (95% CrI) for head-to-head comparisons of DOACs — ACUTE treatment

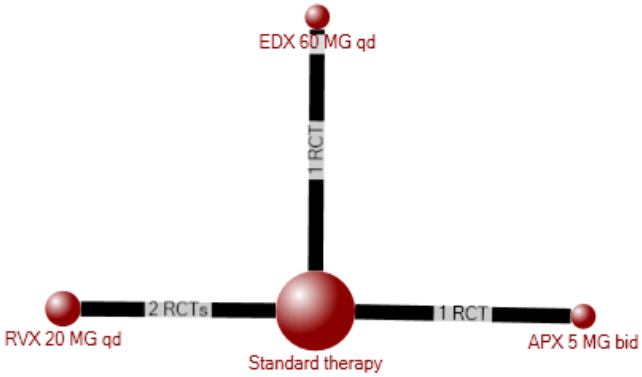
	Standard therapy	DBG 150 mg bid	RVX 20 mg qd	EDX 60 mg qd	APX 5 mg bid
DBG 150 mg bid	1.05 (0.39, 2.98)	—			
RVX 20 mg qd	0.96 (0.36, 2.61)	0.91 (0.21, 3.74)	—		
EDX 60 mg qd	1.06 (0.27, 4.24)	1.02 (0.18, 5.48)	1.10 (0.20, 6.25)	—	
APX 5 mg bid	0.80 (0.19, 3.20)	0.74 (0.13, 4.28)	0.83 (0.14, 4.60)	0.76 (0.10, 5.33)	–

Note: APX = apixaban, DBG = dabigatran, EDX = edoxaban, RVX = rivaroxaban.

4.1.9. CARDIOVASCULAR DEATH

The evidence network for cardiovascular death included 4 studies (6, 24-26) and a total of 21,969 participants. Overall, 4 different treatments were considered, providing for 4 comparisons based on 4 studies designed with 2 treatment arms each (Figure 10).

Figure 10: Evidence network for CV death — ACUTE treatment



There were no significant differences in CV death between any of the DOACs and standard therapy, and there were no significant differences in the head-to-head comparisons of the DOACs (Table 14).

Table 14: Cardiovascular death: Hazard ratios (95% CrI) for head-to-head comparisons of DOACs — ACUTE treatment

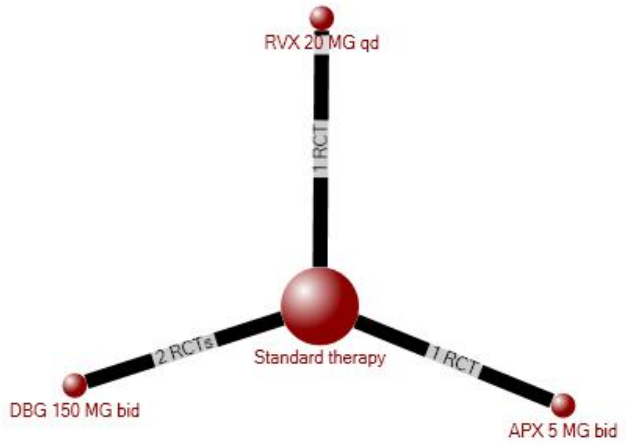
	Standard therapy	RVX 20 mg qd	EDX 60 mg qd	APX 5 mg bid
RVX 20 mg qd	1.55 (0.17, 14.16)	—		
EDX 60 mg qd	1.25 (0.06, 25.01)	0.81 (0.02, 34.02)	—	
APX 5 mg bid	0.38 (0.02, 9.40)	0.24 (0.00, 13.03)	0.30 (0.00, 24.57)	—

Note: APX = apixaban, EDX = edoxaban, RVX = rivaroxaban.

4.1.10.STROKE

The evidence network for stroke included 4 studies (6, 22, 23, 25) and a total of 13,997 participants. Overall, 4 different treatments were considered, providing for 4 comparisons based on 4 studies designed with 2 treatment arms (Figure 11).

Figure 11: Evidence network for stroke — ACUTE treatment



There were no significant differences in stroke between any of the DOACs and standard therapy, and there were no significant differences in the head-to-head comparisons of the DOACs (Table 15).

Table 15: Stroke: Hazard ratios (95% CrI) for head-to-head comparisons of DOACs — ACUTE treatment

	Standard therapy	DBG 150 mg bid	RVX 20 mg qd	APX 5 mg bid
DBG 150 mg bid	3.10 (0.72, 44.31)	—		
RVX 20 mg qd	0.53 (0.15, 1.50)	0.16 (0.01, 1.13)	—	
APX 5 mg bid	1.47 (0.59, 4.03)	0.46 (0.03, 3.80)	2.81 (0.68, 15.18)	—

Note: APX = apixaban, DBG = dabigatran, RVX = rivaroxaban.

4.1.11. ACUTE CORONARY SYNDROME

The evidence network for ACS included 2 studies (22, 23) and a total of 5,153 participants. Overall, 2 treatments were considered, providing for 2 comparisons based on 2 studies designed with 2 treatment arms comparing dabigatran 150 mg bid to standard therapy.

There were no significant differences in stroke between standard therapy and dabigatran (1.70, 95% CrI 0.26, 11.69).

4.2. EXTENDED TREATMENT

Eleven studies met the inclusion and exclusion criteria; 10 of these were included in the network meta-analysis. The study by Schulman and colleagues (DURACII) (20) reported the combined results for the acute (months 0–6) and extended therapy (up to 4 years) periods. We were unable to determine which events occurred during the

acute phase and which occurred during the extended phase; as such, these data were not included in our analyses.

Most studies included patients with unprovoked VTE; however, some did not comment on whether the qualifying event was provoked or unprovoked (Table 16). The initial duration of treatment (acute) was at least 3 months in all studies, and the duration of extended therapy was between 3 months and 4 years.

The mean age of participants ranged from 53 years in the VKA arm of AUREC-VFIII to 68 years in the discontinuation arm of the WODIT-DVT trial. Most trials enrolled more men than women; however, the WODIT-PE and AUREC-VFIII trials enrolled more than 50% women. Patients with provoked VTE were excluded in most trials (LAFIT, WODIT-DVT, AUREC-VFII, WARFASA, ASPIRE). RE-SONATE and RE-MEDY allowed patients with immobilization or known thrombophilia; however, only a small proportion of patients had these risk factors (Table 17).

Table 16: Study Characteristics —EXTENDED treatment

Study	Population	Initial acute therapy		Extended therapy		End of study	Length of follow-up; comparator /intervention	No. randomized		
		Treatment	Duration	Treatment	Treatment duration			Comparator	Intervention 1	Intervention 2
Standard-dose VKA										
Kearon 1999: LAFIT	Unprovoked VTE	UH or LMWH, followed by oral anticoagulant	3 mo	Placebo/VKA	24 mo	24 mo after randomization	Mean: 9/ 12 mo	83	79	NA
Agnelli 2001: WODIT-DVT	Symptomatic first unprovoked DVT	UH or LMWH, followed by warfarin or acenocoumarol	3 mo	Discont. /VKA	9 mo	36 mo	Mean: 37.0/37.8 mo	133	134	NA
Agnelli 2003: WODIT-PE	Symptomatic first PE	Warfarin or acenocoumarol	3 mo	Discont. /VKA	3 mo or 9 mo	36 mo	Mean: 32.7/34.9 mo	161	165	NA
Eischer 2009: AUREC-VFIII	First unprovoked DVT or PE	UH or LMWH, followed by VKA	6 mo	Discont. /VKA	2 yr	3 yr	Mean: 37 mo (both)	17	17	NA
Direct thrombin inhibitors										
Schulman 2013: RE-SONATE	Symptomatic DVT or PE	Approved anticoagulant or DOAC (DBG; from RECOVER or RECOVER II trials)	6-18	Placebo/DBG, 150 mg, BID	6 mo	12 mo after completion of treatment	Intended: 18 mo	668	685	NA
Schulman 2013: RE-MEDY	Symptomatic DVT or PE	Approved anticoagulant or DOAC (DBG; from RECOVER or RECOVER II trials)	3-12	VKA/ DBG, 150 mg, BID	36 mo	1 additional follow-up visit 30 days after end of treatment	Intended: 36 mo	1431	1435	NA
Factor Xa Inhibitors										
Bauersachs 2010: EINSTEIN-EXT	Symptomatic DVT	Acenocoumarol or warfarin (EINSTEIN trial or routine care) or RVX (EINSTEIN trials)	6–12 mo	Placebo/RVX, 20 mg, QD	6 or 12 mo	1 additional follow-up visit 30 days after end of treatment	Intended: 7 or 13 mo	595	602	NA
Agnelli 2013: AMPLIFY-EXT	Symptomatic DVT or PE	Standard anticoagulant	6–12 mo	Placebo/APX, 2.5 mg, BID/APX, 5	12 mo	1 additional follow-up visit 30	Intended: 13 mo	829	842	813

Study	Population	Initial acute therapy		Extended therapy		End of study	Length of follow-up; comparator /intervention	No. randomized		
		Treatment	Duration	Treatment	Treatment duration			Comparator	Intervention 1	Intervention 2
		therapy or APX, ENOX or warfarin (AMPLIFY trial)		mg, BID		days after end of treatment				
Low-dose ASA										
Becattini 2012: WARFASA	Symptomatic unprovoked DVT or PE	UH or LMWH, followed by warfarin	6–18 mo	Placebo/ASA, 100 mg, QD	2 yr with option of extension	Appears to be equal to treatment duration	Median: 24.2/24.8 mo	198	205	NA
Brighton 2012: ASPIRE	Symptomatic unprovoked DVT or PE	Heparin followed by warfarin (or an effective alternative anticoagulant)	6 wk to 24 mo	Placebo/ASA, 100 mg, QD	2–4 yr	4 yr	Median: 37.2/37.2 mo	411	411	NA

Note: ASA = acetylsalicylic acid, APX = apixaban, BID = twice daily, DBG = dabigatran, EDX = edoxaban, ENOX = enoxaparin, DVT = deep vein thrombosis, LMWH = low-molecular-weight heparin, DOAC = new oral anticoagulant, PE = pulmonary embolism, QD = once daily, RVX = rivaroxaban, UH = unfractionated heparin, VKA = vitamin k antagonist, VTE = venous thromboembolism.

Table 17: Participant characteristics — EXTENDED treatment studies

Study	Comparator/ intervention	% of participants*; comparator/intervention 1/intervention 2									
		Mean age, yr	Men	DVT	PE	PE +/- DVT	Unprovoked VTE	Surgery	Immobilization	Cancer†	Known thrombophilia
Kearon 1999: LAFIT	PLACEBO/VKA	58/59	53/68	73/76	27/24	NR	Unprovoked only	Excluded	Excluded	Excluded	Excluded
Agnelli 2001: WODIT-DVT	DISCT/VKA	68/67	61/55	DVT only	NR	NR	Unprovoked only	Excluded	Excluded	Excluded	Excluded
Agnelli 2003: WODIT-PE	DISCT/VKA	61/63	42/39	NA (PE only)	PE only	55/55	57/56	NR	NR	Excluded	Excluded

Study	Comparator/ intervention	% of participants*; comparator/intervention 1/intervention 2									
		Mean age, yr	Men	DVT	PE	PE +/- DVT	Unprovoked VTE	Surgery	Immobilization	Cancer†	Known thrombophilia
Eischer 2009: AUREC-VFIII	DISCT/VKA	54/53	35/29	65/53	35/47	NR	Unprovoked only	Excluded	Excluded	Excluded	NR
Schulman 2013: RE-SONATE	PLACEBO/ DBG	56/56	56/55	67/63	27/27	5/7	NR	Excluded	5/8	Previous cancer excluded; active: 13/10	10/13
Schulman 2013: RE-MEDY	WARF/DBG	54/55	61/61	65/66	24/23	12/12	NR	Excluded	7/7	Active: 18/18 previous: 4/4	18/18
Bauersachs 2010: EINSTEIN-EXT	PLACEBO/RVX	58/58	57/59	64/60	40/36	NR	74/73	5/4‡	13/15	Active: 4/5	8/8
Agnelli 2013: AMPLIFY-EXT	PLACEBO /APX 2.5 /APX 5.0	57/57/56	57/58/58	67/65/65	34/35/35	NR	91/93/91	Excluded	3/2/4	Active: 2/2/1; previous excluded	NR
Becattini 2012: WARFASA	PLACEBO/ASA	62/62	62/66	67/60	34/41	NR	Unprovoked only	NR	NR	Excluded	Excluded
Brighton 2012: ASPIRE	PLACEBO/ASA	54/55	54/55	56/57	29/27	14/14	Unprovoked only	Excluded	Excluded	NR	NR

Note: APX = apixaban, ASA = acetylsalicylic acid, DBG = dabigatran, DISCT = discontinuation, DVT = deep vein thrombosis, PE = pulmonary embolism, RVX = rivaroxaban, VTE = venous thromboembolism.
*Unless otherwise stated.
†Active or previous.
‡Reported as "recent surgery or trauma."

Relative to placebo or discontinuation, VKA reduced the risk of recurrent VTE, DVT, total and non-fatal PE, and increased risk of major bleeds (Table 18). Dabigatran reduced the risk of recurrent VTE, DVT, and total and non-fatal PE. There was no significant difference between ASA or apixaban (2.5 or 5 mg bid) and placebo/discontinuation for any outcome reported. The risk of major bleed was increased with rivaroxaban relative to placebo/discontinuation; however, the confidence interval for the hazard ratio is wide (40.13; 95% CrI 4.20, 395.30).

Table 18: Treatment effects relative to placebo or discontinuation — EXTENDED treatment

Treatment	Hazard ratio (95% CrI)									
	Recurrent VTE	Recurrent DVT	Recurrent PE (total)	Recurrent PE (non-fatal)	Recurrent PE (fatal)	Major bleed	All-cause death	CV death	Stroke	ACS
VKA	**0.09 (0.03, 0.36)***	**0.03 (0.00, 0.17)***	**0.05 (0.00, 0.63)***	**0.06 (0.00, 0.75)***	0.43 (0.09, 1.49)	**4.49 (1.30, 31.25)***	0.23 (0.01, 2.79)	0.22 (0.01, 1.08)	—	5.70 (0.08, 272.10)
DBG 150 mg bid	**0.10 (0.02, 0.52)***	**0.05 (0.00, 0.24)***	**0.08 (0.00, 0.82)***	**0.09 (0.01, 0.91)***	0.90 (0.30, 3.23)	2.91 (0.57, 19.13)	0.21 (0.01, 2.97)	—	0.21 (0.00, 11.62)	4.41 (0.84, 35.46)
ASA 100 mg qd	0.64 (0.17, 2.38)	—	0.74 (0.06, 9.13)	0.75 (0.06, 8.97)	0.44 (0.12, 3.72)	1.47 (0.19, 28.93)	—	—	—	—
RVX 20 mg qd	0.19 (0.03, 1.31)	0.28 (0.07, 1.07)	0.23 (0.02, 3.06)	0.12 (0.01, 1.86)	0.62 (0.04, 4.37)	**40.13 (4.20, 395.30)***	1.73 (0.02, 200.60)	2.21 (0.04, 21.91)	—	—
APX 2.5 mg bid	0.19 (0.03, 1.23)	—	0.52 (0.04, 6.38)	0.51 (0.04, 6.26)	9.08 (0.10, 132.90)	0.86 (0.34, 3.90)	2.02 (0.06, 118.50)	0.16 (0.05, 0.80)	—	—
APX 5 mg bid	0.19 (0.03, 1.31)	—	0.26 (0.02, 3.25)	0.25 (0.02, 3.43)	1.07 (0.04, 13.02)	0.43 (0.09, 1.54)	1.12 (0.03, 66.89)	0.35 (0.10, 0.80)	—	—

Note: ACS = acute coronary syndrome, APX = apixaban, ASA = acetylsalicylic acid, CV = cardiovascular, DBG = dabigatran, DVT = deep vein thrombosis, RVX = rivaroxaban, VKA = vitamin K antagonist, VTE = venous thromboembolism.
*Statistically significant ($p < 0.05$).
None of the included studies reported intracranial hemorrhage.
Green cells indicate that the treatment is significantly better than placebo/discontinuation. Red indicates that the treatment is significantly worse than placebo/discontinuation.

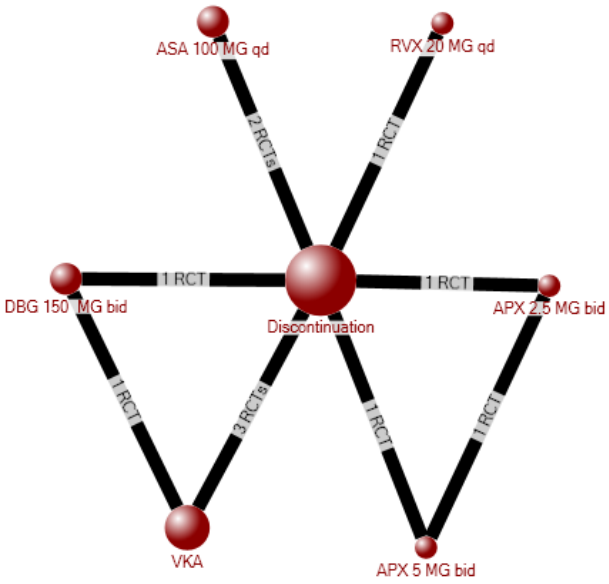
4.2.1. RECURRENT VTE

The evidence network for recurrent VTE included 9 studies (6, 21, 27-32) and a total of 9590 participants. Overall, 7 different treatments were considered, providing for 11 comparisons based on 8 studies designed with 2 treatment arms and one study with three treatment arms (Figure 12).

Data for WODIT-PE was not included in the network because the treatment period was 3 or 9 months, but outcomes were reported as end of study only. The on-treatment period data for the ASPIRE study includes up to 7 days after discontinuation of the study drug; these data were included in the network.

Figure 12: Evidence network for recurrent VTEs — EXTENDED treatment

Compared with those taking placebo or who discontinued therapy, patients taking VKA or dabigatran



had a lower risk of recurrent VTE (HR 0.09, 95% CI 0.03, 0.36; HR 0.10, 95% CI 0.02, 0.52, respectively; Table 19). Patients taking ASA had a higher risk of recurrent VTE compared to those taking VKA (HR 7.41, 95% CI 1.00, 41.48)

Table 19: Recurrent VTE: hazard ratios (95% CrI) for head-to-head comparisons of DOACs — EXTENDED treatment

	DISCONT/ Placebo	VKA	DBG 150 mg bid	ASA 100 mg qd	RVX 20 mg qd	APX 2.5 mg bid	APX 5 mg bid
VKA	0.09 (0.03, 0.36)*	—					
DBG 150 mg bid	**0.10 (0.02, 0.52)***	1.19 (0.22, 4.80)	—				
ASA 100 mg qd	0.64 (0.17, 2.38)	**7.41 (1.00, 41.48)***	6.26 (0.76, 48.86)	—			
RVX 20 mg qd	0.19 (0.03, 1.31)	2.17 (0.17, 19.64)	1.81 (0.14, 22.76)	0.29 (0.03, 3.07)	—		
APX 2.5 mg bid	0.19 (0.03, 1.23)	2.17 (0.18, 19.30)	1.84 (0.14, 21.60)	0.29 (0.03, 3.03)	0.97 (0.06, 16.01)	—	
APX 5 mg bid	0.19 (0.03, 1.31)	2.19 (0.19, 19.43)	1.87 (0.15, 21.14)	0.30 (0.03, 2.92)	1.02 (0.07, 16.02)	1.03 (0.14, 7.05)	—

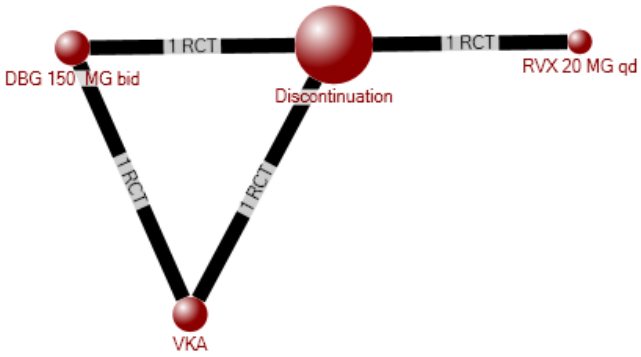
Note: APX = apixaban, ASA = acetylsalicylic acid, DBG = dabigatran, DISCONT = discontinuation, RVX = rivaroxaban, VKA = vitamin k antagonist.
*p < 0.05.
Green cells indicate that the "row" treatment is significantly better than the "column" treatment. Red indicates that the "row" treatment is significantly worse than the "column" treatment.

4.2.2. RECURRENT DVT

The evidence network for recurrent DVT included 4 studies (6, 27, 30) and a total of 5578 participants. Overall, 4 different treatments were considered, providing for 4 comparisons based on 4 studies designed with 2 treatment arms each.

Data from the WARFASA trial were not included in this analysis. WARFASA reported the number of DVT events, while the other 4 included trials reported the number of patients with a recurrent DVT (Figure 13).

Figure 13: Evidence network for recurrent DVT — EXTENDED treatment



Compared with those taking placebo or who discontinued therapy, patients taking VKA or dabigatran had a lower risk of recurrent DVT (HR 0.03, 95% CI 0.0, 0.17; HR 0.05, 95% CI 0.00, 0.24, respectively; Table 20). Patients taking rivaroxaban had a higher risk of recurrent DVT compared to those taking VKA (HR 9.58, 95% CI 1.001, 167.10).

Table 20: Recurrent DVT: hazard ratios (95% CrI) for head-to-head comparisons of DOACs — EXTENDED treatment

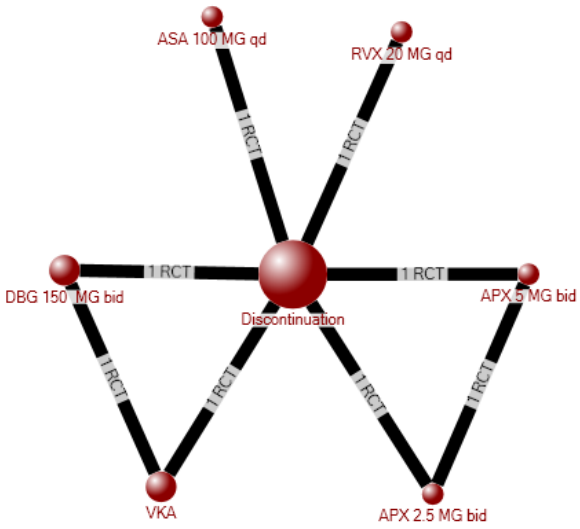
	DISCONT/ Placebo	VKA	DBG 150 mg bid	RVX 20 mg qd
VKA	**0.03 (0.00, 0.17)***	—		
DBG 150 mg bid	**0.05 (0.00, 0.24)***	1.56 (0.46, 7.14)	—	
RVX 20 mg qd	0.28 (0.07, 1.07)	**9.58 (1.001, 167.10)***	5.87 (0.70, 79.77)	—

Note: APX = apixaban, , DBG = dabigatran, DISCONT = discontinuation, RVX = rivaroxaban, VKA = vitamin k antagonist
*p < 0.05.
Green cells indicate that the "row" treatment is significantly better than the "column" treatment. Red indicates that the "row" treatment is significantly worse than the "column" treatment.

4.2.3. RECURRENT PE

The evidence network for recurrent PE (total) included 6 studies (6, 21, 27, 30, 31) and a total of 8467 participants. Overall, 7 different treatments were considered, providing for 8 comparisons based on 5 studies with 2 treatment arms and 1 study with 3 arms (Figure 14). RE-MEDY reported "deaths related to VTE", which were judged to be due to fatal PE and were included for this outcome.

Figure 14: Evidence network for recurrent PE (fatal and non-fatal) — EXTENDED treatment



Compared with discontinuation or placebo, the risk of recurrent PE was lower among patients taking VKA (HR 0.05, 95% CI 0.00, 0.63) or dabigatran (HR 0.08, 95% CI 0.00, 0.82; Table 21).

Table 21: Total recurrent PE — Hazard ratio (95% CrI) for head-to-head comparisons of DOACs — EXTENDED treatment

	DISCONT/ Placebo	VKA	DBG 150 mg bid	ASA 100 mg qd	RVX 20 mg qd	APX 2.5 mg bid	APX 5 mg bid
VKA	**0.05 (0.00, 0.63)***	—					
DBG 150 mg bid	**0.08 (0.00, 0.82)***	1.49 (0.15, 12.37)	—				
ASA 100 mg qd	0.74 (0.06, 9.13)	14.48 (0.45, 541.90)	9.44 (0.34, 405.50)	—			
RVX 20 mg qd	0.23 (0.02, 3.06)	4.58 (0.12, 185.90)	2.99 (0.09, 133.60)	0.31 (0.01, 10.79)	—		
APX 2.5 mg bid	0.52 (0.04, 6.38)	10.07 (0.29, 379.70)	6.56 (0.24, 276.00)	0.70 (0.02, 23.63)	2.19 (0.06, 81.18)	—	

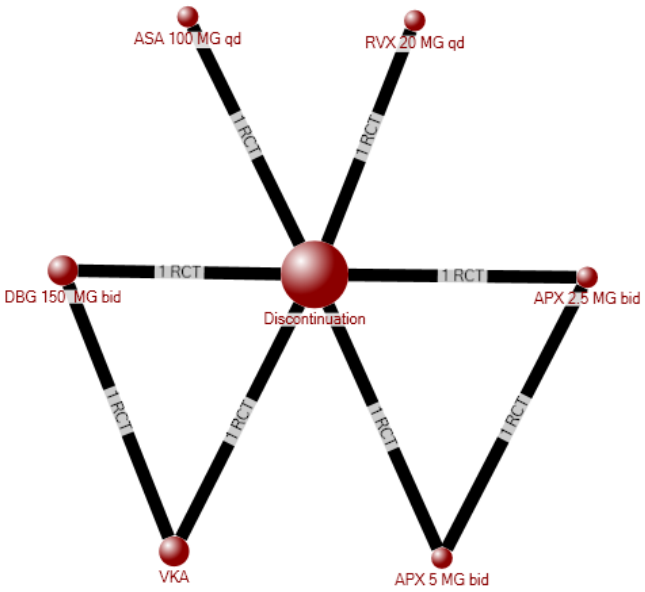
	DISCONT/ Placebo	VKA	DBG 150 mg bid	ASA 100 mg qd	RVX 20 mg qd	APX 2.5 mg bid	APX 5 mg bid
APX 5 mg bid	0.26 (0.02, 3.25)	4.92 (0.13, 211.80)	3.24 (0.10, 139.30)	0.35 (0.01, 11.90)	1.09 (0.03,43.52)	0.50 (0.03, 6.38)	—

Note: APX = apixaban, ASA = acetylsalicylic acid, DBG = dabigatran, DISCONT = discontinuation, RVX = rivaroxaban, VKA = vitamin k antagonist.
*p < 0.05.
Green cells indicate that the "row" treatment is significantly better than the "column" treatment. Red indicates that the "row" treatment is significantly worse than the "column" treatment.

4.2.4. NON-FATAL RECURRENT PE

The evidence network for recurrent nonfatal PE included 6 studies (6, 21, 27, 30, 31) and a total of 8467 participants. Overall, 7 different treatments were considered, providing for 8 comparisons based on 5 studies with 2 treatment arms and 1 study with 3 arms (Figure 15).

Figure 15: Evidence network for non-fatal PE — EXTENDED treatment



The risk of non-fatal recurrent PE was lower among patients taking VKA (HR 0.06, 95% CI 0.00, 0.75) or dabigatran (HR 0.09, 95% CI 0.01, 0.91) compared to discontinuation or placebo (Table 22). There were no significant differences among the DOACs.

Table 22: Non-fatal recurrent PE: Hazard ratio (95% CrI) for head-to-head comparisons of DOACs — EXTENDED

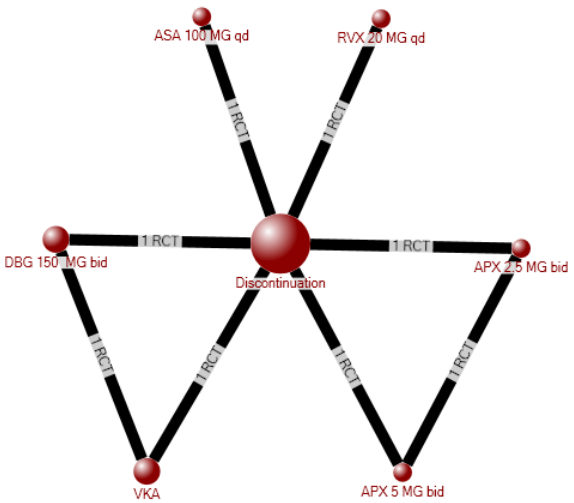
	DISCONT/ Placebo	VKA	DBG 150 mg bid	ASA 100 mg qd	RVX 20 mg qd	APX 2.5 mg bid	APX 5 mg bid
VKA	**0.06 (0.00, 0.75)***	—					
DBG 150 mg bid	**0.09 (0.01, 0.91)***	1.49 (0.14, 13.39)	—				
ASA 100 mg qd	0.75 (0.06, 8.97)	13.11 (0.34, 520.30)	8.77 (0.29, 343.90)	—			
RVX 20 mg qd	0.12 (0.01, 1.86)	2.16 (0.04, 98.82)	1.41 (0.03, 68.47)	0.16 (0.00, 6.80)	—		
APX 2.5 mg bid	0.51 (0.04, 6.26)	8.86 (0.25, 356.40)	6.01 (0.19, 244.50)	0.68 (0.02, 22.26)	4.22 (0.10, 203.30)	—	
APX 5 mg bid	0.25 (0.02, 3.43)	4.40 (0.11, 195.80)	2.89 (0.08, 131.50)	0.32 (0.01, 12.35)	2.00 (0.04, 102.10)	0.49 (0.03, 7.23)	—

Note: APX = apixaban, ASA = acetylsalicylic acid, DBG = dabigatran, DISCONT = discontinuation, RVX = rivaroxaban, VKA = vitamin k antagonist.
*p < 0.05.
Green cells indicate that the "row" treatment is significantly better than the "column" treatment. Red indicates that the "row" treatment is significantly worse than the "column" treatment.

4.2.5. FATAL RECURRENT PE

The evidence network for fatal recurrent PE included 6 studies (6, 21, 27, 30, 31) and a total of 8467 participants. Overall, 7 different treatments were considered, providing for 8 comparisons based on 5 studies designed with 2 treatment arms and one study with 3 arms (Figure 16).

Figure 16: Evidence network for fatal recurrent PE — EXTENDED treatment



There were no significant differences among the DOACs or between any of the DOACs and discontinuation/placebo (Table 23).

Table 23: Fatal recurrent PE: Hazard ratio (95% CrI) for head-to-head comparisons of DOACs — EXTENDED treatment

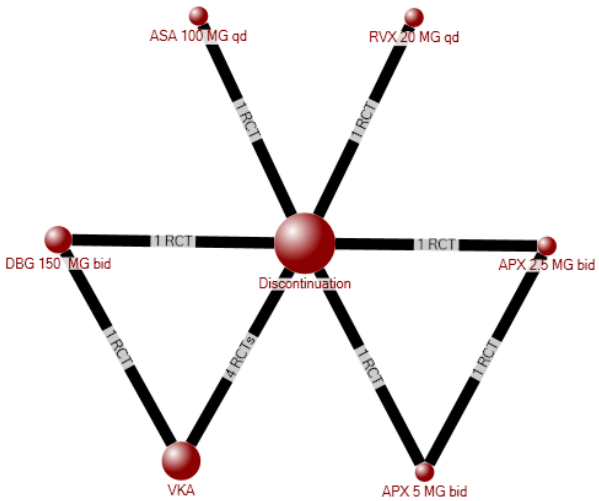
	DISCONT/ Placebo	VKA	ASA 100 mg qd	DBG 150 mg bid	RVX 20 mg qd	APX 2.5 mg bid	APX 5 mg bid
VKA	0.43 (0.09, 1.49)	—					
ASA 100 mg qd	0.44 (0.12, 3.72)	1.79 (0.18, 6.29)	—				
DBG 150 mg bid	0.90 (0.30, 3.23)	2.34 (0.63, 9.51)	1.95 (0.22, 7.63)	—			
RVX 20 mg qd	0.26 (0.01, 2.21)	0.62 (0.04, 4.37)	0.27 (0.02, 14.60)	0.22 (0.01, 3.64)	—		
APX 2.5 mg bid	2.92 (0.04, 16.15)	9.08 (0.10, 132.90)	5.14 (0.03, 89.46)	2.63 (0.05, 31.36)	6.76 (0.10, 422.60)	—	
APX 5 mg bid	0.32 (0.05, 2.36)	1.07 (0.04, 13.02)	0.66 (0.02, 12.34)	0.45 (0.02, 3.04)	1.15 (0.08, 36.79)	0.14 (0.02, 2.60)	—

Note: APX = apixaban, ASA = acetylsalicylic acid, DBG = dabigatran, DISCONT = discontinuation, RVX = rivaroxaban, VKA = vitamin k antagonist.

4.2.6. MAJOR BLEEDS

The evidence network for major bleeds included 8 studies (6, 21, 27-31) and a total of 8768 participants. Overall, 7 different treatments were considered, providing for 10 comparisons based on 7 studies designed with 2 treatment arms and one study with 3 arms (Figure 17).

Figure 17: Evidence network for major bleeds — EXTENDED treatment



Compared to placebo or discontinuation, patients taking VKA (HR 4.49, 95% CI 1.30, 31.25) or rivaroxaban (HR 40.13, 95% CI 4.20, 395.30) had a higher risk of major bleed (Table 24, Figure 17). Patients taking rivaroxaban had a higher risk of major bleed compared to those taking VKA (HR 7.04, 95% CI 1.34, 79.20), dabigatran (HR 12.59, 95% CI 2.96, 92.49), or ASA (HR 23.76, 95% 1.30, 706.10). The risk of major bleeding was lower among patients taking apixaban 2.5 mg compared with VKA (HR 0.23, 95% CI 0.01, 0.87) or rivaroxaban (0.02, 95% CI 0.00, 0.22), and lower among patients taking apixaban 5 mg compared with VKA (HR 0.10, 95% CI 0.00, 0.41), dabigatran (HR 0.19, 95% CI 0.01, 0.87) and rivaroxaban (HR 0.01, 95% CI 0.00, 0.13).

Table 24: Major bleeds: Hazard ratio (95% CrI) for head-to-head comparisons of DOACs — EXTENDED

	DISCONT/ Placebo	VKA	DBG 150 mg bid	ASA 100 mg qd	RVX 20 mg qd	APX 2.5 mg bid	APX 5 mg bid
VKA	**4.49 (1.30, 31.25)***	—					
DBG 150 mg bid	2.91 (0.57, 19.13)	0.58 (0.19, 1.19)	—				
ASA 100 mg qd	1.47 (0.19, 28.93)	0.19 (0.04, 9.63)	0.32 (0.07, 11.81)	—			
RVX 20 mg qd	**40.13 (4.20, 395.30)***	**7.04 (1.34, 79.20)***	**12.59 (2.96, 92.49)***	**23.76 (1.30, 706.10)***	—		
APX 2.5 mg bid	0.86 (0.34, 3.90)	**0.23 (0.01, 0.87)***	0.39 (0.02, 1.75)	0.52 (0.02, 10.87)	**0.02 (0.00, 0.22)***	—	
APX 5 mg bid	0.43 (0.09, 1.54)	**0.10 (0.00, 0.41)***	**0.19 (0.01, 0.87)***	0.18 (0.01, 4.69)	**0.01 (0.00, 0.13)***	0.45 (0.13, 2.64)	—

Note: APX = apixaban, ASA = acetylsalicylic acid, DBG = dabigatran, DISCONT = discontinuation, RVX = rivaroxaban, VKA = vitamin k antagonist. Green cells indicate that the "row" treatment is significantly better than the "column" treatment. Red indicates that the "row" treatment is significantly worse than the "column" treatment.

*p < 0.05.

As can be seen in Table 24, the credible intervals for comparisons involving rivaroxaban are very wide. Rivaroxaban was used as a treatment in only one study (EINSTEIN-EXT), with zero major bleeds in the placebo/discontinuation arm and four in the rivaroxaban arm.

An additional analysis was performed in which we removed all studies that reported zero events in either study arm. Zero events were reported in the placebo/discontinuation arms of the LAFIT (v. VKA), AURC-VFIII (v. VKA), and RE-SONATE (v. dabigatran) trials; however additional data for these comparisons was obtained from studies reporting no zero counts, thus allowing these drugs to remain in the network. Because the EINSTEIN-EXT trial was the only trial involving rivaroxaban, the removal of this trial from the analysis meant that this arm was lost from the network. This alternative analysis is presented in Table 25.

Table 25: Major bleeds: Hazard ratio (95% CrI) for head-to-head comparisons of DOACs — EXTENDED, zero count trials removed from network

	DISCONT/ Placebo	VKA	DBG 150 mg bid	ASA 100 mg qd	APX 2.5 mg bid	APX 5 mg bid
VKA	**4.73 (1.63, 27.23)***	—				
DBG 150 mg bid	2.22 (0.67, 14.45)	**0.46 (0.23, 0.98)***	—			
ASA 100 mg qd	0.61 (0.06, 6.89)	0.12 (0.01, 2.67)	0.26 (0.01, 7.43)	—		
APX 2.5 mg bid	0.63 (0.19, 1.91)	**0.13 (0.02, 0.36)***	**0.29 (0.05, 0.83)***	1.20 (0.08, 8.78)	—	
APX 5 mg bid	0.33 (0.03, 1.01)	**0.05 (0.01, 0.46)***	0.10 (0.02, 1.15)	0.59 (0.01, 4.65)	0.41 (0.07, 3.34)	—

Note: APX = apixaban, ASA = acetylsalicylic acid, DBG = dabigatran, DISCONT = discontinuation, RVX = rivaroxaban, VKA = vitamin k antagonist.
*p < 0.05.
Green cells indicate that the "row" treatment is significantly better than the "column" treatment. Red indicates that the "row" treatment is significantly worse than the "column" treatment.

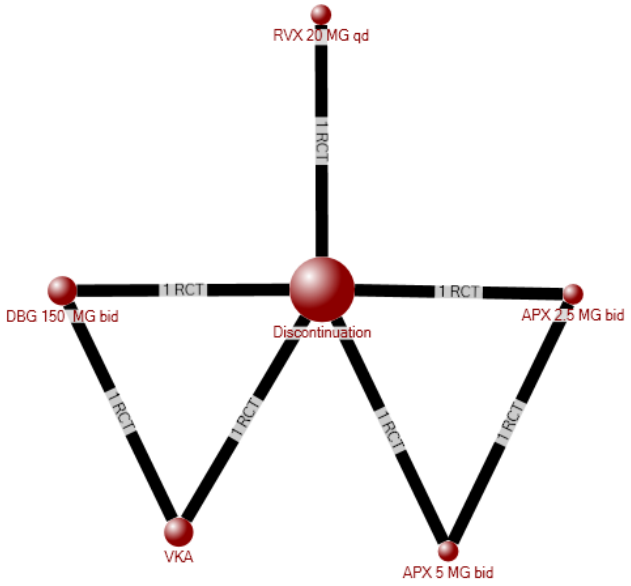
4.2.7. INTRACRANIAL BLEEDS

No studies reported intracranial bleeds during the treatment period.

4.2.8. ALL-CAUSE DEATH

The evidence network for all-cause death included 5 studies (6, 21, 27, 30) and a total of 8064 participants. Overall, 6 different treatments were considered, providing for 7 comparisons based on 4 studies designed with 2 treatment arms and one study with 3 arms (Figure 18).

Figure 188: Evidence network for all-cause death — EXTENDED treatment



There were no significant differences between the DOACs or between DOACs and placebo/discontinuation for all-cause death (Table 26).

Table 26: All-cause death: Hazard ratio (95% CrI) for head-to-head comparisons of DOACs — EXTENDED treatment

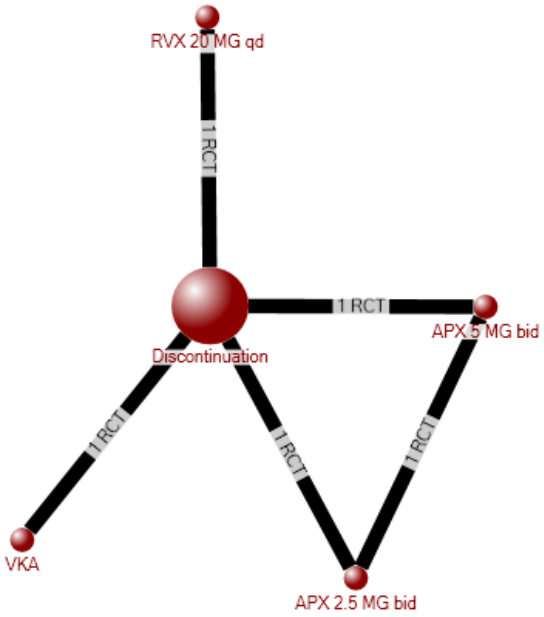
	DISCONT/ Placebo	VKA	DBG 150 mg bid	RVX 20 mg qd	APX 2.5 mg bid	APX 5 mg bid
VKA	0.23 (0.01, 2.79)	—				
DBG 150 mg bid	0.21 (0.01, 2.97)	0.88 (0.10, 7.85)	—			
RVX 20 mg qd	0.43 (0.01, 12.34)	1.73 (0.02, 200.60)	1.97 (0.02, 249.60)	—		
APX 2.5 mg bid	0.46 (0.04, 5.87)	2.02 (0.06, 118.50)	2.22 (0.06, 151.70)	1.12 (0.02, 133.20)	—	
APX 5 mg bid	0.26 (0.02, 3.54)	1.12 (0.03, 66.89)	1.25 (0.03, 84.84)	0.64 (0.01, 80.10)	0.56 (0.04, 7.23)	—

Note: APX = apixaban, ASA = acetylsalicylic acid, DBG = dabigatran, DISCONT = discontinuation, RVX = rivaroxaban, VKA = vitamin k antagonist.

4.2.9. CARDIOVASCULAR DEATH

The evidence network for all-cause death included 3 studies (6, 21, 27) and a total of 3845 participants. Overall, 5 different treatments were considered, providing for 5 comparisons based on 2 studies designed with 2 treatment arms and one study with 3 arms (Figure 19).

Figure 19: Evidence network for CV death — EXTENDED treatment



The risk of CV death was lower among patients taking apixaban at 2.5 mg (HR 0.16, 95% CI 0.05, 0.80) or 5 mg (HR 0.35, 95% CI 0.10, 0.80) compared to patients taking placebo or who discontinued treatment (Table 27).

Table 27: CV death: Hazard ratio (95% CrI) for head-to-head comparisons of DOACs — EXTENDED treatment

	DISCONT/ Placebo	VKA	RVX 20 mg qd	APX 2.5 mg bid	APX 5 mg bid
VKA	0.22 (0.01, 1.08)	—			
RVX 20 mg qd	2.21 (0.04, 21.91)	12.96 (0.16, 526.80)	—		
APX 2.5 mg bid	**0.16 (0.05, 0.80)***	0.95 (0.07, 32.57)	0.10 (0.00, 2.56)	—	
APX 5 mg bid	**0.35 (0.10, 0.80)***	1.38 (0.27, 75.44)	0.19 (0.02, 5.13)	1.87 (0.38, 8.00)	—

Note: APX = apixaban, DBG = dabigatran, DISCONT = discontinuation, RVX = rivaroxaban, VKA = vitamin k antagonist.
*p < 0.05.
Green cells indicate that the "row" treatment is significantly better than the "column" treatment. Red indicates that the "row" treatment is significantly worse than the "column" treatment.

4.2.10. STROKE

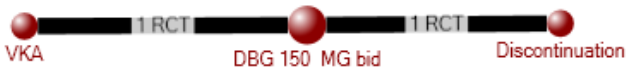
The evidence network for recurrent DVT included 1 study (RESONATE; (30)) and a total of 1353 participants. Overall, 2 different treatments were considered, providing for 2 comparisons based on 1 study with 2 treatment arms, comparing discontinuation/placebo with dabigatran 150 mg bid.

There was no significant difference in the risk of stroke among patients taking dabigatran or those taking placebo or who had discontinued treatment (HR 0.21, 95% CrI 0.00, 11.62).

4.2.11.ACUTE CORONARY SYNDROME

The evidence network for acute coronary syndrome included 2 studies (30) and a total of 4219 participants. Overall, 3 treatments were considered, providing for 2 comparisons based on 2 studies with 2 treatment arms each (Figure 20).

Figure 19: Evidence network acute coronary syndrome — EXTENDED treatment



There was no statistically significant difference between the treatments for the risk of acute coronary syndrome (Table 28).

Table 28: Acute coronary syndrome: Hazard ratios (95% CrI) for head-to-head comparisons of DOACs — EXTENDED treatment

	Discontinuation/ Placebo	VKA	DBG 150 mg bid
VKA	5.70 (0.08, 272.10)	—	
DBG 150 mg bid	4.41 (0.84, 35.46)	0.81 (0.02, 46.74)	—

Note: DBG = dabigatran, VKA = vitamin k antagonist.

5. SUBGROUPS

The subgroups specified a priori were age, weight, renal function, time in therapeutic range, qualifying event (DVT or PE), and comorbidities (diabetes, cardiovascular disease using antiplatelet therapy). Among the ACUTE studies, recurrent VTE was reported for each subgroup (excluding time in therapeutic range), and major bleeding was reported among patients with initial PE or DVT. No other outcomes were reported by subgroup.

Among the EXTENDED studies, recurrent VTE was reported for each subgroup (excluding time in therapeutic range). No other outcomes were reported by subgroup.

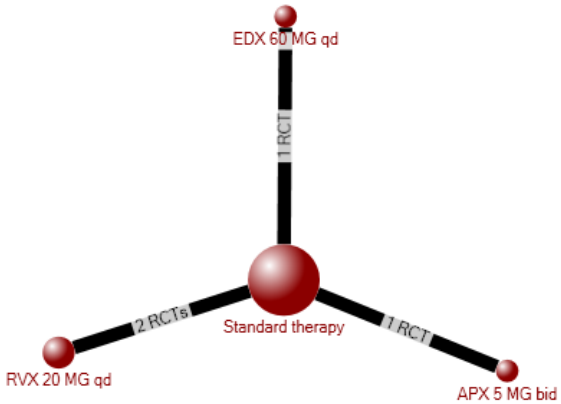
No studies were identified that reported outcomes for patients with diabetes or those with cardiovascular disease using antiplatelet therapy.

5.1. ACUTE TREATMENT

5.1.1. AGE

Recurrent VTE was reported by age group for 4 studies (6, 24-26). The cut-off point of 75 years was chosen based on the data reported in the primary studies. The network geometry is shown in Figure 21.

Figure 20: Evidence network recurrent VTE — ACUTE treatment, age subgroups



Overall, there were no differences in outcomes between patients aged more or less than 75 years; all resulting hazard ratios were not statistically significant in both age groups (Table 29, Table 30).

< 75 YEARS

The network for recurrent VTE among patients aged 75 years or younger included 18,629 patients. Each of the 4 included studies included 2 arms, resulting in 4 comparisons of 4 treatments (Figure 22).

Table 29: Recurrent VTEs among patients aged 75 years or younger: Hazard ratio (95% CrI) for head-to-head comparisons of DOACs — ACUTE treatment

	Standard therapy	RVX 20 mg qd	EDX 60 mg qd	APX 5 mg bid
RVX 20 mg qd	0.98 (0.22,4.44)	—		
EDX 60 mg qd	0.99 (0.12, 7.92)	1.00 (0.07, 12.99)	—	
APX 5 mg bid	0.92 (0.11, 7.76)	0.94 (0.07, 12.45)	0.95 (0.05, 18.56)	—

Note: APX = apixaban, EDX = edoxaban, DBG = dabigatran, RVX = rivaroxaban, VKA = vitamin k antagonist.

> 75 YEARS

The network for recurrent VTE among patients aged 75 years or older included 3136 patients. Each of the 4 included studies included 2 arms, resulting in 4 comparisons of 4 treatments (Figure 22).

Table 30: Recurrent VTEs among patients aged 75 years or older: Hazard ratio (95% CrI) for head-to-head comparisons of DOACs — ACUTE treatment

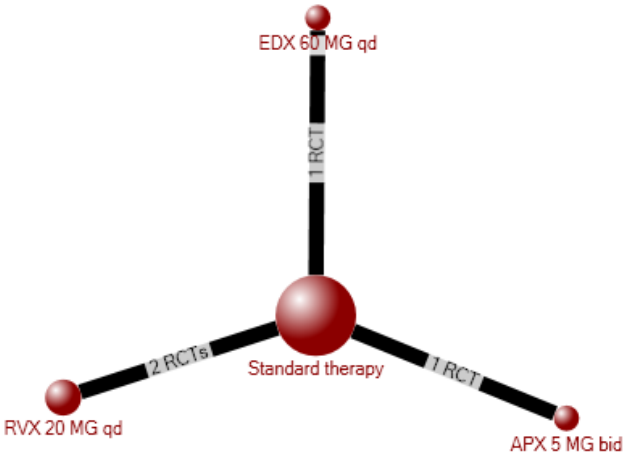
	Standard therapy	RVX 20 mg qd	EDX 60 mg qd	APX 5 mg bid
RVX 20 mg qd	0.60 (0.11, 2.86)	—		
EDX 60 mg qd	0.50 (0.05, 4.66)	0.84 (0.06, 13.65)	—	
APX 5 mg bid	0.47 (0.05, 5.03)	0.81 (0.05, 15.56)	0.94 (0.04, 25.32)	—

Note: APX = apixaban, EDX = edoxaban, RVX = rivaroxaban.

5.1.2. WEIGHT

Recurrent VTE was reported by weight for 4 studies (6, 24-26). The cut-off point of 60 kg years was based on the data reported in the primary studies (Figure 23). Some simplifications were made when combining data. The Einstein DVT (6) and Einstein PE (26) studies both reported data as > 70 kg and < 70 kg — these were included with the > 60 kg and < 60 kg groups respectively.

Figure 21: Evidence network recurrent VTE: — ACUTE treatment, weight subgroups



Overall, there were no differences in outcomes between patients aged who weighted less than or more than 60 kg; all resulting hazard ratios were not statistically significant in both weight groups (Table 31, Table 32).

< 60 KG

The network for recurrent VTE among patients under 60 kg included 3,792 patients. Each of the 4 included studies included 2 arms, resulting in 4 comparisons of 4 treatments (Figure 22).

Table 31: Recurrent VTEs among patients < 60 kg: Hazard ratio (95% CrI) for head-to-head comparisons of DOACs — ACUTE treatment

	Standard therapy	RVX 20 mg qd	EDX 60 mg qd	APX 5 mg bid
RVX 20 mg qd	0.96 (0.17, 5.57)	—		
EDX 60 mg qd	0.79 (0.07, 8.99)	0.83 (0.04, 16.44)	—	
APX 5 mg bid	0.61 (0.05, 7.13)	0.64 (0.03, 12.53)	0.77 (0.02, 23.60)	—

Note: APX = apixaban, EDX = edoxaban, RVX = rivaroxaban.

> 60 KG

The network for recurrent VTE among patients under 60 kg included 17,955 patients. Each of the 4 included studies included 2 arms, resulting in 4 comparisons of 4 treatments (Figure 22).

Table 32: Recurrent VTEs among patients > 60 kg: Hazard ratio (95% CrI) for head-to-head comparisons of DOACs — ACUTE treatment

	Standard therapy	RVX 20 mg qd	EDX 60 mg qd	APX 5 mg bid
RVX 20 mg qd	0.87 (0.21, 3.62)	—		
EDX 60 mg qd	0.90 (0.12, 6.33)	1.04 (0.09, 11.75)	—	
APX 5 mg bid	0.87 (0.12, 6.60)	0.99 (0.08, 12.30)	0.97 (0.06, 16.07)	—

Note: APX = apixaban, EDX = edoxaban, RVX = rivaroxaban.

5.1.3. RENAL FUNCTION

Recurrent VTE was reported by renal function in 3 studies (6, 25, 26). The cut-off point of 80 ml/min is based on normal kidney function and is consistent with data reported in the primary studies. One study was excluded from this analysis because all patients had creatinine clearance less than 80 ml/min (24); the subgroups reported in this study were 30–50 ml/min and > 50 ml/min.

Figure 22: Evidence network recurrent VTE — ACUTE treatment, renal function subgroups

Overall, there were no differences in outcomes between patients with normal or abnormal renal clearance; all resulting hazard ratios were not statistically significant in both renal function groups (Table 33, Table 34).

CREATININE CLEARANCE < 80 ML/MIN

The network for recurrent VTE among patients with creatinine clearance less than 80 ml/min included 4640 patients. Each of the 3 included studies included 2 arms, resulting in 3 comparisons of 3 treatments (Figure 23).

Table 33: Recurrent VTEs among patients with creatinine clearance < 80 ml/min: Hazard ratio (95% CrI) for head-to-head comparisons of DOACs — ACUTE treatment

	Standard therapy	RVX 20 mg qd	APX 5 mg bid
RVX 20 mg qd	0.83 (0.19, 3.60)	—	
APX 5 mg bid	1.09 (0.14, 8.68)	1.30 (0.11, 16.46)	—

Note: APX = apixaban, RVX = rivaroxaban.

CREATININE CLEARANCE > 80 ML/MIN

The network for recurrent VTE among patients with creatinine clearance less than 80 ml/min included 8930 patients. Each of the 3 included studies included 2 arms, resulting in 3 comparisons of 3 treatments (Figure 23).

Table 34: Recurrent VTEs among patients with creatinine clearance > 80 ml/min: Hazard ratio (95% CrI) for head-to-head comparisons of DOACs — ACUTE treatment

	Standard therapy	RVX 20 mg qd	APX 5 mg bid
RVX 20 mg qd	0.95 (0.17, 5.14)	—	
APX 5 mg bid	0.92 (0.08, 10.06)	0.97 (0.05, 18.40)	—

Note: APX = apixaban, RVX = rivaroxaban.

5.1.4. QUALITY OF INR CONTROL (TIME IN THERAPEUTIC RANGE)

One study, HOKUSAI (24), reported recurrent VTE among patients with centre-level INR percent time in therapeutic range (< 60% v. ≥ 60%). Among patients in the < 60% group, recurrent VTEs were reported for 45 of 1271 patients (3.5%) receiving warfarin and 38 of 1199 patients (3.2%) receiving edoxaban. Among patients in the ≥ 60% group, VTEs recurred in 101 of 2845 patients (3.6%) receiving warfarin and 89 of 2876 patients (3.1%) receiving edoxaban.

One abstract reporting on the EINSTEIN-DVT trial (33) reported the incidence of recurrent VTE in the rivaroxaban and VKA groups in relation to adjusted time in therapeutic range per center. The authors defined “adjusted time in therapeutic range per center” as excluding INRs where VKA therapy was intentionally interrupted (including the period of 8 days after restart), where heparins or fondaparinux were used, after a primary efficacy outcome or major bleeding.

The adjusted TTR (INR 2.0–3.0) was 55.4% in the 3-month group, 60.1% in the 6-month group, and 62.8% in the 12-month groups. The hazard ratio for recurrent VTE in centers with mean 'adjusted' TTR < 55.9% was 0.78 (95% CI 0.38, 1.63); the hazard ratio in centers with mean adjusted TTR between 55.9% and 65.3% was 0.68 (95% CI 0.29, 1.59) and was 0.68 (95% CI 0.35, 1.35) in centers with mean adjusted TTR greater than 65.3%.

The data were not sufficiently similar for pooling.

5.1.5. COMORBIDITIES

No studies were identified that reported recurrent VTEs or other outcomes among patients with diabetes or cardiovascular disease taking antiplatelet therapy.

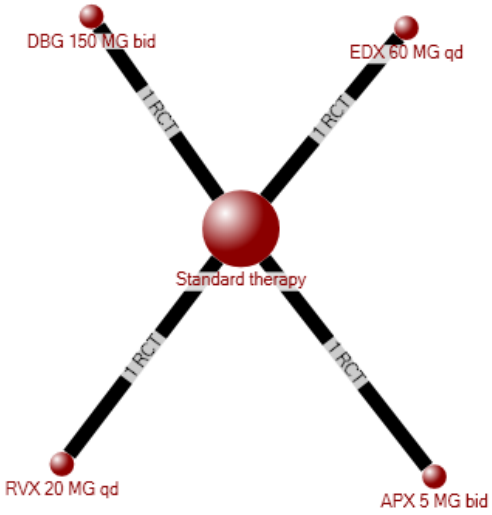
5.1.6. INITIAL DVT

RECURRENT VTE

Recurrent VTE was reported among patients with DVT as the qualifying event in 4 studies (6, 22, 24, 25). The Einstein DVT study enrolled patients only with DVT, while the other studies report events among patients with initial DVT as a subgroup.

The network for recurrent VTE among patients with initial DVT included 13,557 patients. Each of the 4 included studies included 2 arms, resulting in 4 comparisons of 5 treatments (Figure 24).

Figure 23: Evidence network recurrent VTE — ACUTE treatment, initial DVT subgroup



There were no significant differences in the risk of recurrent VTE among the DOACs in the head-to-head comparisons or compared to standard therapy among patients with initial DVT (Table 35).

Table 35: Recurrent VTEs among patients with initial DVT: Hazard ratio (95% CrI) for head-to-head comparisons of DOACs — ACUTE treatment

	Standard therapy	RVX 20 mg qd	DBG 150 mg bid	EDX 60 mg qd	APX 5 mg bid
RVX 20 mg qd	0.81 (0.06, 10.50)	—			

	Standard therapy	RVX 20 mg qd	DBG 150 mg bid	EDX 60 mg qd	APX 5 mg bid
DBG 150 mg bid	1.34 (0.10, 17.44)	1.66 (0.05, 62.59)	—		
EDX 60 mg qd	0.99 (0.08, 12.51)	1.25 (0.03, 42.60)	0.74 (0.02, 26.91)	—	
APX 5 mg bid	0.83 (0.06, 10.57)	1.02 (0.03, 39.85)	0.62 (0.02, 24.77)	0.83 (0.02, 31.98)	—

Note: APX = apixaban, DBG = dabigatran, EDX = edoxaban, RVX = rivaroxaban.

MAJOR BLEEDS

Major bleeds were reported among patients with DVT as the qualifying event in 2 studies (6, 25). Einstein DVT enrolled patients only with DVT, while AMPLIFY reported events among patients with initial DVT as a subgroup.

The network for major bleeds among patients with initial DVT included 6960 patients. Both of the included studies had 2 arms, resulting in 2 comparisons of 3 treatments (Figure 25).

Figure 24: Evidence network for major bleeds — ACUTE treatment, initial DVT subgroup

There were no significant differences in the risk of major bleeds among the DOACs in the head-to-head comparisons or compared to standard therapy among patients with initial DVT (Table 36).

Table 36: Major bleeds among patients with initial DVT: Hazard ratio (95% CrI) for head-to-head comparisons of DOACs — ACUTE treatment

	Standard therapy	RVX 20 mg qd	APX 5 mg bid
RVX 20 mg qd	0.62 (0.05, 7.92)	—	
APX 5 mg bid	0.46 (0.03, 6.12)	0.75 (0.02, 29.93)	—

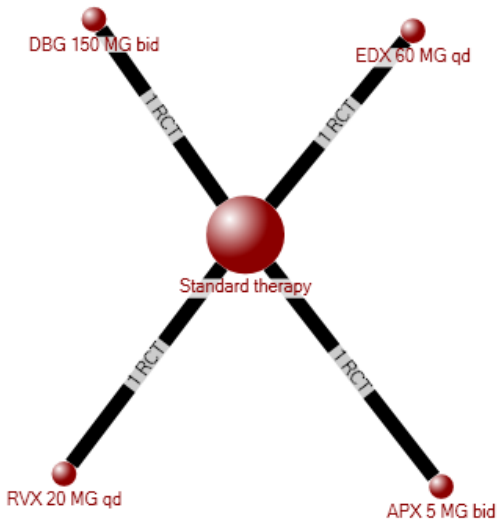
Note: APX = apixaban, RVX = rivaroxaban.

5.1.7. INITIAL PE

Recurrent VTE was reported among patients with PE as the qualifying event in 4 studies (22, 24-26). EINSTEIN-PE enrolled patients only with PE, while the other studies report events among patients with initial PE as a subgroup.

The network for recurrent VTE among patients with initial PE included 10,724 patients. Each of the 4 included studies included 2 arms, resulting in 4 comparisons of 5 treatments (Figure 26).

Figure 25: Evidence network recurrent VTE — ACUTE treatment, initial PE subgroup



There were no significant differences in the risk of recurrent VTEs among the DOACs in the head-to-head comparisons or compared to standard therapy among patients with initial PE (Table 37).

Table 37: Recurrent VTEs among patients with initial PE: Hazard ratio (95% CrI) for head-to-head comparisons of DOACs — ACUTE treatment

	Standard therapy	RVX 20 mg qd	DBG 150 mg bid	EDX 60 mg qd	APX 5 mg bid
RVX 20 mg qd	1.19 (0.09, 15.75)	—			
DBG 150 mg bid	0.85 (0.06, 11.30)	0.71 (0.02, 28.19)	—		
EDX 60 mg qd	0.72 (0.06, 9.06)	0.61 (0.02, 21.78)	0.84 (0.02, 32.15)	—	
APX 5 mg bid	0.91 (0.07, 11.73)	0.76 (0.02, 29.48)	1.08 (0.03, 44.41)	1.26 (0.03, 48.44)	—

Note: APX = apixaban, DBG = dabigatran, EDX = edoxaban, RVX = rivaroxaban.

MAJOR BLEEDS

Major bleeds were reported among patients with PE as the qualifying event in 2 studies (25, 26). EINSTEIN PE enrolled patients only with PE, while AMPLIFY reported events among patients with initial PE as a subgroup.

The network for major bleeds among patients with initial DVT included 6960 patients. Both of the included studies had 2 arms, resulting in 2 comparisons of 3 treatments (Figure 27).

Figure 26: Evidence network for major bleeds — ACUTE treatment, initial PE subgroup

There were no significant differences in the risk of major bleeds among the DOACs in the head-to-head comparisons or compared to standard therapy among patients with initial PE (Table 38).

Table 38: Major bleeds among patients with initial DVT: Hazard ratio (95% CrI) for head-to-head comparisons of DOACs — ACUTE treatment

	Standard therapy	RVX 20 mg qd	APX 5 mg bid
RVX 20 mg qd	0.52 (0.04, 6.41)	—	
APX 5 mg bid	0.14 (0.01, 2.05)	0.28 (0.01, 11.36)	—

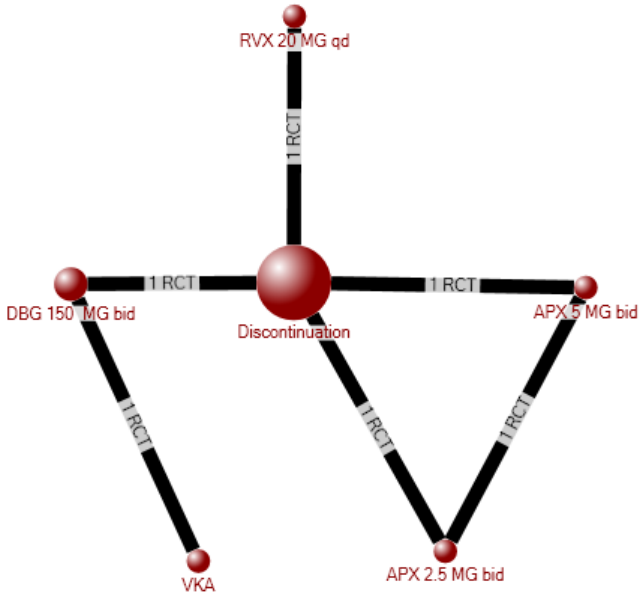
Note: APX = apixaban, RVX = rivaroxaban.

5.2. EXTENDED TREATMENT

5.2.1. AGE

Recurrent VTE was reported by age group for 4 studies (6, 21, 30). The cut-off point of 75 years was based on the data reported in the primary studies. RE-SONATE (30) reported patients aged less than or greater than 65 years; these were grouped with those aged less than or greater than 75 years respectively. There were differences in the risk of recurrent VTE between patients aged more or less than 75 years; these are outlined below (Table 39, Table 40; Figure 28).

Figure 27: Evidence network recurrent VTE — EXTENDED treatment, age subgroups



< 75 YEARS

The network for recurrent VTE among patients aged 75 years or younger included 6649 patients. Three of the included studies had 2 treatment arms and one study had 3 arms, resulting in 6 comparisons of 6 treatments (Figure 28).

There were no significant differences among the treatments in the head-to-head comparisons or compared to placebo/discontinuation among patients aged less than 75 years (Table 39).

Table 39: Recurrent VTEs among patients aged 75 years or younger: Hazard ratio (95% CrI) for head-to-head comparisons of DOACs — EXTENDED treatment

	DISCONT/ placebo	VKA	DBG 150 mg bid	RVX 20 mg qd	APX 2.5 mg bid	APX 5 mg bid
VKA	0.06 (0.00, 2.74)	—				
DBG 150 mg bid	0.09 (0.00, 1.51)	1.48 (0.11, 19.37)	—			
RVX 20 mg qd	0.21 (0.01, 2.95)	3.49 (0.03, 387.40)	2.34 (0.05, 120.00)	—		
APX 2.5 mg bid	0.16 (0.01, 2.04)	2.55 (0.02, 280.80)	1.72 (0.04, 92.99)	0.74 (0.02, 28.71)	—	
APX 5 mg bid	0.21 (0.02, 2.72)	3.50 (0.04, 417.80)	2.37 (0.05, 131.90)	1.02 (0.03, 40.72)	1.36 (0.10, 20.14)	—

Note: APX = apixaban, DBG = dabigatran, DISCONT = discontinuation, RVX = rivaroxaban, VKA = vitamin K antagonist.

> 75 YEARS

The network for recurrent VTE among patients aged 75 years or older included 3136 patients. Each of the 4 included studies included 2 arms, resulting in 4 comparisons of 4 treatments (Figure 28).

Compared with placebo or discontinuation, the risk of recurrent VTE was lower among patients taking dabigatran (HR 0.08, 95% CI 0.02, 0.22), rivaroxaban (HR 0.09, 95% CI 0.02, 0.77), apixaban 2.5 mg (HR 0.34, 95% CI 0.13, 0.97), and apixaban 5 mg (HR 0.10, 95% CI 0.02, 0.26) (Table 40). There were no significant differences among the treatments in the head-to-head comparisons.

Table 40: Recurrent VTEs among patients aged 75 years or older — Hazard ratio (95% CrI) for head-to-head comparisons of DOACs — EXTENDED treatment

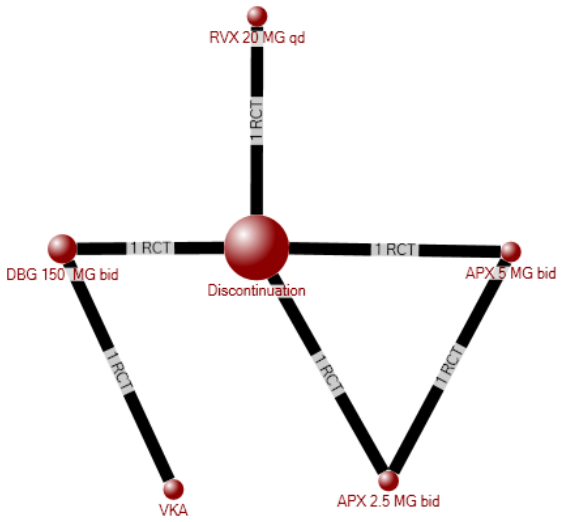
	DISCONT/ placebo	VKA	DBG 150 mg bid	RVX 20 mg qd	APX 2.5 mg bid	APX 5 mg bid
VKA	0.04 (0.00, 1.09)	—				
DBG 150 mg bid	**0.08 (0.02, 0.22)***	1.35 (0.07, 31.23)	—			
RVX 20 mg qd	**0.09 (0.02, 0.77)***	3.38 (0.03, 112.20)	1.45 (0.16, 15.37)	—		
APX 2.5 mg bid	**0.34 (0.13, 0.97)***	9.22 (0.20, 278.60)	4.88 (0.87, 32.14)	3.65 (0.26, 29.25)	—	
APX 5 mg bid	**0.10 (0.02, 0.26)***	2.01 (0.15, 153.30)	1.29 (0.16, 7.67)	1.07 (0.05, 7.60)	0.27 (0.05, 1.08)	—

Note: APX = apixaban, DBG = dabigatran, DISCONT = discontinuation, RVX = rivaroxaban, VKA = vitamin K antagonist.
*p < 0.05.
Green cells indicate that the "row" treatment is significantly better than the "column" treatment. Red indicates that the "row" treatment is significantly worse than the "column" treatment.

5.2.2. WEIGHT

Recurrent VTE was reported by weight for 4 studies (6, 21, 30). The cut-off point of 60 kg years was based on the data reported in the primary studies. Some simplifications were made when combining data. The EINSTEIN DVT (6) study reported weight subgroup data as > 70 kg and < 70 kg, which were included with the > 60 kg and < 60 kg groups, respectively. The RE-SONATE and RE-MEDY studies (30) reported weight subgroups as < 50 kg and > 50 kg; these were grouped with the > 60 kg and < 60 kg groups, respectively.

Figure 29: Evidence network recurrent VTE —EXTENDED treatment, weight subgroups



< 60 KG

The network for recurrent VTE among patients under 60 kg included 490 patients. Three of the included studies had two arms, and one study had three arms, resulting in 6 comparisons of 6 treatments (Figure 29).

Compared to discontinuation or placebo, the risk of recurrent VTE was significantly lower among patients taking rivaroxaban (HR 0.34, 95% CI 0.14, 0.95), apixaban 2.5 mg (HR 0.08, 95% CI 0.02, 0.36), or apixaban 5 mg (HR 0.36, 95% CI 0.16, 0.86) (Table 41). There were no significant differences in the head-to-head comparisons of the treatments.

Table 41: Recurrent VTEs among patients < 60 kg: Hazard ratio (95% CrI) for head-to-head comparisons of DOACs — EXTENDED treatment

	DISCONT/ placebo	VKA	DBG 150 mg bid	RVX 20 mg qd	APX 2.5 mg bid	APX 5 mg bid
VKA	0.34 (0.00, 28.61)	—				
DBG 150 mg bid	0.90 (0.04, 4.37)	0.95 (0.04, 606.40)	—			
RVX 20 mg qd	**0.34 (0.14, 0.95)***	1.44 (0.01, 263.80)	0.40 (0.07, 7.11)	—		
APX 2.5 mg bid	**0.08 (0.02, 0.36)***	0.21 (0.00, 27.22)	0.07 (0.01, 8.60)	0.24 (0.03, 1.32)	—	
APX 5 mg bid	**0.36 (0.16, 0.86)***	0.98 (0.02, 163.10)	0.40 (0.08, 18.71)	1.02 (0.26, 4.22)		—

Note: APX = apixaban, DBG = dabigatran, DISCONT = discontinuation, RVX = rivaroxaban, VKA = vitamin K antagonist.
Green cells indicate that the "row" treatment is significantly better than the "column" treatment. Red indicates that the "row" treatment is significantly worse than the "column" treatment.

> 60 KG

The network for recurrent VTE among patients under 60 kg included 7344 patients. Three of the included studies had two arms, and one study had three arms, resulting in 6 comparisons of 6 treatments.

The risk of recurrent VTE was significantly lower among patients taking VKA, dabigatran, rivaroxaban and apixaban compared to discontinuation or placebo (Table 42). The risk of recurrent VTE was significantly higher among patients taking apixaban at 2.5 mg or 5 mg bid than among those taking VKA (Figure 29).

Table 42: Recurrent VTEs among patients > 60 kg: Hazard ratio (95% CrI) for head-to-head comparisons of DOACs — EXTENDED treatment

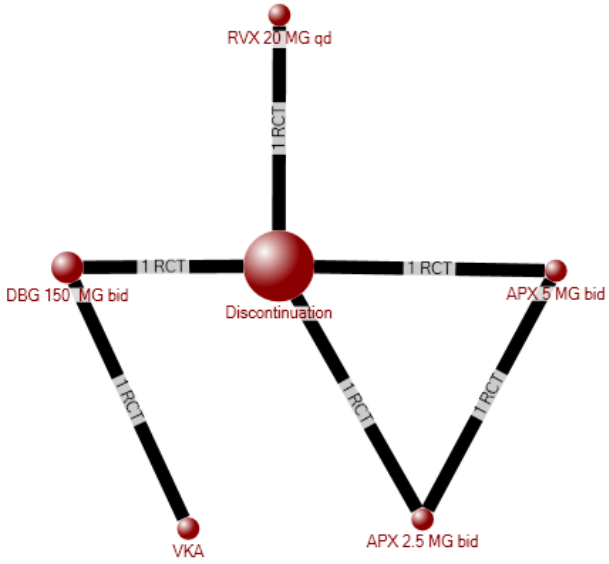
	DISCONT/ placebo	VKA	DBG 150 mg bid	RVX 20 mg qd	APX 2.5 mg bid	APX 5 mg bid
VKA	**0.04 (0.01, 0.16)***	—				
DBG 150 mg bid	**0.06 (0.02, 0.21)***	1.51 (0.81, 2.70)	—			
RVX 20 mg qd	**0.22 (0.05, 0.53)***	5.39 (0.89, 27.61)	3.53 (0.63, 17.45)	—		
APX 2.5 mg bid	**0.20 (0.10, 0.36)***	**5.19 (1.32, 20.04)***	3.63 (0.91, 10.13)	0.97 (0.30, 4.04)		
APX 5 mg bid	**0.17 (0.09, 0.32)***	**4.25 (1.32, 15.52)***	2.97 (0.94, 8.52)	0.75 (0.31, 3.56)	0.87 (0.40, 1.82)	—

Note: APX = apixaban, DBG = dabigatran, DISCONT = discontinuation, RVX = rivaroxaban, VKA = vitamin K antagonist.
*p < 0.05.
Green cells indicate that the "row" treatment is significantly better than the "column" treatment. Red indicates that the "row" treatment is significantly worse than the "column" treatment.

5.2.3. RENAL FUNCTION

Recurrent VTE was reported by renal function in 4 studies (6, 21, 30). The cut-off point of 80 ml/min (creatinine clearance) was chosen based on normal kidney function and is consistent with data reported in the primary studies.

Figure 28: Evidence network recurrent VTE — EXTENDED treatment, renal function subgroups



CREATININE CLEARANCE < 80 ML/MIN

The network for recurrent VTE among patients with creatinine clearance less than 80 ml/min included 2146 patients (Figure 30). Three of the included studies had two arms, and one study had three arms, resulting in 6 comparisons of 6 treatments.

There were no significant differences between any of the treatments and discontinuation or placebo, or between any of the treatments in head-to-head comparisons (Table 43).

Table 43: Recurrent VTEs among patients with creatinine clearance < 80 ml/min: Hazard ratio (95% CrI) for head-to-head comparisons of DOACs — EXTENDED treatment

	DISCONT/ placebo	VKA	DBG 150 mg bid	RVX 20 mg qd	APX 2.5 mg bid	APX 5 mg bid
VKA	0.95 (0.24, 2.59)	—				
DBG 150 mg bid	0.68 (0.38, 1.77)	0.77 (0.54, 1.85)	—			
RVX 20 mg qd	0.48 (0.19, 3.18)	0.83 (0.33, 1.29)	0.77 (0.46, 2.16)	—		
APX 2.5 mg bid	0.48 (0.31, 4.03)	1.26 (0.32, 1.81)	0.86 (0.52, 2.85)	1.42 (0.64, 1.99)	—	
APX 5 mg bid	0.39 (0.25, 2.31)	0.90 (0.21, 1.22)	0.75 (0.34, 1.94)	0.96 (0.51, 1.60)	0.73 (0.52, 1.19)	—

Note: APX = apixaban, DBG = dabigatran, DISCONT = discontinuation, RVX = rivaroxaban, VKA = vitamin K antagonist.

CREATININE CLEARANCE > 80 ML/MIN

The network for recurrent VTE among patients with creatinine clearance above 80 ml/min included 5522 patients. Three of the included studies had two arms, and one study had three arms, resulting in 6 comparisons of 6 treatments (Figure 30).

The risk of recurrent VTE was lower among patients taking dabigatran than among those taking placebo or who discontinued treatment (HR 0.40, 95% CrI 0.20, 0.88) (Table 44). In head-to-head comparisons, the risk of recurrent VTE was greater among patients taking rivaroxaban than among those taking VKA (HR 7.79, 95% CI 4.89, 18.07) or dabigatran (HR 8.13, 95% CI 4.89, 19.61). The risk of recurrence was lower among those taking apixaban at 2.5 mg (HR 0.11, 95% CI 0.05, 0.24) or 5 mg (HR 0.09, 95% CI 0.05, 0.16) than among those taking rivaroxaban (Figure 33).

Table 44: Recurrent VTEs among patients with creatinine clearance > 80 ml/min: Hazard ratio (95% CrI) for head-to-head comparisons of DOACs — EXTENDED treatment

	DISCONT/ placebo	VKA	DBG 150 mg bid	RVX 20 mg qd	APX 2.5 mg bid	APX 5 mg bid
VKA	0.45 (0.21, 1.01)	—				
DBG 150 mg bid	**0.40 (0.20, 0.88)***	0.92 (0.78, 1.10)	—			
RVX 20 mg qd	**2.81 (1.70, 9.61)***	**7.79 (4.48, 18.07)***	**8.13 (4.89, 19.61)***	—		
APX 2.5 mg bid	0.28 (0.16, 2.13)	0.92 (0.31, 2.39)	0.94 (0.32, 2.52)	**0.11 (0.05, 0.24)***	—	
APX 5 mg bid	0.31 (0.12, 1.39)	0.74 (0.39, 1.49)	0.80 (0.43, 1.61)	**0.09 (0.05, 0.16)***	0.67 (0.44, 2.02)	—

Note: APX = apixaban, DBG = dabigatran, DISCONT = discontinuation, RVX = rivaroxaban, VKA = vitamin K antagonist.
*p < 0.05.
Green cells indicate that the "row" treatment is significantly better than the "column" treatment. Red indicates that the "row" treatment is significantly worse than the "column" treatment.

5.2.4. COMORBIDITIES

No studies were identified that reported recurrent VTEs or other outcomes among patients with diabetes or cardiovascular disease taking antiplatelet therapy.

5.2.5. QUALITY OF INR CONTROL/TIME IN THERAPEUTIC RANGE

No studies were identified that reported outcome data by the quality of INR control or time in therapeutic range.

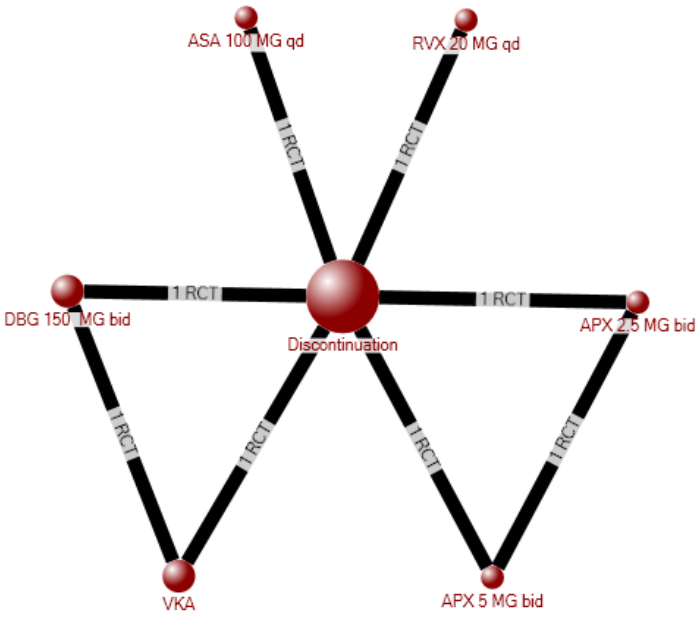
5.2.6. INITIAL DVT

RECURRENT VTE

Recurrent VTE was reported among patients with DVT as the qualifying event in 6 studies (6, 21, 28, 30, 31). EINSTEIN (6) and WODIT-DVT (28) enrolled patients only with DVT, while the other studies report events among patients with initial DVT as a subgroup.

The network for recurrent VTE among patients with initial DVT included 6100 patients. Six studies were included: 5 with 2 arms and 1 with 3 arms, resulting in 8 comparisons of 7 treatments (Figure 31).

Figure 29: Evidence network recurrent VTE — EXTENDED treatment, initial DVT subgroup



VKA and dabigatran reduced the risk of recurrent VTE relative to discontinuation/placebo (HR 0.08, 95% CI 0.01, 0.63; HR 0.10, 95% CI 0.01, 0.70, respectively) (Table 45). There were no significant differences in the risk of recurrent VTE among the DOACs in the head-to-head comparisons among patients with initial DVT.

Table 45: Recurrent VTEs among patients with initial DVT: Hazard ratio (95% CrI) for head-to-head comparisons of DOACs — EXTENDED treatment

	DISCONT/ placebo	VKA	DBG 150 mg bid	ASA 100 mg qd	RVX 20 mg qd	APX 2.5 mg bid	APX 5 mg bid
VKA	**0.08 (0.01, 0.63)***	—					
DBG 150 mg bid	**0.10 (0.01, 0.70)***	1.15 (0.18, 9.25)	—				
ASA 100 mg qd	0.67 (0.07, 6.43)	7.82 (0.37, 219.80)	6.72 (0.32, 150.20)	—			
RVX 20 mg qd	0.18 (0.02, 1.83)	2.17 (0.11, 58.64)	1.83 (0.09, 41.10)	0.27 (0.01, 7.28)	—		
APX 2.5 mg bid	0.11 (0.01, 1.10)	1.29 (0.06, 34.08)	1.10 (0.05, 24.33)	0.16 (0.01, 4.07)	0.59 (0.02, 16.03)	—	
APX 5 mg bid	0.19 (0.02, 1.84)	2.25 (0.12, 58.80)	1.92 (0.09, 42.84)	0.28 (0.01, 7.33)	1.05 (0.04, 26.51)	1.78 (0.16, 20.06)	—

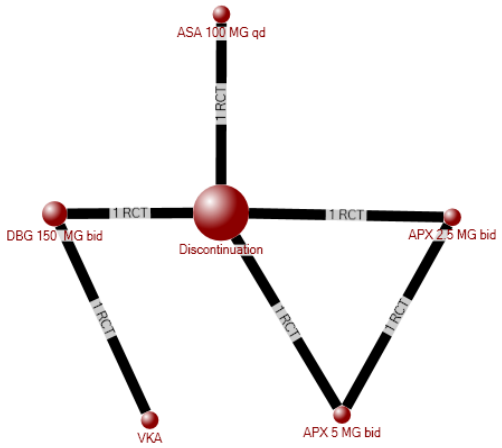
Note: APX = apixaban, ASA = acetylsalicylic acid, DBG = dabigatran, DISCONT = discontinuation, RVX = rivaroxaban, VKA = vitamin K antagonist.
*p < 0.05.
Green cells indicate that the "row" treatment is significantly better than the "column" treatment. Red indicates that the "row" treatment is significantly worse than the "column" treatment.

5.2.7. INITIAL PE

Recurrent VTE was reported among patients with PE as the qualifying event in 6 studies (21, 30-32, 34). EINSTEIN-PE and WODIT-PE enrolled patients only with PE, while the other studies report events among patients with initial PE as a subgroup.

The network for recurrent VTE among patients with initial PE included 2,447 patients. This network involved 4 studies: three with 2 arms and one with 3 arms, resulting in 6 comparisons of 6 treatments (Figure 32).

Figure 30: Evidence network recurrent VTE — EXTENDED treatment, initial PE subgroup



Compared with discontinuation or placebo, the risk of recurrent VTE was significantly reduced among patients taking VKA (HR 0.02, 95% CI 0.00, 0.10), dabigatran (HR 0.03, 95% CI 0.00, 0.19), apixaban 2.5 mg (HR 0.34, 95% CI 0.13, 0.74), and apixaban 5 mg (HR 0.19, 95% CI 0.07, 0.47) (Table 46).

Compared to patients taking VKA, the risk of recurrent VTE was increased among patients taking ASA (HR 35.37, 95% CI 3.97, 357.30), apixaban 2.5 mg (HR 19.04, 95% CI 2.59, 269.50), and apixaban 5 mg (HR 10.39, 95% CI 1.61, 210.00). The risk was also increased among patients taking ASA (HR 18.01, 95% CI 1.90, 141.90) or apixaban 2.5 mg (9.98, 95% CI 1.43, 94.43) relative to those taking dabigatran.

Table 46: Recurrent VTEs among patients with initial PE: Hazard ratio (95% CrI) for head-to-head comparisons of DOACs — EXTENDED treatment

	DISCONT/ placebo	VKA	DBG 150 mg bid	ASA 100 mg qd	APX 2.5 mg bid	APX 5 mg bid
VKA	**0.02 (0.00, 0.10)***	—				
DBG 150 mg bid	**0.03 (0.00, 0.19)***	2.05 (0.91, 4.51)	—			
ASA 100 mg qd	0.57 (0.27, 1.29)	**35.37 (3.97, 357.30)***	**18.01 (1.90, 141.90)***	—		
APX 2.5 mg bid	**0.34 (0.13, 0.74)***	**19.04 (2.59, 269.50)***	**9.98 (1.43, 94.43)***	0.60 (0.17, 1.74)	—	
APX 5 mg bid	**0.19 (0.07, 0.47)***	**10.39 (1.61, 210.00)***	5.10 (0.80, 71.59)	0.32 (0.09, 1.12)	0.55 (0.18, 1.70)	—

Note: APX = apixaban, ASA = acetylsalicylic acid, DBG = dabigatran, DISCONT = discontinuation, RVX = rivaroxaban, VKA = vitamin K antagonist.
*p < 0.05.
Green cells indicate that the "row" treatment is significantly better than the "column" treatment. Red indicates that the "row" treatment is significantly worse than the "column" treatment.

6. DISCUSSION

Venous thromboembolism is estimated to affect 34,500 Canadians each year and is associated with significant health impact, for patients, their caregivers, and the health care system. Traditional treatment with an injectable heparin product (heparin or low-molecular weight heparin) followed by an oral vitamin K antagonist (VKA) is associated with a 5%–10% risk of VTE recurrence during the first year; however, the risk of recurrence must be balanced with the risk of long-term bleeding. Direct oral anticoagulants are approved in Canada for treatment of VTEs and prevention of recurrent VTEs; DOACs do not require the same laboratory monitoring requirements as oral VKA, and are less prone to dietary and drug interactions compared to VKA. They are, however, more expensive and there is less clinical experience with these agents.

In this study, we evaluated the current evidence for the efficacy and harms of DOACs compared to current standard therapy (heparin followed by oral VKA) for the acute and extended treatment of VTE. We performed a broad systematic review and network meta-analysis to assess the efficacy (prevention of recurrent VTE, DVT, PE) and safety (major and intracranial bleeding, all-cause death, cardiovascular death, MACE, stroke, ACS) based on evidence from randomized controlled trials. No data were located for MACE among acute treatment studies.

ACUTE TREATMENT OF VTE

Among the studies that assessed the acute treatment of VTE, we found no significant differences in the risk of efficacy or safety outcomes between any of the treatments compared with placebo. There were no significant differences between the DOACs for prevention of recurrent VTE, recurrent DVT, recurrent PE (fatal or non-fatal) or for risk of major bleeds, intracranial bleeds, death (all-cause or cardiovascular), or stroke.

EXTENDED TREATMENT OF VTE

Comparison with placebo or discontinuation:

- VKA was associated with a reduced risk of recurrent VTE, DVT, and PE. However, there was an increased risk of major bleeding. There were no differences for all-cause death, CV death, or ACS.
- Dabigatran was associated with a reduced risk of recurrent VTE, DVT, and PE. There was no difference in the risk of major bleeding compared with placebo, and there were no differences in risk for all-cause death, stroke, or ACS.
- Rivaroxaban was associated with an increased risk of major bleeding, and no differences in risk for recurrent VTE, DVT, PE, or death.
- ASA was associated with no significant differences in risk for recurrent VTE, PE, or major bleeds.

- Apixaban (2.5, 5 mg) was associated with no significant differences in risk for recurrent VTE, PE, major bleeds, or death (all-cause or CV).

Head-to-head comparisons:

- ASA was associated with an increased risk of recurrent VTE compared with VKA
- Rivaroxaban was associated with an increased risk of recurrent DVT compared to VKA
- Rivaroxaban was associated with an increased risk of major bleeds compared with VKA, dabigatran, and ASA. Apixaban (2.5 and 5 mg) was associated with a lower risk of major bleed compared to VKA and rivaroxaban. Apixaban 5 mg was associated with a lower risk of major bleed compared to VKA, dabigatran, and rivaroxaban.

6.1. LIMITATIONS

Our study has several limitations that warrant discussion. First, despite the inclusion of several large trials, there was limited evidence for the use of some DOACs in the extended treatment of VTEs, resulting in wide credible intervals for some outcomes. For example, although rivaroxaban was associated with an increased risk of major bleeding relative to placebo (HR 40.13), the 95% credible interval was wide (4.20–395.30). This was primarily due to the limited number of events in the analysis. Only one included trial evaluated rivaroxaban, with zero major bleeds in the placebo arm and 4 in the rivaroxaban arm, resulting in a wide credible interval.

Second, although we analyzed the data according to a priori defined subgroups, limited data were available for these comparisons. The subgroups of interest were age, quality of INR control/time in therapeutic range, weight, renal function, and co-morbidities (diabetes, cardiovascular disease using antiplatelet therapy). No data were identified for patients with diabetes or with cardiovascular disease using antiplatelet therapy. Only one study reported outcome data by quality of INR control, and the data were summarized narratively. The estimates for efficacy and safety for subgroups should be interpreted with caution because they are based on limited data.

Third, no data were identified for the composite outcome MACE; as such, we cannot comment on whether there is a difference in risk between DOACs and standard care for this outcome.

7. KEY MESSAGES

7.1. ACUTE TREATMENT

- There were no significant differences between any of the DOACs and standard therapy for recurrent VTE, recurrent PE, recurrent DVT, major bleeds, intracranial hemorrhage, all-cause death, cardiovascular death, stroke, or acute coronary syndrome.

- There were no differences in recurrent VTE by age, weight, or renal function.

7.2. EXTENDED TREATMENT

- Compared to discontinuation or placebo, patients taking VKA a lower risk of recurrent VTE, DVT and PE, but a higher risk of major bleeding.
- Compared to discontinuation or placebo, patients taking dabigatran had a lower risk of recurrent VTE, DVT =m and PE, with no increased risk of major bleeding.
- There were no significant differences between any of the DOACs and placebo/discontinuation for all-cause death, cardiovascular death, stroke, acute coronary syndrome.
- Compared with VKA, ASA was associated with an increased risk of recurrent VTE.
- Compared with VKA, rivaroxaban was associated with an increased risk of recurrent DVT.
- "The risk of major bleeding was lower among patients taking 5 mg APX compared with VKA, DBG or RVX. The risk of major bleeding was lower among patients taking 2.5 mg APX compared with VKA and RVX".
- There were no differences among the DOACs in recurrent VTE by age (< 75 v. >75 yr).
- Compared with discontinuation or placebo, the risk of recurrent VTE was lower among patients who weigh more than 60 kg taking VKA, dabigatran, rivaroxaban, or apixaban. Among patients who weigh less than 60 kg, the risk was lower among patients taking rivaroxaban or apixaban; However, the risk between stratum (>60 kg vs < 60 kg) were not statistically different. The risk of recurrent VTE was higher among patients who weigh more than 60 kg taking apixaban (2.5 or 5 mg bid) compared to VKA; there was no difference in risk among patients who weigh less than 60 kg.
- The risk of recurrent VTE was increased among patients taking rivaroxaban compared with VKA or dabigatran among patients with creatinine clearance above 80 ml/min but not less than 80 ml/min. The risk of recurrent VTE was lower among patients taking apixaban (2.5 and 5 mg) compared with rivaroxaban among patients with creatinine clearance above 80 ml/min but not less than 80 ml/min.

8. REFERENCES

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APPENDIX 1: SEARCH STRATEGY

VTE DVT PE NOACs – Network Meta-Analysis
Final – Multifile + Cochrane
2014 Nov 5

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present>, Embase <1980 to 2014 Week 44> Search Strategy:
---

1 Venous Thromboembolism/ (24963)
2 ((venous or vein$1 or vena) adj2 (thromboemboli* or thrombo-emboli*)).tw. (33936)
3 (VTE or VTEs).tw. (15087)
4 exp Venous Thrombosis/ (135524)
5 ((venous or vein$1 or vena) adj2 thrombos*).tw. (90211)
6 (("deep venous" or "deep vein") adj2 (thrombus or thrombophlebitis or "thrombo-phlebitis")).tw. (535)
7 (DVT or DVTs).tw. (18078)
8 (phlebothrombos* or phlebo-thrombos*).tw. (1038)
9 exp Pulmonary Embolism/ (93355)
10 ((pulmonary or lung or lungs) adj2 (emboli* or embolus or emboly or microemboli* or micro-emboli* or microembolus or micro-embolus or microemboly or micro-emboly or thromboemboli* or thrombo-emboli*)).tw. (74669)
11 or/1-10 (263652)
12 ((new or novel) adj1 (oral anticoagulant* or oral anti-coagulant*)).tw. (3290)
13 (NOA or NOAs or NOAC or NOACs).tw. (2091)
14 ((new or novel) adj1 (direct oral anticoagulant* or direct oral anti-coagulant*)).tw. (76)
15 (DOAC or DOACs).tw. (112)
16 (Apixaban or BMS 562247 or BMS562247 or Eliques or Eliquis).tw. (2402)
17 apixaban.rn. (3128)
18 (Dabigatran or Pradax or Pradaxa or Prazaxa or Rendix).tw. (5394)
19 dabigatran.rn. (910)
20 (Rivaroxaban or BAY 59-7939 or BAY59-7939 or HSDB 5717 or Xarelto or UNII-9NDF7JZ4M3).tw. (4339)
21 rivaroxaban.rn. (4844)
22 (Edoxaban or DU176 or DU-176 or DU176b or DU-176b or Savaysa or UNII-NDU3J18APO).tw. (764)
23 edoxaban.rn. (792)
24 exp Heparin, Low-Molecular-Weight/ (53231)
25 LMWH.tw. (9187)
26 ((low molecular or low molecular weight or LMW) adj1 heparin).tw. (1994)
27 Heparin, Low-Molecular-Weight.rn. (7063)
28 (unfractionated heparin or UFH).tw. (11280)
29 (Dalteparin* or FR-860 or Fragmin or Fragmine or Kabi-2165 or "K 2165'" or K2165 or Tedelparin or low liquemin).tw. (4133)
30 dalteparin.rn. (776)
31 (Enoxaparin* or Clexan* or EMT-966 or EMT-967 or HSDB 7846 or Klexane or Lovenox or PK10169 or PK 10169 or "PK-10,169" or RP 54563 or UNII-8NZ41MIK1O).tw. (10466)
32 enoxaparin.rn. (17927)
33 (nadroparin* or CY 216 or CY 216d or CY216 or CY216d or Fraxiparin* or LMF CY-216 or Nadrohep or Fraxodi or Seleparin* or Tedegliparin*).tw. (2682)
34 nadroparin.rn. (4189)
35 (tinzaparin* or Innohep or lhn1 or logiparin or UNII-7UQ7X4Y489).tw. (1416)

36 tinzaparin.rn. (251)
37 (fondaparin* or Arixtra or Quixidar or HSDB 7845 or Org-31540 or PENTA or SR 90107 or UNII-J177FOW5JL).tw. (12965)
38 Fondaparinux.rn. (5614)
39 exp Vitamin K/ai (1664)
40 ((Vitamin K or Vit K) adj1 antagonist*).tw. (5936)
41 (VKA or VKAs or "anti vitamin K" or "antivitamin K" or "anti vitamins K" or "antivitamins K").tw. (2843)
42 warfarin/ (79142)
43 (Warfarin* or Aldocumar or Apo-Warfarin or BRN 1293536 or Brumolin or Coumafen* or Coumaphene or Coumadan or Coumadin* or Coumafene or Coumaphene or Coumefene or Dethmor or Dethnel or "Dicusat E" or Gen-Warfarin or Kumader or Kumadu or Kumatox or Kypfarin or "Latka 42" or Marevan or Panwarfin or Prothromadin or Tedicumar or Warfant or Warfarat).tw. (44251)
44 warfarin.rn. (73265)
45 Acenocoumarol/ (5592)
46 (Acenocoumarol* or Acenocoumarin* or Acenocumarol* or Acenokumarin* or Acitrom or Ascumar or G-23350 or G23350 or HSDB 3201 or Neo sintrom or Neosintrom or Neo sitron or Neositron or Nicoumalone or Nicumalon or Nitrovarfarian or Nitrowarfarin or Sincoumar or Sinkumar or Sinthrom* or Sintrom or Syncoumar or Syncumar or Synthrom or Trombostop or UNII-I6WP63U32H or Zotil).tw. (2931)
47 acenocoumarol.rn. (5351)
48 Aspirin/ (194520)
49 (Aspirin or Acetylsalicylic Acid or Acetysal or Acylpyrin or Aloxiprimum or ASA or Colfarit or Dispril or Easprin or Ecotrin or Endosprin or Magnecyl or Micristin or Polopirin or Polopiryna or Solprin or Solupsan or Zorprin).tw. (180754)
50 aspirin.rn. (39425)
51 or/12-50 (384226)
52 11 and 51 (45947)
53 randomized controlled trial/ or controlled clinical trial/ (970376)
54 clinical trials as topic.sh. (175982)
55 (randomi#ed or randomly or RCT$1 or placebo*).tw. (1480528)
56 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (297700)
57 trial.ti. (302130)
58 or/53-57 (2071374)
59 52 and 58 (7426)
60 exp Animals/ not (exp Animals/ and Humans/) (8110914)
61 59 not 60 (7333)
62 (comment or editorial or interview or letter or news).pt. (2889704)
63 61 not 62 (7139)
64 limit 63 to yr="2008-current" (3237)
65 64 use prmz (950)
66 exp venous thromboembolism/ (100943)
67 ((venous or vein$1 or vena) adj2 (thromboemboli* or thrombo-emboli*)).tw. (33936)
68 (VTE or VTEs).tw. (15087)
69 vein thrombosis/ (25779)
70 ((venous or vein$1 or vena) adj2 thrombos*).tw. (90211)
71 (("deep venous" or "deep vein") adj2 (thrombus or thrombophlebitis or "thrombo-phlebitis")).tw. (535)
72 (DVT or DVTs).tw. (18078)
73 (phlebothrombos* or phlebo-thrombos*).tw. (1038)
74 ((pulmonary or lung or lungs) adj2 (emboli* or embolus or emboly or microemboli* or micro-emboli* or microembolus or micro-embolus or microemboly or micro-emboly or thromboemboli* or thrombo-emboli*)).tw. (74669)

75 or/66-74 (216003)
76 ((new or novel) adj1 (oral anticoagulant* or oral anti-coagulant*)).tw. (3290)
77 (NOA or NOAs or NOAC or NOACs).tw. (2091)
78 ((new or novel) adj1 (direct oral anticoagulant* or direct oral anti-coagulant*)).tw. (76)
79 (DOAC or DOACs).tw. (112)
80 apixaban/ (3099)
81 (Apixaban or BMS 562247 or BMS562247 or Eliques or Eliquis).tw. (2402)
82 apixaban.rn. (3128)
83 dabigatran/ or dabigatran etexilate/ (5890)
84 (Dabigatran or Pradax or Pradaxa or Prazaxa or Rendix).tw. (5394)
85 (dabigatran or dabigatran etexilate).rn. (1237)
86 rivaroxaban/ (4953)
87 (Rivaroxaban or BAY 59-7939 or BAY59-7939 or HSDB 5717 or Xarelto or UNII-9NDF7JZ4M3).tw. (4339)
88 rivaroxaban.rn. (4844)
89 edoxaban/ (789)
90 (Edoxaban or DU176 or DU-176 or DU176b or DU-176b or Savaysa or UNII-NDU3J18APO).tw. (764)
91 edoxaban.rn. (792)
92 low molecular weight heparin/ (34814)
93 LMWH.tw. (9187)
94 ((low molecular or low molecular weight or LMW) adj1 heparin).tw. (1994)
95 low molecular weight heparin.rn. (0)
96 (unfractionated heparin or UFH).tw. (11280)
97 dalteparin/ (7086)
98 (Dalteparin* or FR-860 or Fragmin or Fragmine or Kabi-2165 or "K 2165'" or K2165 or Tedelparin or low liquemin).tw. (4133)
99 dalteparin.rn. (776)
100 enoxaparin/ (19502)
101 (Enoxaparin* or Clexan* or EMT-966 or EMT-967 or HSDB 7846 or Klexane or Lovenox or PK10169 or PK 10169 or "PK-10,169" or RP 54563 or UNII-8NZ41MIK1O).tw. (10466)
102 enoxaparin.rn. (17927)
103 nadroparin/ (4372)
104 (nadroparin* or CY 216 or CY 216d or CY216 or CY216d or Fraxiparin* or LMF CY-216 or Nadrohep or Fraxodi or Seleparin* or Tedegliparin*).tw. (2682)
105 nadroparin.rn. (4189)
106 tinzaparin/ (2526)
107 (tinzaparin* or Innohep or lhn1 or logiparin or UNII-7UQ7X4Y489).tw. (1416)
108 tinzaparin.rn. (251)
109 fondaparinux/ (5268)
110 (fondaparin* or Arixtra or Quixidar or HSDB 7845 or Org-31540 or PENTA or SR 90107 or UNII-J177FOW5JL).tw. (12965)
111 fondaparinux.rn. (5614)
112 antivitamin K/ (6948)
113 ((Vitamin K or Vit K) adj1 antagonist*).tw. (5936)
114 (VKA or VKAs or "anti vitamin K" or "antivitamin K" or "anti vitamins K" or "antivitamins K").tw. (2843)
115 "antivitamin K".rn. (0)
116 warfarin/ (79142)
117 (Warfarin* or Aldocumar or Apo-Warfarin or BRN 1293536 or Brumolin or Coumafen* or Coumaphene or Coumadan or Coumadin* or Coumafene or Coumaphene or Coumefene or Dethmor or Dethnel or "Dicusat E" or Gen-Warfarin or Kumader or Kumadu or Kumatox or Kypfarin or "Latka 42" or Marevan or Panwarfin or Prothromadin or Tedicumar or Warfant or Warfarat).tw. (44251)

118 warfarin.rn. (73265)
119 acenocoumarol/ (5592)
120 (Acenocoumarol* or Acenocoumarin* or Acenocumarol* or Acenokumarin* or Acitrom or Ascumar or G-23350 or G23350 or HSDB 3201 or Neo sintrom or Neosintrom or Neo sitron or Neositron or Nicoumalone or Nicumalon or Nitrovarfarian or Nitrowarfarin or Sincoumar or Sinkumar or Sinthrom* or Sintrom or Syncoumar or Syncumar or Synthrom or Trombostop or UNII-I6WP63U32H or Zotil).tw. (2931)
121 acenocoumarol.rn. (5351)
122 acetylsalicylic acid/ (194520)
123 (Aspirin or Acetylsalicylic Acid or Acetysal or Acylpyrin or Aloxiprimum or ASA or Colfarit or Dispril or Easprin or Ecotrin or Endosprin or Magnecyl or Micristin or Polopirin or Polopiryna or Solprin or Solupsan or Zorprin).tw. (180754)
124 acetylsalicylic acid.rn. (145681)
125 or/76-124 (384150)
126 75 and 125 (43203)
127 randomized controlled trial/ or controlled clinical trial/ (970376)
128 exp "clinical trial (topic)"/ (119539)
129 (randomi#ed or randomly or RCT$1 or placebo*).tw. (1480528)
130 ((singl* or doubl* or trebl* or tripl*) adj (mask* or blind* or dumm*)).tw. (297700)
131 trial.ti. (302130)
132 or/127-131 (2029113)
133 126 and 132 (7669)
134 exp animal experimentation/ or exp models animal/ or exp animal experiment/ or nonhuman/ or exp vertebrate/ (37627542)
135 exp humans/ or exp human experimentation/ or exp human experiment/ (29119173)
136 134 not 135 (8509968)
137 133 not 136 (7590)
138 (editorial or letter).pt. (2557675)
139 137 not 138 (7401)
140 limit 139 to yr="2008-current" (3898)
141 140 use emez (3075)
142 65 or 141 (4025)
143 remove duplicates from 142 (3248) [TOTAL UNIQUE RECORDS]
144 143 use prmz (872) [UNIQUE MEDLINE HITS]
145 143 use emez (2376) [UNIQUE EMBASE HITS]
****

Cochrane Library

Search Name: VTE DVT PE - NOACs - Anti-Platelets Removed
Date Run: 05/11/14 13:49:36.484
Description: Ottawa Heart institute - Final - 2014 Nov 5

ID	Search	Hits
#1	[mh "Venous Thromboembolism"]	417
#2	((venous or vein or veins or vena) NEAR/j2 (thromboemboli* or thrombo-emboli*)):ti,ab,kw	0
#3	(VTE or VTEs):ti,ab,kw	442
#4	[mh "Venous Thrombosis"]	2296
#5	((venous or vein or veins or vena) near/2 thrombos*):ti,ab,kw	4167

#6 ("deep venous" or "deep vein") near/2 (thrombus or thrombophlebitis or "thrombo-phlebitis"):ti,ab,kw 9
#7 (DVT or DVTs):ti,ab,kw 980
#8 (phlebothrombos* or phlebo-thrombos*):ti,ab,kw 13
#9 [mh "Pulmonary Embolism"] 920
#10 ((pulmonary or lung or lungs) near/2 (emboli* or embolus or emboly or microemboli* or micro-emboli* or microembolus or micro-embolus or microemboly or micro-emboly or thromboemboli* or thrombo-emboli*)):ti,ab,kw 2240
#11 {or #1-#10} 6200
#12 ((new or novel) near/1 ((oral next anticoagulant*) or (oral next anti-coagulant*))):ti,ab,kw 74
#13 (NOA or NOAs or NOAC or NOACs):ti,ab,kw 30
#14 ((new or novel) near/1 (("direct oral" next anticoagulant*) or ("direct oral" next anti-coagulant*))):ti,ab,kw 0
#15 (DOAC or DOACs):ti,ab,kw 0
#16 (Apixaban or "BMS 562247" or BMS562247 or Eliques or Eliquis):ti,ab,kw 155
#17 (Dabigatran or Pradax or Pradaxa or Prazaxa or Rendix):ti,ab,kw 247
#18 (Rivaroxaban or "BAY 59-7939" or "BAY59-7939" or "HSDB 5717" or Xarelto or UNII-9NDF7JZ4M3):ti,ab,kw 281
#19 (Edoxaban or DU176 or "DU-176" or DU176b or "DU-176b" or Savaysa or UNII-NDU3J18APO):ti,ab,kw 56
#20 [mh "Heparin, Low-Molecular-Weight"] 1750
#21 LMWH:ti,ab,kw 694
#22 (("low molecular weight" or "low molecular" or LMW) near/1 heparin):ti,ab,kw 2477
#23 ("unfractionated heparin" or UFH):ti,ab,kw 1135
#24 (Dalteparin* or "FR-860" or Fragmin or Fragmine or "Kabi-2165" or "K 2165'" or K2165 or Tedelparin or "low liquemin"):ti,ab,kw 544
#25 (Enoxaparin* or Clexan* or "EMT-966" or "EMT-967" or "HSDB 7846" or Klexane or Lovenox or PK10169 or "PK 10169" or "PK-10,169" or "RP 54563" or UNII-8NZ41MIK1O):ti,ab,kw 1262
#26 (nadroparin* or "CY 216" or "CY 216d" or CY216 or CY216d or Fraxiparin* or Nadrohep or Fraxodi or Seleparin* or Tedegliparin*):ti,ab,kw 304
#27 (tinzaparin* or Innohep or lhn1 or logiparin or UNII-7UQ7X4Y489):ti,ab,kw 169
#28 (fondaparin* or Arixtra or Quixidar or "HSDB 7845" or "Org-31540" or PENTA or "SR 90107" or UNII-J177FOW5JL):ti,ab,kw 324
#29 [mh "Vitamin K"/ai] 102
#30 (("Vitamin K" or "Vit K") near/1 antagonist*):ti,ab,kw 207
#31 (VKA or VKAs or "anti vitamin K" or "antivitamin K" or "anti vitamins K" or "antivitamins K"):ti,ab,kw 132
#32 [mh warfarin] 1223
#33 (Warfarin* or Aldocumar or "Apo-Warfarin" or "BRN 1293536" or Brumolin or Coumafen* or Coumaphene or Coumadan or Coumadin* or Coumafene or Coumaphene or Coumefene or Dethmor or Dethnel or "Dicusat E" or "Gen-Warfarin" or Kumader or Kumadu or Kumatox or Kypfarin or "Latka 42" or Marevan or Panwarfin or Prothromadin or Tedicumar or Warfant or Warfarat):ti,ab,kw 2384
#34 [mh Acenocoumarol] 108
#35 (Acenocoumarol* or Acenocoumarin* or Acenocumarol* or Acenokumarin* or Acitrom or Ascumar or "G-23350" or G23350 or "HSDB 3201" or "Neo sintrom" or Neosintrom or "Neo sitron" or

Neositron or Nicoumalone or Nicumalon or Nitrovarfarian or Nitrowarfarin or Sincoumar or Sinkumar or Sinthrom* or Sintrom or Syncoumar or Syncumar or Synthrom or Trombostop or UNII-I6WP63U32H or Zotil):ti,ab,kw 186
#36 [mh Aspirin] 4492
#37 (Aspirin or Acetylsalicylic Acid or Acetysal or Acylpyrin or Aloxiprimum or ASA or Colfarit or Dispril or Easprin or Ecotrin or Endosprin or Magnecyl or Micristin or Polopirin or Polopiryna or Solprin or Solupsan or Zorprin):ti,ab,kw 15815
#38 {or #12-#37} 21520
#39 #11 and #38 Publication Year from 2008 to 2014 646

DSR - 39
DARE - 64
CENTRAL – 466 (RCTs)
Methods – 2
HTA – 29
NHS EED – 46

APPENDIX 2: INCLUDED STUDIES

ACUTE

1. Agnelli G, Buller HR, Cohen A, et al. Oral apixaban for the treatment of acute venous thromboembolism. *N Engl J Med.* 2013;369(9):799-808.

2. Bamber L, Wang MY, Prins MH, et al. Patient-reported treatment satisfaction with oral rivaroxaban versus standard therapy in the treatment of acute symptomatic deep-vein thrombosis. *Thromb Haemost.* 2013;110(4):732-741.

3. Barrett YC, Wang J, Knabb R, Mohan P. Apixaban decreases coagulation activity in patients with acute deep-vein thrombosis. *Thromb Haemost.* 2011;105(1):181-189.

4. Bookhart BK, Haskell L, Bamber L, Wang M, Schein J, Mody SH. Length of stay and economic consequences with rivaroxaban vs enoxaparin/vitamin K antagonist in patients with DVT and PE: findings from the North American EINSTEIN clinical trial program. *J Med Econ.* 2014;17(10):691-695.

5. Einstein I, Bauersachs R, Berkowitz SD, et al. Oral rivaroxaban for symptomatic venous thromboembolism. *N Engl J Med.* 2010;363(26):2499-2510.

6. Einstein-Pe I, Buller HR, Prins MH, et al. Oral rivaroxaban for the treatment of symptomatic pulmonary embolism. *N Engl J Med.* 2012;366(14):1287-1297.

7. Hokusai-Vte I, Buller HR, Decousus H, et al. Edoxaban versus warfarin for the treatment of symptomatic venous thromboembolism. *N Engl J Med.* 2013;369(15):1406-1415.

8. Prins MH, Lensing AW, Bauersachs R, et al. Oral rivaroxaban versus standard therapy for the treatment of symptomatic venous thromboembolism: a pooled analysis of the EINSTEIN-DVT and PE randomized studies. *Thromb J.* 2013;11(1):21, 2013.

9. Raskob G, Buller H, Prins M, et al. Edoxaban for the long-term treatment of venous thromboembolism: rationale and design of the Hokusai-venous thromboembolism study--methodological implications for clinical trials. *Journal of thrombosis and haemostasis : JTH.* 2013;11(7):1287-1294.

10. Schulman S, Kakkar AK, Goldhaber SZ, et al. Treatment of acute venous thromboembolism with dabigatran or warfarin and pooled analysis. *Circulation.* 2014;129(7):764-772.

11. Schulman S, Kearon C, Kakkar AK, et al. Dabigatran versus warfarin in the treatment of acute venous thromboembolism. *N Engl J Med.* 2009;361(24):2342-2352.

12. van BB, Bamber L, Correa De CF, Prins M, Wang M, Lensing AWA. Reduction in the length of stay with rivaroxaban as a single-drug regimen for the treatment of deep vein thrombosis and

pulmonary embolism. *Current Medical Research and Opinion.30 (5) ()(pp 829-837), 2014.Date of Publication: May 2014.* 2014(5):829-837.

13. van EJ, Douma RA, Kamphuisen PW, et al. Clot resolution after 3 weeks of anticoagulant treatment for pulmonary embolism: comparison of computed tomography and perfusion scintigraphy. *Journal of thrombosis and haemostasis : JTH.* 2013;11(4):679-685.

14. Wang Y, Wang C, Chen Z, et al. Rivaroxaban for the treatment of symptomatic deep-vein thrombosis and pulmonary embolism in Chinese patients: a subgroup analysis of the EINSTEIN DVT and PE studies. *Thromb J.* 2013;11(1):25, 2013.

Protocols

1. NCT0223483 - EINSTEIN JUNIOR PHASE III
2. EINSTEIN JUNIOR (NCT01684423) – currently recruiting
3. NCT01895777 – Dabigatran v. standard care in pediatric patients with VTE
4. NCT00680186 – unpublished RECOVER

EXTENDED

1. Agnelli G, Buller HR, Cohen A, et al. Apixaban for extended treatment of venous thromboembolism. N Engl J Med. 2013;368(8):699-708.

2. Agnelli G, Prandoni P, Becattini C, et al. Extended oral anticoagulant therapy after a first episode of pulmonary embolism. Ann Intern Med. 2003;139(1):19-25.

3. Agnelli G, Prandoni P, Santamaria MG, et al. Three months versus one year of oral anticoagulant therapy for idiopathic deep venous thrombosis. Warfarin Optimal Duration Italian Trial Investigators. N Engl J Med. 2001;345(3):165-169.

4. Becattini C, Agnelli G, Schenone A, et al. Aspirin for preventing the recurrence of venous thromboembolism. N Engl J Med. 2012;366(21):1959-1967.

5. Brighton TA, Eikelboom JW, Mann K, et al. Low-dose aspirin for preventing recurrent venous thromboembolism. N Engl J Med. 2012;367(21):1979-1987.

6. Cosmi B, Legnani C, Iorio A, et al. Residual Venous Obstruction, alone and in Combination with D-Dimer, as a Risk Factor for Recurrence after Anticoagulation Withdrawal following a First Idiopathic Deep Vein Thrombosis in the Prolong Study. European Journal of Vascular and Endovascular Surgery.39 (3) ()(pp 356-365), 2010.Date of Publication: March 2010. 2010(3):356-365.

7. Cosmi B, Legnani C, Tosetto A, et al. Sex, age and normal post-anticoagulation D-dimer as risk factors for recurrence after idiopathic venous thromboembolism in the Prolong study extension. Journal of Thrombosis and Haemostasis.8 (9) ()(pp 1933-1942), 2010.Date of Publication: September 2010. 2010(9):1933-1942.

8. Cosmi B, Legnani C, Tosetto A, et al. Comorbidities, alone and in combination with D-dimer, as risk factors for recurrence after a first episode of unprovoked venous thromboembolism in the extended follow-up of the PROLONG study. Thromb Haemost. 2010;103(6):1152-1160.

9. Einstein I, Bauersachs R, Berkowitz SD, et al. Oral rivaroxaban for symptomatic venous thromboembolism. N Engl J Med. 2010;363(26):2499-2510.

10. Eischer L, Gartner V, Schulman S, Kyrle PA, Eichinger S, Aurec-Fviii i. 6 versus 30 months anticoagulation for recurrent venous thrombosis in patients with high factor VIII. Ann Hematol. 2009;88(5):485-490.

11. Kearon C, Gent M, Hirsh J, et al. A comparison of three months of anticoagulation with extended anticoagulation for a first episode of idiopathic venous thromboembolism. N Engl J Med. 1999;340(12):901-907.

12. Ott P, Eldrup E, Oxholm P. [Value of anticoagulant therapy in deep venous thrombosis in the lower limb in elderly, mobilized patients. A double-blind placebo controlled study with open therapeutic guidance]. Ugeskr Laeger. 1988;150(4):218-221.

13. Schulman S, Granqvist S, Holmstrom M, et al. The duration of oral anticoagulant therapy after a second episode of venous thromboembolism. The Duration of Anticoagulation Trial Study Group. N Engl J Med. 1997;336(6):393-398.

14. Schulman S, Kearon C, Kakkar AK, et al. Extended use of dabigatran, warfarin, or placebo in venous thromboembolism. N Engl J Med. 2013;368(8):709-718.

15. Simes J, Becattini C, Agnelli G, et al. Aspirin for the Prevention of Recurrent Venous Thromboembolism: The INSPIRE Collaboration. Circulation. 2014;130(13):1062-1071.

Protocols

1. EINSTEIN CHOICE (NCT02064439)
2. ID110 – ALICAT (NCT01817257, ISRCTN37913976)
3. ID266 – ExACT study (ISRCTN73819751)
4. PADIS-EP trial - Coutarud 2008 (ID777), Coutarud 2008 (ID797)

INCLUDED ABSTRACTS

1. Agnelli G., H.R. Buller, A. Cohen, et al. Apixaban for the treatment of symptomatic deep-vein thrombosis and pulmonary embolism: A randomized, double-blind trial (AMPLIFY). 24th Congress of the International Society on Thrombosis and Haemostasis; 2013 June 29-July 4; Amsterdam, Netherlands. *Thrombo Haemostasis* 2013;11:18.

2. Agnelli G., H.R. Buller, A. Cohen, et al. Two doses of apixaban for the extended treatment of venous thromboembolism. 54th Annual Meeting of the American Society of Hematology; 2012 Dec 8-11;Atlanta, GA. *Blood* 2012;120(21).

3. Bamber L., S.J. Cano, D.L. Lamping, et al. Patient-reported treatment satisfaction with oral rivaroxaban vs. standard therapy in the treatment of symptomatic deep vein thrombosis (DVT). 23rd Congress of the International Society on Thrombosis and Haemostasis; 2011 July 23-28; Kyoto, Japan. Conference Start: 20110723 Conference End: 20110728. *J Thromb Haemostasis* 2011.

4. Becattini C., G. Agnelli, R. Poggio, et al. Aspirin after oral anticoagulants for prevention of recurrence in patients with unprovoked venous thromboembolism: the WARFASA study. 53rd Annual Meeting of the American Society of Hematology; 2011 Dec 10-13; San Diego, CA. *Blood* 2011;118(21).

5. Brighton T., J. Eikelboom, K. Mann, et al. Aspirin for the prevention of recurrent venous thromboembolism after a first unprovoked event: results of the ASPIRE randomized controlled trial. American Heart Association 2012 Scientific Sessions and Resuscitation Science Symposium. 2012; Nov 3-6; Los Angeles, CA. *Circulation* 2012;126(23):2777.

6. Buller H.R. Once-daily oral rivaroxaban versus placebo in the long-term prevention of recurrent symptomatic venous thromboembolism. The EINSTEIN-extension study. 51st Annual Meeting of the American Society of Hematology; 2009 Dec 5-8; New Orleans, LA. *Blood* 2009;114(22).

7. Buller H.R. Oral rivaroxaban for the acute and continued treatment of symptomatic venous thromboembolism. The EINSTEIN-DVT and EINSTEIN-extension study. 52nd Annual Meeting of the American Society of Hematology; 2010 Dec 4-7; Orlando, FL. *Blood* 2010;116(21).

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9. Davidson, B.L. A.W.A. Lensing, B. Brenner, et al. Anticoagulation and bleeding: The effect of nonsteroidal anti-inflammatory drugs, acetylsalicylic acid, or other platelet aggregation inhibitors. 23rd Congress of the International Society on Thrombosis and Haemostasis; 2011 July 23-28; Kyoto, Japan. Conference Start: 20110723 Conference End: 20110728. *J Thromb Haemostasis* 2011.

10. Decousus H., A.W.A. Lensing, F. Piovella, et al. Anticoagulation and bleeding: The effect of blood pressure. Journal of Thrombosis and Haemostasis. 23rd Congress of the International Society on Thrombosis and Haemostasis; 2011 July 23-28; Kyoto, Japan. Conference Start: 20110723 Conference End: 20110728. *J Thromb Haemostasis* 2011.

11. Liu X., J. Thompson, H. Phatak, et al. Apixaban reduces hospitalization in patients with venous thromboembolism: An analysis of the AMPLIFY-EXT. *Blood*. 55th Annual Meeting of the American Society of Hematology; 2013 Dec 7-10; New Orleans, LA.

12. Liu X., M. Johnson, J. Mardekian, et al. Apixaban reduces hospitalizations in patients with VTE: An analysis of the amplify trial. Journal of the American College of Cardiology meeting; 2014 Mar; Washington, DC.

13. Prins M., L. Bamber, S. Cano, et al. Patient-reported treatment satisfaction with oral rivaroxaban versus standard therapy in the treatment of acute symptomatic pulmonary embolism. 54th Annual Meeting of the American Society of Hematology; 2012 Dec 8-11;Atlanta, GA. *Blood* 2012;120(21).

14. Prins M.H., A.W.A. Lensing, G.E. Raskob, et al. The risk of recurrent venous thromboembolism during vitamin K antagonist treatment in relation to time in therapeutic range in patients with deep vein thrombosis. 23rd Congress of the International Society on Thrombosis and Haemostasis; 2011 July 23-28; Kyoto, Japan. Conference Start: 20110723 Conference End: 20110728. *J Thromb Haemostasis* 2011.

15. Prins M.H., A.W.A. Lensing, P. Wells, et al. The relative efficacy of rivaroxaban vs. vitamin K antagonists (VKA) in relation to time in therapeutic range (TTR) in patients with deep vein thrombosis (DVT). 23rd Congress of the International Society on Thrombosis and Haemostasis; 2011 July 23-28; Kyoto, Japan. Conference Start: 20110723 Conference End: 20110728. *J Thromb Haemostasis* 2011.

16. Prins M.H., P. Prandoni, A.W. Lensing, et al. The EINSTEIN DVT study: Does localization of the initial DVT affect the occurrence of recurrent VTE while patients are on anticoagulation? 53rd Annual Meeting of the American Society of Hematology; 2011 Dec 10-13; San Diego, CA. *Blood* 2011;118(21).

17. Raskob G.E., H. Buller, P. Angchaisuksiri, et al. Edoxaban for long-term treatment of venous thromboembolism in cancer patients. 55th Annual Meeting of the American Society of Hematology; 2013 Dec 7-10; New Orleans, LA. *Blood 2013;*122 (21).

18. Raskob, G.E. L.W.A. Anthonie, M.H. Prins, et al. Risk assessment for recurrent venous thromboembolism (VTE) after 6-14 months of anticoagulant treatment. 23rd Congress of the International Society on Thrombosis and Haemostasis; 2011 July 23-28; Kyoto, Japan. Conference Start: 20110723 Conference End: 20110728. *J Thromb Haemostasis* 2011.

19. Schulman S., A.K. Kakkar, S.M. Schellong, et al. A randomized trial of dabigatran versus warfarin in the treatment of acute venous thromboembolism (RE-COVER II). 53rd Annual Meeting of the American Society of Hematology; 2011 Dec 10-13; San Diego, CA. *Blood* 2011;118(21).

20. Schulman S., D. Baanstra, H. Eriksson, et al. Benefit of extended maintenance therapy for venous thromboembolism with dabigatran etexilate is maintained over 1 year of post-treatment follow-up. 54th Annual Meeting of the American Society of Hematology; 2012 Dec 8-11;Atlanta, GA. *Blood* 2012;120(21).

21. Schulman S., D. Baanstra, H. Eriksson, et al. Dabigatran vs. placebo for extended maintenance therapy of venous thromboembolism. 23rd Congress of the International Society on Thrombosis and Haemostasis; 2011 July 23-28; Kyoto, Japan. Conference Start: 20110723 Conference End: 20110728. *J Thromb Haemostasis* 2011.

22. Schulman S., H. Eriksson, S.Z. Goldhaber, et al. Dabigatran etexilate versus warfarin in the treatment of venous thromboembolism. 51st Annual Meeting of the American Society of Hematology; 2009 Dec 5-8; New Orleans, LA. *Blood* 2009;114(22).

23. Schulman S., H. Eriksson, S.Z. Goldhaber, et al. Dabigatran or warfarin for extended maintenance therapy of venous thromboembolism. 23rd Congress of the International Society on Thrombosis and Haemostasis; 2011 July 23-28; Kyoto, Japan. Conference Start: 20110723 Conference End: 20110728. *J Thromb Haemostasis* 2011.

24. Sullivan P., M. Fraessdorf, M. Feuring, et al. Health-related quality of life after venous thromboembolism. ISPOR 14th Annual European Congress; 2011 Nov 5-8; Madrid, Spain. *Value in Health* 2011;14(7):A384.

25. Van Es J., R.A. Douma, P.W. Kamphuisen, et al. Clot resolution after 3 weeks of anticoagulant treatment of pulmonary embolism: Comparison of computed tomography and perfusion scintigraphy. 24th Congress of the International Society on Thrombosis and Haemostasis; 2013 June 29-July 4; Amsterdam Netherlands. *J Thrombo Haemostasis* 2013;11:242.

26. Verhamme P., A.W.A. Lensing, B. Jacobson, et al. The risk of recurrent venous thromboembolism and major bleeding in fragile patients with deep vein thrombosis. 23rd Congress of the International Society on Thrombosis and Haemostasis; 2011 July 23-28; Kyoto, Japan. Conference Start: 20110723 Conference End: 20110728. *J Thromb Haemostasis* 2011.

APPENDIX 3: EXCLUDED PUBLICATIONS

1. Ageno W., L.G. Mantovani, S. Haas, et al. XALIA: rationale and design of a non-interventional study of rivaroxaban compared with standard therapy for initial and long-term anticoagulation in deep vein thrombosis. *Thromb J*. 2014;12:16.

2. Agnelli A., D.J. George, W. Fisher, et al. The ultra-low molecular weight heparin (ULMWH) semuloparin for prevention of venous thromboembolism (VTE) in patients with cancer receiving chemotherapy: SAVE ONCO study. *J Clin Oncol.* 2011;29.

3. Agnelli A. Apixaban was noninferior to enoxaparin plus warfarin in patients with acute venous thromboembolism. *Ann Intern Med* 2013;159(8):JC2.

4. Akl E.A., L. Kahale, M. Barba, et al. Anticoagulation for the long-term treatment of venous thromboembolism in patients with cancer. *Cochrane Database Syst Rev* 2014;7:CD006650.

5. Al-Lawati A.A.M., V. Muthuswamy. Continuing aspirin causes higher drainage even under full protection with antifibrinolytics. *Thorac Cardiovasc Surg* 2013;61(8):726-730.

6. Anderson D.R. Aspirin after dalteparin was noninferior to continued dalteparin for preventing VTE after total hip arthroplasty. *Ann Intern Med* 2013;159(6):JC12.

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8. Apostolakis S., E. Shantsila, G.Y. Lip. New anticoagulants for the prevention of deep venous thrombosis: time to consider cost effectiveness? *PharmacoEconomics*. 2009;27:793.

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13. Bain J., D.R. Oyler, S.S. Smyth, T.E. Macaulay. Pathophysiology and pharmacologic treatment of venous thromboembolism. *CurrDrug Targets* 2014;15:199.

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15. Becattini A., G. Agnelli, A. Schenone. Aspirin reduced recurrence of venous thromboembolism (VTE) after a first-ever, unprovoked VTE. *Ann Intern Med* 2012;157(8):JC4-JC3.

16. Becattini C., G. Agnelli. Aspirin for prevention and treatment of venous thromboembolism. *Blood Rev* 2014;28:103.

17. Bona R. Review: Factor Xa inhibitors reduce DVT more than LMWH in total knee or hip replacement. *Ann Inten Med* 2012;157(4):JC4-JC5.

18. Bounameaux H., A. Perrier. Duration of anticoagulation therapy for venous thromboembolism. Hematology Am Soc Hematol Edu Program 2008:252-8.

19. Boutitie A., L. Pinede, S. Schulman, et al. Influence of preceding length of anticoagulant treatment and initial presentation of venous thromboembolism on risk of recurrence after stopping treatment: Analysis of individual participants' data from seven trials. *BMJ* 2011;342(7810):d3036.

20. Boyer T.D., S. Habib. Portal vein thrombosis in patients with cirrhosis. *Clinical Liver Disease* 2014;3(6):111-113.

21. Brighton T.A, J.W. Eikelboom, K. Mann. Aspirin did not reduce recurrence after a first-ever, unprovoked venous thromboembolism. *Ann Intern Med* 2013;158(6):JC2.

22. Brown R., G.Y. Lip, P. Gallego. Dabigatran etexilate for venous thromboembolism: a safety evaluation. *Expert Opin Drug Saf* 2014;13:639.

23. Brown T.S., S. Banerjee, R.D. Russell, et al. What's new in total hip arthroplasty. *J Bone Joint Surg* 2014;96:1576-1582.

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27. Buller H.R. Edoxaban was noninferior to warfarin for preventing recurrent venous thromboembolism, with less bleeding. *Ann Intern Med* 2014;160(2):JC4.

28. Buller H.R. Enoxaparin plus idrabiotaparinux was noninferior to enoxaparin plus warfarin for recurrent VTE in acute PE. *Ann Intern Med* 2012;156(10):JC5-4.

29. Buller H.R., A.S. Gallus, G. Pillion, et al. Enoxaparin followed by once-weekly idrabiotaparinux versus enoxaparin plus warfarin for patients with acute symptomatic pulmonary embolism: a randomised, double-blind, double-dummy, non-inferiority trial. *Lancet* 2012;379:123.

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35. Chalikias G., S. Konstantinides. Acute phase treatment of pulmonary embolism. *Curr Vasc Pharmacol.* 2014;12:393.

36. Chan C.M., A.F. Shorr. Economic and outcomes aspects of venous thromboembolic disease. *Crit Care Clin* 2012;28(1):113-123.

37. Chaudhari K., B. Hamad, B.A. Syed. Antithrombotic drugs market. *Nat Rev Drug Discov 2014;*13(8):571-572.

38. Christersson C., L. Wallentin, U. Andersson, et al. D-dimer and risk of thromboembolic and bleeding events in patients with atrial fibrillation — observations from the ARISTOTLE trial. *J Thromb Haemost* 2014;12:1401.

39. Claxton R., R.M. Arnold. Pharmacologic treatment of acute venous thromboembolism in patients with advanced cancer #236. *J Palliat Med* 2012;15(7):828-829.

40. Clayville L.R., Anderson K. Vogel, S.A. Miller, E.L. St.Onge. New options in anticoagulation for the prevention of venous thromboembolism and stroke. *P and T*. 2011;36(2):86.

41. Clemens A., M. Fraessdorf, J. Friedman. Cardiovascular outcomes during treatment with dabigatran: comprehensive analysis of individual subject data by treatment. *Vasc Health Risk Manag* 2013;9:599-615.

42. Clinical Evaluation of GSK576428 (Fondaparinux Sodium) in Prevention of Venous Thromboembolism (VTE) after Abdominal Surgery.

43. Cohen A.T., T.E. Spiro, H.R. Buller, et al. Extended-duration rivaroxaban thromboprophylaxis in acutely ill medical patients: MAGELLAN study protocol. *J Thromb Thrombolysi*s 2011;31:407.

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APPENDIX 4: RISK OF BIAS

TRIAL (AUTHOR, YEAR)	ADEQUATE SEQUENCE GENERATION	ALLOCATION CONCEALMENT	BLINDING OF OUTCOMES ASSESSMENT (Objective)	INCOMPLETE OUTCOME DATA ADDRESSED – EFFICACY OUTCOMES	INCOMPLETE OUTCOME DATA ADDRESSED – SAFETY OUTCOMES
ACUTE					
RE-COVER (Schulman 2009)	Low	Low	Low	Low	Unclear
RE-COVER II (Schulman 2014)	Low	Low	Low	Low	Low
HOKUSAI (Buller 2013)	Low	Unclear	Low	Low	Low
AMPLIFY (Agnelli, 2013)	Low	Low	Low	Low	Low
EINSTEIN-DVT (Bauersachs, 2010)	Low	Low	Low	Low	Low
EINSTEIN-PE (Buller 2012)	Low	Low	Low	Low	Low
EXTENDED					
DURACII (Schulman 1997)	Low	Low	Low	Low	Low
LAFIT (Kearon 1999)	Low	Unclear	Low	Unclear	Unclear
WODIT-DVT (Agnelli 2001)	Low	Low	Low	Low	Low
WODIT-PE (Agnelli 2003)	Low	Low	Low	Low	Low
AUREC-VFII (Eischer 2009)	Unclear	Unclear	Low	Low	Low
RE-SONATE (Schulman 2013)	Low	Low	Low	Low	Low
RE-MEDY (Schulman 2013)	Low	Low	Low	Low	Low
EINSTEIN-EXT (Bauersachs, 2010)	Low	Low	Low	Low	Low
AMPLIFY-EXT (Agnelli 2013)	Low	Low	Low	High	High
WARFASA (Becattini 2012)	Low	Unclear	Low	Low	Low
ASPIRE (Brighton 2012)	Low	Low	Low	Low	Low

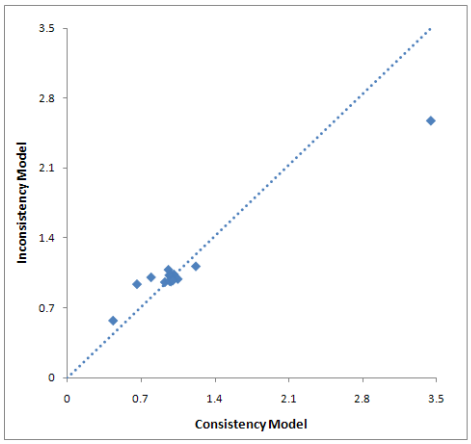
Low = low risk of bias; Unclear = insufficient detail to make judgment; High = high risk of bias

APPENDIX 5: ASSESSMENT OF INCONSISTENCY

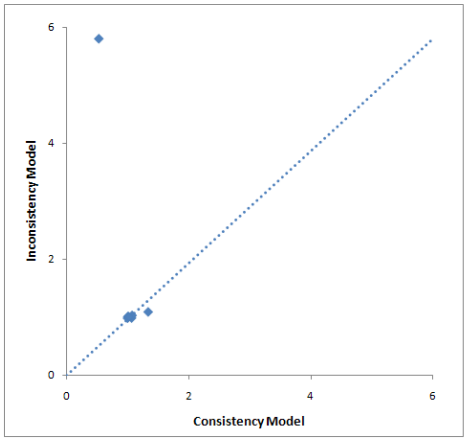
Two analyses were conducted, one using the standard consistency model and the other using an inconsistency model. The residual deviance and DIC statistics of the consistency and inconsistency models were then compared. To help identify the loops in which inconsistency is present, the posterior mean deviance of the individual data points in the inconsistency model were plotted against their posterior mean deviance in the consistency model.

In general, the consistency model has a lower posterior mean of the residual deviance and DIC and hence is a better fit than the inconsistency model for all outcomes.

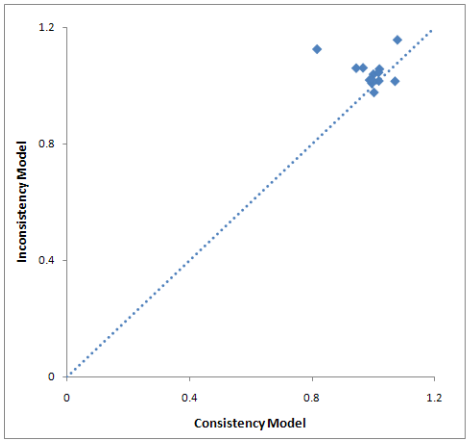
Extended: Recurrent VTEs – Plot of posterior mean deviance of the individual data points in the inconsistency model against their posterior mean deviance in the consistency model



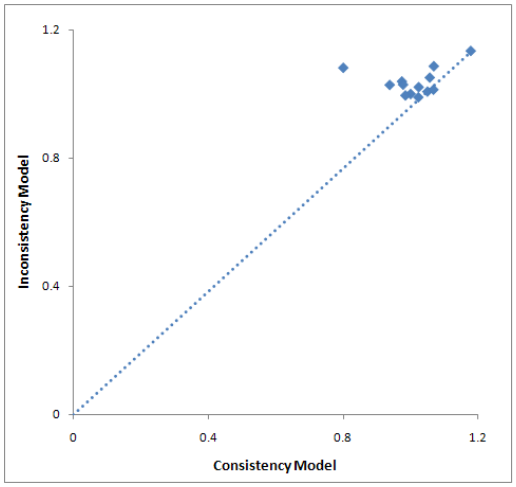
Extended: Recurrent DVTs – Plot of posterior mean deviance of the individual data points in the inconsistency model against their posterior mean deviance in the consistency model



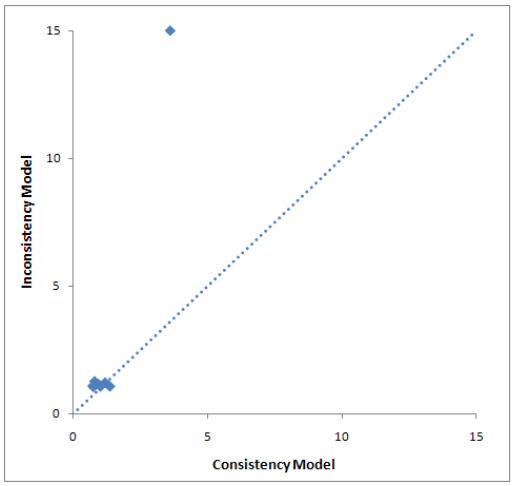
Extended: Recurrent PE (total) – Plot of posterior mean deviance of the individual data points in the inconsistency model against their posterior mean deviance in the consistency model



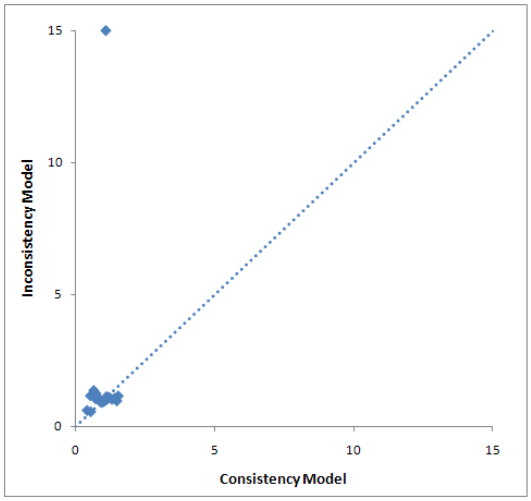
Extended: Recurrent non-fatal PE – Plot of posterior mean deviance of the individual data points in the inconsistency model against their posterior mean deviance in the consistency model



Extended: Recurrent fatal PE – Plot of posterior mean deviance of the individual data points in the inconsistency model against their posterior mean deviance in the consistency model



Extended: Major bleeds – Plot of posterior mean deviance of the individual data points in the inconsistency model against their posterior mean deviance in the consistency model



Extended: All-cause death – Plot of posterior mean deviance of the individual data points in the inconsistency model against their posterior mean deviance in the consistency model