Supplementary Material

Contents

Search history

((rivaroxaban OR apixaban OR dabigatran OR edoxaban) OR (pulmonary AND embolism) OR ((vein OR venous) AND (thrombosis OR thromboses OR thrombembolism OR thromboembolism)) OR (atrial AND (fibrillation OR flutter)) OR thromboprophylaxis OR anticoagulation OR prophylaxis OR prevention) AND (rivaroxaban OR apixaban OR dabigatran OR edoxaban)

Study acronyms

AMPLIFY: Apixaban for the Initial Management of Pulmonary Embolism and Deep-Vein Thrombosis as First-Line Therapy

APPRAISE-2: Apixaban for Prevention of Acute Ischemic Events 2

ARISTOTLE: Apixaban for Reduction in Stroke and Other Thromboembolic Events in Atrial Fibrillation

ATLAS ACS 2-TIMI 51: Anti-Xa Therapy to Lower Cardiovascular Events in Addition to Standard Therapy in Subjects with Acute Coronary Syndrome–Thrombolysis in Myocardial Infarction 51

AUGUSTUS: Aspirin Placebo in Patients with Atrial Fibrillation and Acute Coronary Syndrome or Percutaneous Coronary Intervention

AVARROES: Apixaban Versus Acetylsalicylic Acid to Prevent Stroke in Atrial Fibrillation Patients Who Have Failed or Are Unsuitable for Vitamin K Antagonist Treatment

COMMANDER HF: A Study to Assess the Effectiveness and Safety of Rivaroxaban in Reducing the Risk of Death, Myocardial Infarction, or Stroke in Participants with Heart Failure and Coronary Artery Disease Following an Episode of Decompensated Heart Failure

COMPASS: Cardiovascular Outcomes for People Using Anticoagulation Strategies

EINSTEIN-DVT: Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Deep Vein Thrombosis

EINSTEIN-CHOICE: Reduced-dosed Rivaroxaban in the Long-term Prevention of Recurrent Symptomatic Venous Thromboembolism

EINSTEIN-PE: Oral Direct Factor Xa Inhibitor Rivaroxaban in Patients With Acute Symptomatic Pulmonary Embolism

EMANATE: Eliquis evaluated in acute cardioversion compared to usual treatments for anticoagulation in subjects with atrial fibrillation

ENGAGE-AF – TIMI 48: Effective Anticoagulation with Factor Xa Next Generation in Atrial Fibrillation–Thrombolysis in Myocardial Infarction 48

ENSURE-AF: Edoxaban vs. Warfarin in Subjects Undergoing Cardioversion of Nonvalvular Atrial Fibrillation

Hokusai VTE: Comparative Investigation of Low Molecular Weight Heparin/Edoxaban Tosylate Versus Heparin/Warfarin in the Treatment of Symptomatic Deep-Vein Blood Clots and/or Lung Blood Clots

J-ROCKET AF: Japanese Rivaroxaban Once daily oral direct factor Xa inhibition Compared with vitamin K antagonism for prevention of stroke and Embolism Trial in Atrial Fibrillation

MANAGE: Management of Myocardial Injury After Noncardiac Surgery

NAVIGATE ESUS: New Approach Rivaroxaban Inhibition of Factor Xa in a Global Trial versus ASA to Prevent Embolism in Embolic Stroke of Undetermined Source

PIONEER AF: A Study Exploring Two Strategies of Rivaroxaban and One of Oral Vitamin K Antagonist in Patients With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention

RE-COVER: Efficacy and Safety of Dabigatran Compared to Warfarin for 6 Month Treatment of Acute Symptomatic Venous Thromboembolism

RE-COVER II: Phase III Study Testing Efficacy & Safety of Oral Dabigatran Etexilate vs Warfarin for 6 m Treatment for Acute Symp Venous Thromboembolism

RE-DUAL: Evaluation of Dual Therapy With Dabigatran vs. Triple Therapy With Warfarin in Patients With AF That Undergo a PCI With Stenting

RE-LY: Randomized Evaluation of Long-Term Anticoagulation Therapy

RE-MEDY: Secondary Prevention of Venous Thrombo Embolism

RE-SONATE: Twice-daily Oral Direct Thrombin Inhibitor Dabigatran Etexilate in the Long Term Prevention of Recurrent Symptomatic VTE

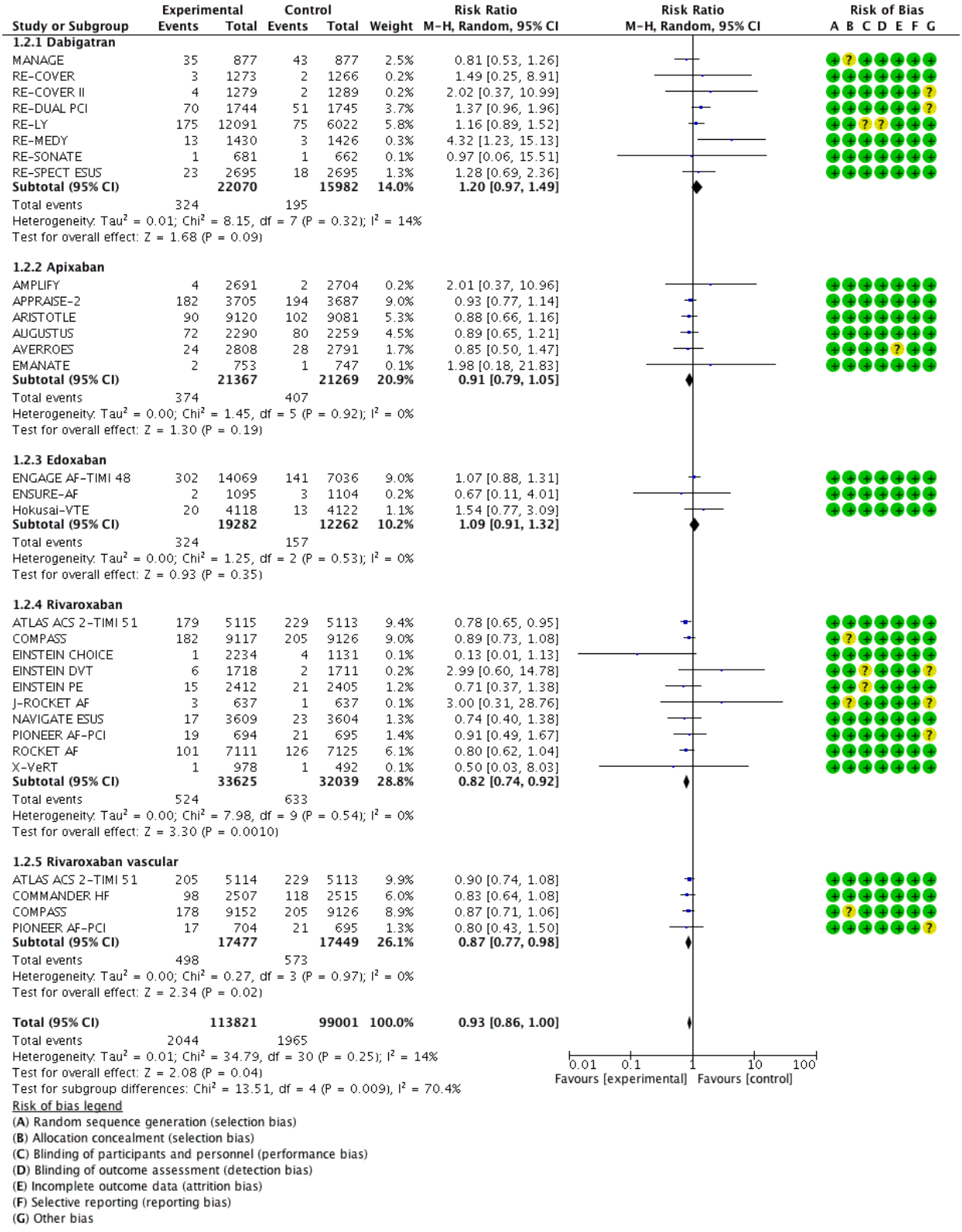
RE-SPECT ESUS: Dabigatran Etexilate for Secondary Stroke Prevention in Patients With Embolic Stroke of Undetermined Source

ROCKET-AF: An Efficacy and Safety Study of Rivaroxaban With Warfarin for the Prevention of Stroke and Non-Central Nervous System Systemic Embolism in Patients With Non-Valvular Atrial Fibrillation

X-VeRT: Explore the Efficacy and Safety of Once-daily Oral Rivaroxaban for the Prevention of Cardiovascular Events in Subjects With Nonvalvular Atrial Fibrillation Scheduled for Cardioversion

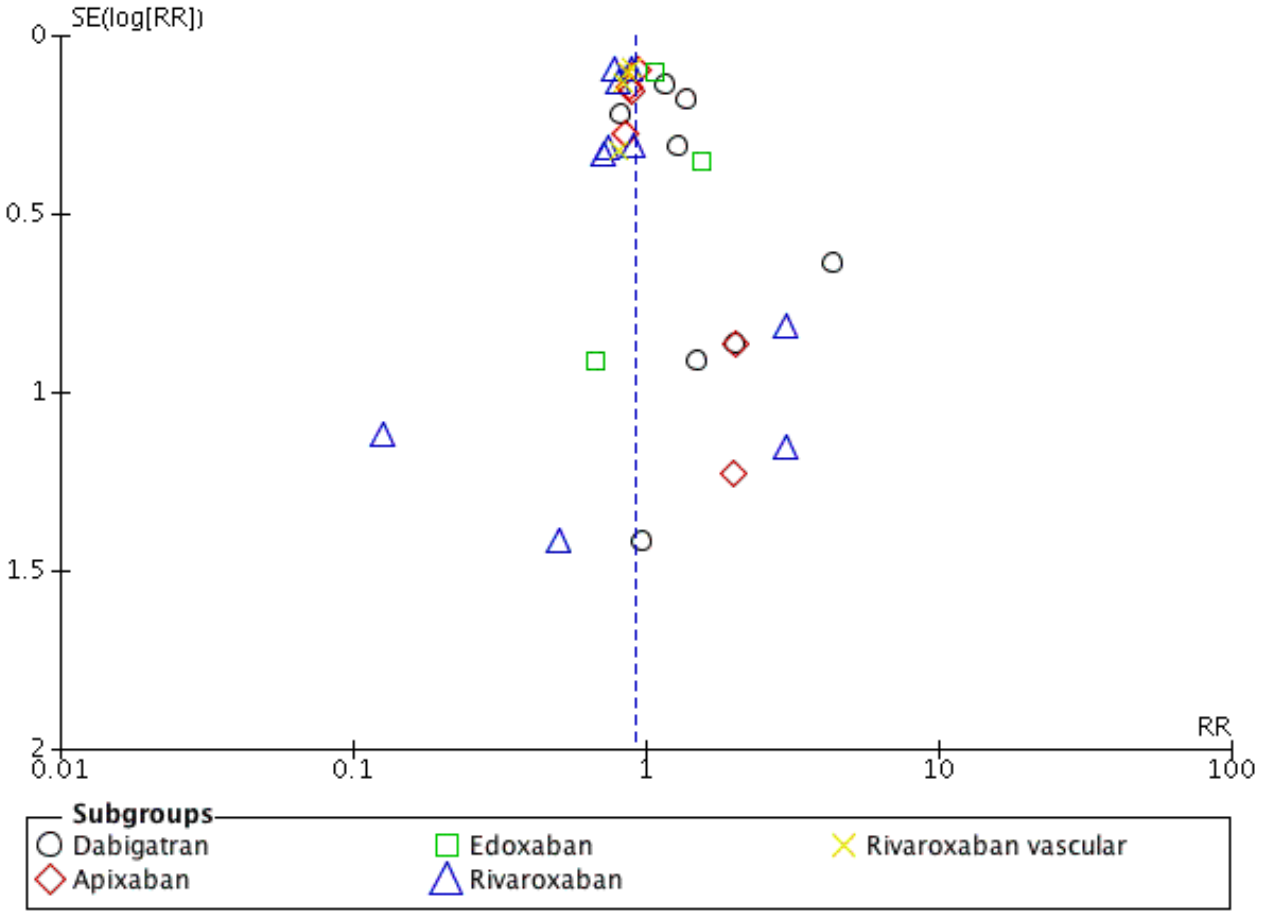
Supplementary Figure 1. Subgroup analysis according to DOAC treatment groups and risk of bias assessment.

Abbreviations: CI: confidence interval; M-H: Mantel-Haenszel. df: degree of freedom; For resolution of study acronyms please refer to the Supplementary data.



Supplementary Figure 2. Funnel plot of publication bias analysis

Abbreviations: SE: standard error; RR: risk ratio



Supplementary Table 1 Patient characteristics of the included trials.

Hypercholesterolemia defined as hypercholesterolemia and statin use. Abbreviations: DM: diabetes mellitus; NA: not available. For resolution of study acronyms please refer to the Supplementary data.

Study name/ First author (publication year)	Mean age (year)	Male	DM	Hypercholesterolaemia (%)	Hypertension (%)
AMPLIFY/G. Agnelli (2013)	57.2/56.7	58.3/59.1	NA	NA	NA
APPRAISE-2/ J. H. Alexander (2011)	67/67	67.4/68.3	48.7/47.0	NA	NA
ARISTOTLE/ C.B. Granger (2011)	70/70	64.5/65	25/24.9	45.0/45.1	87.3/87.6
ATLAS ACS 2-TIMI 51/ J. L. Mega (2012)	61.8/61.9/61.5	74.9/74.2/75.0	32.3/31.8/31.8	48.3/49.1/48.2	67.1667.6/67.5
AUGUSTUS/ R. D. Lopes (2019)	70.4/70.9	69.9/71.1	36.5/36.2	NA	88.6/88
AVARROES/ S. J. Connolly (2011)	70/70	59/58	19/20	NA	86/87
COMMANDER HF/ F. Zannad (2018)	66.5/66.3	78.0/76.2	40.8/40.9	NA	75.7/75.0
COMPASS/ J. W. Eikelboom (2017)	68.3/68.2/68.2	77.5/78.4/78.2	37.7/37.5/38.1	NA	75.5/75.1/75.4
EINSTEIN- DVT/ R. Bauersachs (2010)	55.8/56.4	57.4/56.3	NA	NA	NA
EINSTEIN-CHOICE/ J. I. Weitz (2017)	57.9/58.8	54.4/55.0	NA	NA	NA
EINSTEIN-PE/ H. R. Büller (2012)	57.9/57.5	54.1/51.7	NA	NA	NA
EMANATE/ M. D. Ezekowitz (2018)	64.5/64.7	66.5/67.1	18.7/20.5	NA	64.4/65.9
ENGAGE AF - TIMI 48/ R. P. Giugliano (2013)	72/72/72	62.5/62.1/61.2	35.8/35.4/36.2	NA	93.6/93.7/93.5
ENSURE-AF/ A. Goette (2016)	64.3/64.2	66/65	20/18	NA	78/78
Hokusai-VTE/ Hokusai investigators (2013)	55.7/55.9	57.3/57.2	NA	NA	NA
J-ROCKET AF/ M. Hori (2012)	71.0/71.2	82.9/78.2	39.0/37.1	NA	79.5/79.5
MANAGE/ Manage investigators (2018)	70/70	52/51	NA	NA	NA
NAVIGATE ESUS/ R. G. Hart (2018)	66.9/66.9	62/61	25/25	NA	77/78
PIONEER AF-PCI/ C.M. Gibson (2016)	70.4/70.0/69.9	74.5/75.5/73.4	NA	NA	NA
RE-COVER/ S. Schulman (2009)	56/55	58/58.9	NA	NA	NA

RE-COVER II/ S. Schulman (2014)	54.7/55.1	61.0/60.2	NA	NA	NA
RE-DUAL/ C. P. Cannon (2017)	71.5/71.7 68.6/68.8	74.2/76.5 77.6/77.7	36.9/37.9 34.1/39.7	NA	NA
RE-LY/ S. J. Connolly (2009)	71.4/71.5/71.6	64.3/63.2/63.3	23.4/23.1/23.4	44.9/43.9/44.4	78.8/78.9/78.9
RE-MEDY/ S. Schulman (2013)	55.4/53.9	60.9/61.1	10.5/7.6	NA	NA
RE-SONATE/ S. Schilman (2013)	56.1/55.5	65.9/65.0	8.4/7.6	NA	NA
RE-SPECT ESUS/ H. C. Diener (2019)	64.5/63.9	62.9/63.4	21.7/23.7	56.9/56.0	74.1/73.7
ROCKET AF/ M. R. Patel (2011)	73/73	60.3/60.3	40.4/39.5	NA	NA
X-VeRT/ R. Cappato (2014)	64.9/64.7	72.6/73.1	20.3/20.5	NA	65.0/68.7

Supplementary Table 2 Fixed effects model results of indirect comparisons of the different oral anticoagulants.

League tables shows the risk ratios (RR) and the 95% credible interval (CrI) of the different oral anticoagulants in a fixed effects model for myocardial infarction (Panel A), mortality (Panel B), and major bleeding (Panel C). RR <1 means that the top left treatment (Treatment 1) is better. * marks the comparisons where the CrI did not overlap the line of equivalence. Abbreviation: VKA: Vitamin K antagonist

A

Rivaroxaban				**Treatment 1**			
0.94 (0.82 – 1.08)	**Rivaroxaban vascular**			Risk Ratio (Credible interval) for Myocardial infarction	**Treatment 2**		
0.90 (0.74 – 1.09)	0.96 (0.79 – 1.17)	**Apixaban**					
0.85 (0.72 – 1.01)	0.90 (0.74 – 1.09)	0.94 (0.79 – 1.12)	**VKA**				
0.83 (0.70 – 0.98)*	0.88 (0.74 – 1.04)	0.92 (0.73 – 1.15)	0.97 (0.78 – 1.21)	**Aspirin**			
0.79 (0.68 – 0.92)*	0.84 (0.73 – 0.97)*	0.88 (0.74 – 1.04)	0.93 (0.78 – 1.12)	0.96 (0.79 – 1.17)	**Placebo**		
0.77 (0.60 – 1.00)	0.82 (0.63 – 1.08)	0.86 (0.66 – 1.11)	0.91 (0.75 – 1.10)	0.94 (0.70 – 1.25)	0.98 (0.75 – 1.27)	**Edoxaban**	
0.69 (0.55 – 0.87)*	0.74 (0.58 – 0.94)*	0.77 (0.61 – 0.97)*	0.82 (0.68 – 0.98)*	0.84 (0.65 – 1.08)	0.87 (0.69 – 1.10)	0.89 (0.68 – 1.17)	**Dabigatran**

B

Rivaroxaban vascular							
0.90 (0.73 – 1.09)	Apixaban						
0.88 (0.72 – 1.08)	0.99 (0.82 – 1.18)	Dabigatran					
0.88 (0.69 – 1.13)	0.99 (0.79 – 1.23)	1.00 (0.81 – 1.24)	Edoxaban				
0.88 (0.75 – 1.02)	0.99 (0.81 – 1.18)	1.00 (0.82 – 1.21)	1.00 (0.78 – 1.26)	Placebo			
0.86 (0.73 – 1.00)	0.96 (0.80 – 1.15)	0.97 (0.81 – 1.17)	0.97 (0.78 – 1.21)	0.97 (0.83 – 1.17)	Rivaroxaban		
0.82 (0.69 – 0.98)*	0.92 (0.76 – 1.11)	0.93 (0.77 – 1.14)	0.93 (0.73 – 1.19)	0.93 (0.77 – 1.15)	0.96 (0.82 – 1.12)	Aspirin	
0.81 (0.68 – 0.97)*	0.90 (0.79 – 1.05)	0.92 (0.81 – 1.06)	0.92 (0.78 – 1.09)	0.92 (0.77 – 1.11)	0.94 (0.82 – 1.10)	0.99 (0.83 – 1.18)	VKA

Treatment 1	Treatment 2
Risk Ratio (Credible interval) for Mortality	

C

Placebo				Treatment 1			
0.80 (0.46 – 1.39)	Aspirin			Risk Ratio (Credible interval) for Major bleeding	Treatment 2		
0.66 (0.42 – 1.05)	0.83 (0.51 – 1.36)	Dabigatran					
0.63 (0.37 – 1.06)	0.79 (0.47 – 1.31)	0.95 (0.59 – 1.51)	Apixaban				
0.51 (0.32 – 0.84)	0.64 (0.39 – 1.09)	0.77 (0.46 – 1.30)	0.81 (0.47 – 1.43)	Rivaroxaban vascular			
0.50 (0.25 – 1.00)	0.63 (0.31 – 1.25)	0.76 (0.40 – 1.40)	0.80 (0.41 – 1.52)	0.98 (0.48 – 1.95)	Edoxaban		
0.39 (0.24 – 0.63)*	0.49 (0.32 – 0.75)*	0.59 (0.38 – 0.90)*	0.63 (0.39 – 0.99)*	0.77 (0.49 – 1.17)	0.78 (0.42 – 1.45)	Rivaroxaban	
0.35 (0.22 – 0.56)*	0.45 (0.28 – 0.69)*	0.54 (0.38 – 0.74)*	0.57 (0.38 – 0.82)*	0.69 (0.43 – 1.09)	0.71 (0.42 – 1.19)	0.90 (0.65 – 1.26)	VKA

Sensitivity analyses

Regarding the clinical background 14 studies included patients with high risk for cerebrovascular event including 12 trials in atrial fibrillation (AF) and two trials of embolic stroke of undetermined source (ESUS). Nine studies were performed in patients with deep vein thrombosis and/or pulmonary embolism and eight studies included patient with coronary disease or with high risk for coronary event. (Table 1.) The included studies used different definitions for myocardial infarction (MI). Five studies used biomarker based definitions for MI that is compatible with the universal definition of MI (2012 version)(Definition 1.). Four studies defined MI as 2≥ of the followings: specific symptoms; ECG abnormalities, elevated cardiac biomarkers (Definition 2.) while in 19 studies investigator reported MI events were reported without further definitions (Definition 3.).

Subgroup analysis of studies of the different setting did show consistent results with the main findings of the full analysis. (Supplementary Table 3.) Studies using Definition 1. for MI did not composed a closed network. Both the subgroup analyses of studies using the other two definitions as well as the leave-out analyses of either definition showed consistent results as well. Similarly, ranking of the different treatments were not substantially effected in the subgroup analyses (Supplementary Figure 4.)

Abbreviation: NA: not available

Supplementary Table 3

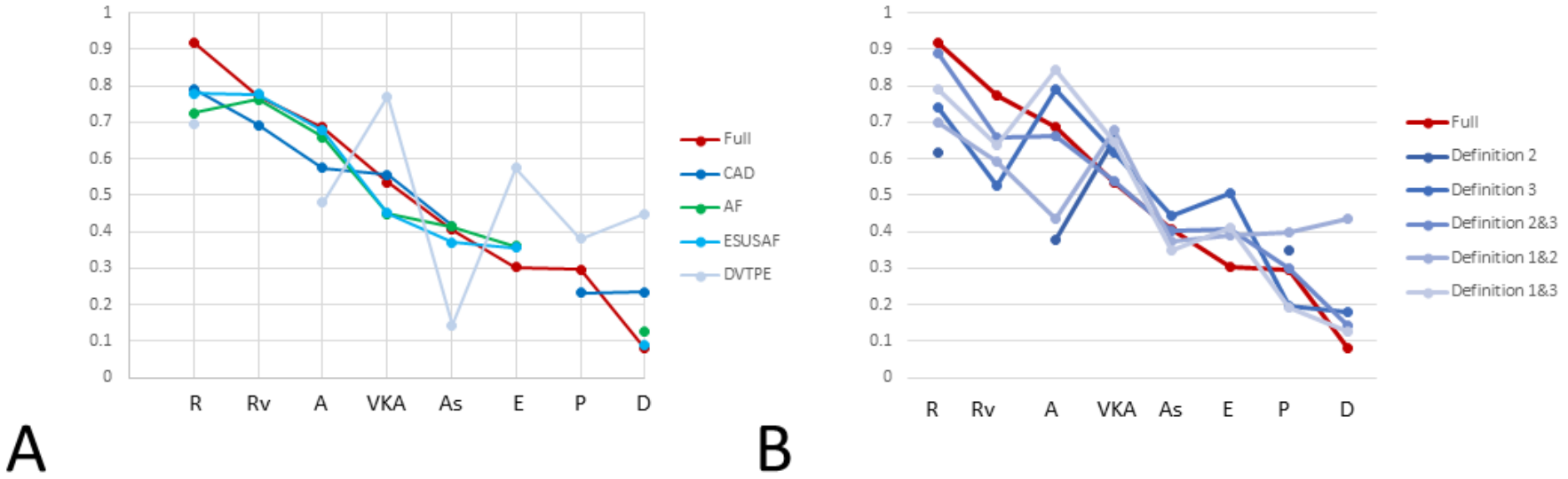
Abbreviation: VKA: Vitamin K antagonist; ESUS: embolic stroke of undetermined source; AF: atrial fibrillation; NA: not available

	number of studies	***Rivaroxaban vs Dabigatran***	***Rivaroxaban vascular vs Dabigatran***	***Apixaban vs Dabigatran***	***VKA vs Dabigatran***	***Rivaroxaban vs Placebo***	***Rivaroxaban vascular vs Placebo***
Full analysis	28	0.69* (0.53 – 0.89)	0.73 (0.56 – 0.96)	0.76 (0.58 – 0.99)	0.81* (0.65 – 0.98)	0.79* (0.65 – 0.94)	0.84* (0.70 – 0.99)
Clinical setting							
Stroke prevention (ESUS or AF)	14	0.66* (0.45 – 0.96)	0.60 (0.29 – 1.17)	0.71 (0.49 – 1.01)	0.79 (0.60 – 1.02)	NA	NA
Atrial fibrillation	12	0.61 (0.29 – 1.26)	0.67 (0.42 – 1.09)	0.71 (0.46 – 1.11)	0.80 (0.58 – 1.07)	NA	NA
Coronary disease (or high risk for coronary event)	8	0.69* (0.53 – 0.89)	0.73* (0.56 – 0.96)	0.76 (0.58 – 0.99)	0.81* (0.65 – 0.98)	0.79* (0.65 – 0.94)	0.84* (0.70 – 0.99)
Deep vein thrombosis / Pulmonary embolism	9	0.40 (0.05 – 4.62)	NA	0.80 (0.04 – 19.04)	0.36 (0.08 – 1.61)	0.40 (0.00 – 45.77)	NA
Myocardial infarction definitions							
Definition 1	5	-	-	-	-	-	-
Definition 2	4	NA	NA	NA	NA	0.46 (0.01 – 13.03)	NA
Definition 3	19	0.73 (0.46 – 1.09)	0.82 (0.47 – 1.26)	0.71 (0.43 – 1.05)	0.79 (0.52 – 1.05)	0.74 (0.49 – 1.03)	0.84 (0.52 – 1.15)

Definition 1&2	9	0.71 (0.16 – 5.92)	0.82 (0.15 – 12.40)	1.01 (0.17 – 14.28)	0.73 (0.22 – 2.56)	0.70 (0.09 – 3.78)	0.79 (0.18 – 3.84)
Definition 2&3	23	0.70* (0.49 – 0.97)	0.78 (0.51 – 1.12)	0.78 (0.55 – 1.08)	0.82 (0.59 – 1.07)	0.77* (0.58 – 0.99)	0.86 (0.61 – 1.12)
Definition 1&3	24	0.74 (0.54 – 1.00)	0.78 (0.57 – 1.07)	0.70* (0.51 – 0.95)	0.78* (0.62 – 0.96)	0.77* (0.61 – 0.95)	0.82* (0.67 – 0.99)

Supplementary Figure 4.

Plots showing the effect of the subgroup analyses on the ranking of the different treatment strategies as reflected by the Surface Under the Cumulative Ranking (SUCRA) values in the different subgroups. Abbreviations: CAD: coronary artery disease, AF: atrial fibrillation, ESUS: embolic stroke of undetermined source, DVT: deep vein thrombosis, PE: pulmonary embolism, R: rivaroxaban, Rv: rivaroxaban vascular, A: apixaban, VKA: vitamin K antagonist, As: aspirin, E: edoxaban, P: placebo, D: dabigatran.



Supplementary table 4. Leave-one-out network excluding the data from the Randomized Evaluation of Long Term Anticoagulant Therapy with Dabigatran Etexilate (RE-LY) trial

Abbreviation: VKA: vitamin K antagonist

Rivaroxaban				**Treatment 1**			
0.94 (0.79 – 1.11)	**Rivaroxaban vascular**			Risk Ratio (Credible interval) for Myocardial infarction	**Treatment 2**		
0.90 (0.72 – 1.15)	0.96 (0.76 – 1.24)	**Apixaban**					
0.86 (0.71 – 1.08)	0.92 (0.74 – 1.18)	0.96 (0.78 – 1.18)	**VKA**				
0.82 (0.65 – 0.99)	0.87 (0.69 – 1.08)	0.90 (0.68 – 1.17)	0.94 (0.71 – 1.21)	**Aspirin**			
0.78 (0.57 – 1.08)	0.83 (0.59 – 1.18)	0.86 (0.63 – 1.18)	0.90 (0.70 – 1.14)	0.96 (0.68 – 1.39)	**Edoxaban**		
0.78* (0.64 – 0.94)	0.84 (0.69 – 1.00)	0.87 (0.69 – 1.06)	0.90 (0.70 – 1.12)	0.96 (0.75 – 1.23)	1.00 (0.71 – 1.39)	**Placebo**	
0.66* (0.49 – 0.89)	0.71* (0.51 – 0.96)	0.73 (0.53 – 1.00)	0.76 (0.57 – 1.00)	0.81 (0.59 – 1.13)	0.85 (0.58 – 1.22)	0.85 (0.63 – 1.14)	**Dabigatran**