Efficacy and Harms of Direct Oral Anticoagulants in the Elderly for Stroke Prevention in Atrial Fibrillation and Secondary Prevention of Venous Thromboembolism Systematic Review and Meta-Analysis

Manuj Sharma, MClinRes; Victoria R. Cornelius, PhD; Jignesh P. Patel, PhD; J. Graham Davies, PhD; Mariam Molokhia, PhD

Background—Evidence regarding the use of direct oral anticoagulants (DOACs) in the elderly, particularly bleeding risks, is unclear despite the presence of greater comorbidities, polypharmacy, and altered pharmacokinetics in this age group.

- *Methods and Results*—We performed a systematic review and meta-analysis of randomized trials of DOACs (dabigatran, apixaban, rivaroxaban, and edoxaban) for efficacy and bleeding outcomes in comparison with vitamin K antagonists (VKA) in elderly participants (aged \geq 75 years) treated for acute venous thromboembolism or stroke prevention in atrial fibrillation. Nineteen studies were eligible for inclusion, but only 11 reported data specifically for elderly participants. The efficacy in managing thrombotic risks for each DOAC was similar or superior to VKA in elderly patients. A nonsignificantly higher risk of major bleeding than with VKA was observed with dabigatran 150 mg (odds ratio, 1.18; 95% confidence interval, 0.97–1.44) but not with the 110-mg dose. Significantly higher gastrointestinal bleeding risks with dabigatran 150 mg (1.78, 1.35–2.35) and dabigatran 110 mg (1.40, 1.04–1.90) and lower intracranial bleeding risks than VKA for dabigatran 150 mg (0.43, 0.26–0.72) and dabigatran 110 mg (0.36, 0.22–0.61) were also observed. A significantly lower major bleeding risk in comparison with VKA was observed for apixaban (0.63, 0.51–0.77), edoxaban 60 mg (0.81, 0.67–0.98), and 30 mg (0.46, 0.38–0.57), whereas rivaroxaban showed similar risks.
- *Conclusions*—DOACs demonstrated at least equal efficacy to VKA in managing thrombotic risks in the elderly, but bleeding patterns were distinct. In particular, dabigatran was associated with a higher risk of gastrointestinal bleeding than VKA. Insufficient published data for apixaban, edoxaban, and rivaroxaban indicate that further work is needed to clarify the bleeding risks of these DOACs in the elderly.

Systematic Review Registration—http://www.crd.york.ac.uk/PROSPERO. Unique identifier: PROSPERO CRD42014007171/ (Circulation. 2015;132:194-204. DOI: 10.1161/CIRCULATIONAHA.114.013267.)

> Key Words: aged ■ anticoagulants ■ atrial fibrillation ■ hemorrhage ■ meta-analysis ■ systematic review ■ venous thromboembolism

Advanced age is a significant risk factor for atrial fibrillation (AF) and venous thromboembolism (VTE).^{1,2} AF prevalence estimates are <0.1% in the population aged <55 years and rise to >8% in those aged >80 years.³ Patients with AF have a 5-fold greater risk of stroke.^{1,4} The increased risk of VTE with age is also estimated to double with every decade after the age of 40.^{5,6} The major complication of VTE is recurrence.⁷ Anticoagulant therapy is essential for managing these thrombotic risks, particularly in an older adult population who are at higher risk.

Clinical Perspective on p 204

Vitamin K antagonists (VKAs) have until recently been the only oral anticoagulant treatment option available for patients. However, 4 direct oral anticoagulants (DOACs), dabigatran, rivaroxaban, apixaban, and edoxaban, have now undergone trials to investigate their harm for use and efficacy in the management of thromboembolic risk in AF and acute VTE. They have been adopted into clinical practice because they confer certain practical advantages over VKA.⁸ They are reported to have fewer drug-drug and drug-food interactions and have been licensed for use without the need for routine monitoring of anticoagulation effect. This is attributable to

Circulation is available at http://circ.ahajournals.org

DOI: 10.1161/CIRCULATIONAHA.114.013267

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From Department of Primary Care and Public Health Sciences, King's College London, United Kingdom (M.S., V.R.C., M.M.); Department of Clinical Pharmacy, Guy's and St Thomas Hospital NHS Foundation Trust, London, United Kingdom (M.S.); Department of Haematological Medicine, King's College Hospital, London, United Kingdom (J.P.P.); and Institute of Pharmaceutical Science, King's College London, United Kingdom (J.P.P., J.G.D.).

The online-only Data Supplement is available with this article at http://circ.ahajournals.org/lookup/suppl/doi:10.1161/CIRCULATIONAHA. 114.013267/-/DC1.

Correspondence to Manuj Sharma, MClinRes, and Mariam Molokhia, PhD, Department of Primary Care and Public Health Sciences, King's College London, Capital House, Weston Street, London SE1 3QD, UK. E-mail manujsharma2014@gmail.com or mariam.molokhia@kcl.ac.uk © 2015 American Heart Association, Inc.

their predictable pharmacokinetic profiles.⁹ However, similar to VKA therapy, they pose a significant risk of bleeding that is complicated further by the lack of a reversal agent.¹⁰

Although several reviews have evaluated the efficacy and harms of DOACs in the general population,^{11,12} the specific evidence base for their use in the elderly aged \geq 75 years remains unclear. The risk of harm with DOACs in comparison with VKAs, in particular, bleeding risks, warrants clarity given the presence of greater comorbidities, polypharmacy, and altered pharmacokinetics in the elderly.¹³

We undertook a systematic review and meta-analysis of randomized controlled trials for use of the DOACs in the management of AF and acute VTE, where VKAs were used as a comparator. No randomized controlled trial for DOACs has been conducted thus far that involves only elderly participants. Hence, our approach was to evaluate the DOACs for efficacy and harms in comparison with VKA in the elderly participants aged \geq 75 years from each trial. These results were then put in context by presenting the results from the total trial populations (all ages), based on which marketing authorizations for DOACs have been granted.

Methods

Eligibility Criteria

We identified all phase II and III randomized controlled trials of the DOACs (dabigatran 150 mg and 110 mg, apixaban, rivaroxaban, and edoxaban 60 mg and 30 mg) in patients being treated for acute VTE (deep vein thrombosis and/or pulmonary embolism) and for stroke prevention in AF. We required that studies have a minimum of 3 months of patient follow-up and used VKA as a comparator. For phase II studies, we extracted data for doses that were used for subsequent phase III clinical trials only. We excluded studies if they were extensions of previously completed trials for additional follow-up.

Search Strategy

Medline, Embase, and CENTRAL (Cochrane central register of controlled trials) were searched for articles in English from November 22, 1993 to November 22, 2013. The search was subsequently updated to June 1, 2014. Search strategies for each database are presented in the online-only Data Supplement. Clinical trial registries were also searched and conference proceedings were identified by using Web of Science, Scopus, and International Pharmaceutical abstracts. Additional studies, including unpublished and gray literature, were identified by screening reference lists of retrieved studies and review articles. In instances where subgroup data for elderly patients aged ≥75 years was unpublished, drug manufacturers, authors, and relevant regulatory bodies, eg, US Food and Drug Administration and European Medicines Agency, were contacted to request the data. The search strategy was checked for appropriateness by a second investigator.

Study Selection

One reviewer (M.S.) performed the full search strategy, removed duplicates, and selected the articles. One of three other independent reviewers (V.R.C., J.P.P., J.G.D.) analyzed these selections for the eligibility of inclusion. Studies were screened based on title and abstract initially, after which full texts were obtained and assessed for inclusion.

Data Extraction

All data were extracted by 2 reviewers (M.S. with V.R.C., J.P.P., or J.G.D.) independently into standardized forms and entered into Microsoft Excel. Data extracted included study details, participant details, intervention details (drug name, dose, frequency), and

comparator details (time in therapeutic range). Data were collected for the subgroup of elderly patients aged \geq 75 years and the total trial population (all ages) for each study. The intention-to-treat populations were used where possible. Primary efficacy outcomes were stroke or systemic embolism for AF trials, and recurrent VTE for VTE studies. The primary safety outcome was pooled major bleeding from both AF and VTE studies. Secondary outcomes were gastrointestinal bleeding, intracranial bleeding, clinically relevant bleeding, and fatal bleeding. Studies were also assessed for potential bias (low, unclear, high) using the Cochrane Collaboration risk of bias assessment.¹⁴ All disagreements between reviewers were resolved by consensus or discussion with a third reviewer.

Statistical Analyses

The treatment effect for DOAC in comparison with VKA was estimated by meta-analyses for each drug separately (dabigatran 150 mg and 110 mg, apixaban, rivaroxaban, and edoxaban 60 mg and 30 mg). This was undertaken for elderly participants aged ≥75 years for each outcome of interest. It was then repeated for the total trial participants to allow comparison. Data synthesis was invariably undertaken by using a Peto odds ratio fixed-effects model.¹⁵ However, when there was high heterogeneity with ≥ 4 studies contributing to the estimate, a random-effects model (DerSimonian and Laird) was used.16 Use of a random-effects model to determine estimates is highlighted in the results through use of the annotation "Random Effects" in brackets alongside the odds ratio estimate. Study heterogeneity was analyzed by using the I^2 statistic. Sensitivity analysis was undertaken by indication, mean duration of patient follow-up (<6 months versus ≥ 6 months), and where high heterogeneity (>75%) was evident. A funnel plot was used to assess publication bias. This article was prepared in accordance with the preferred reporting items for systematic reviews and meta-analysis (PRISMA).17 All analyses were performed using Review Manager software (Rev Man 5.2). Where only confidence intervals were available for outcomes, event rates were calculated by using the method detailed by Tierney and colleagues.18

Results

Our search identified 19 multicentered, randomized controlled trials eligible for inclusion with 11 reporting data on elderly patients as shown in online-only Data Supplement Figure I. The detailed rationale behind the exclusion of studies is presented in Table I in the online-only Data Supplement. Additional unpublished data were requested for all 19 studies from manufacturers, authors, and regulatory authorities, but only data for 4 of 19 (21.0%) studies were obtained.¹⁹⁻²² Additional data from documentation published by regulatory authorities and conference proceedings for 6 of 19 (31.6%) studies was also retrieved.^{19,20,23-26}

Study Characteristics

Eleven phase III and 8 phase II studies were identified consisting of 5 dabigatran trials,^{24,27-30} 4 apixaban trials,^{26,31-33} 5 rivaroxaban trials,^{19–23} and 5 edoxaban trials.^{25,34–37} All studies used warfarin as a comparator with 4 studies also allowing use of other VKAs.^{19,20,23,33} Follow-up periods were longest for the phase III AF studies as shown in Table 1. Included studies mostly used definitions for major bleeding as per the International Society of Thrombosis and Haemostasis,³⁸ whereas 2 phase II studies used a slight variation of this definition.^{25,36} Definitions used to classify clinically relevant bleeding showed minimal variation and essentially consisted of a major bleed or any overt bleeding event that did not meet the criteria for major bleeding but led to either hospital admission for bleeding, physician-guided treatment, or an alteration in

Study	Indication	Standard Dose	Phase	Duration, mo
Dabigatran				
Bibr 1048, 200524	AF	110 mg BD or 150 mg BD	Ш	3
Petro, 2007 ³⁰	AF	150 mg BD extracted	Ш	3
Re-ly, 200927	AF	Ш	24*	
Recover I, 2010 ²⁸	VTE	150 mg BD	Ш	6
Recover II, 2013 ²⁹	VTE	150 mg BD	Ш	6
Apixaban				
Aristotle, 2011 ²⁶	AF	5 mg BD	Ш	21.6*
Aristotle-J, 2011 ³²	AF	5 mg BD extracted	Ш	3
Botticelli-DVT, 200833	VTE	5 mg BD	П	3
Amplify, 2013 ³¹	VTE	10 mg BD for 7 days then 5 mg BD	Ш	6
Rivaroxaban				
Rocket-AF, 2011 ²²	AF	20 mg 0D	Ш	23.2*
J-Rocket AF, 2011 ²¹	AF	15 mg OD	Ш	30
Einstein-DVT Dose Study, 200823	VTE	20 mg 0D extracted	П	3
Einstein-DVT, 201019	VTE	15 mg BD for 21 days then 20 mg OD	Ш	3, 6, or 12
Einstein-PE, 2012 ²⁰	VTE	15 mg BD for 21 days then 20 mg 0D	Ш	3, 6, or 12
Edoxaban				
Edox-P2, 2010 ³⁶	AF	30 mg or 60 mg 0D extracted	Ш	3
Edox-P2A, 2010 ²⁵	AF	30 mg OD or 60 mg OD	Ш	3
Edox-J, 2012 ³⁷	AF	30 mg or 60 mg 0D extracted	Ш	3
Engage-AF-Timi 48, 2013 ³⁵	AF	30 mg OD or 60 mg OD	III	33.6*
Hokusai-VTE, 2013 ³⁴	VTE	60 mg OD	Ш	3–12

 Table 1.
 Characteristics of Included Studies for DOACs in Atrial Fibrillation and Venous

 Thromboembolism
 Compared to the studies of the st

AF indicates atrial fibrillation; BD, twice daily; OD, once daily; and VTE, venous thromboembolism.

*Studies with duration reported as median follow-up.

therapy. Intracranial and fatal bleeding were both included as part of the major bleeding events. Gastrointestinal bleeding was recorded also as either a major or clinically relevant bleed based on independent adjudication in each study.

Patient Characteristics

Data were reported for 31 418 elderly participants aged \geq 75 years out of a total of 102 479 participants aged \geq 18 years. Mean age ranged from 64.5 to 71.7 years in AF studies and 54.4 to 59.0 years in VTE studies (Table 2). Mean CHADS₂ scores for AF studies ranged from 1.8 to 3.5 where reported, whereas the percentage of patients recruited with a history of a previous VTE ranged from 15.1% to 29.0% in the VTE studies. The rivaroxaban study, Rocket-AF, recruited patients with the highest CHADS₂ scores of 3.5 in each arm.²² The dabigatran study, Recover I, was the phase III study that recruited the highest percentage of patients with previous VTE for DOAC (25.7%) and VKA (25.4%) therapy, respectively.²⁸ All studies permitted usage of aspirin, if necessary, with DOACs; however, the percentage of patients on aspirin in individual studies was inadequately reported as shown in Table II in the online-only Data Supplement.

Risk of Bias Assessment

Results of the risk of bias assessment for all 19 studies are presented in Figure 1. Eleven studies were open-label and at

high risk of bias because of the lack of blinding of patients and personnel to the intervention.^{19,20,23-25,27,30,32,33,36,37} However, all studies where reported were assessed by blinded adjudicators for the outcomes. Two studies were deemed to be at high risk of bias from incomplete outcome data attributable to unclear attrition.^{22,23} In both Rocket-AF and the Einstein-DVT dose study,^{22,23} 93 patients were omitted from analysis owing to protocol violations. Bibr 1048 was judged to be at risk of other bias because a full publication for the trial was not available.²⁴ The funnel plots as shown in Figure 2 for the total population indicate we obtained a reasonable expected balance of positive and negative results from the included studies. Only 11 studies reported data on the elderly population; hence, the assessment of publication bias was challenging. Data were requested from the pharmaceutical companies and regulatory bodies where elderly subgroup data had not been reported. However, only limited data were made available.

Outcomes

Primary Efficacy Outcomes

Each DOAC was shown to be at least as effective as VKA in elderly patients. This was both in reducing the risk of stroke or systemic embolism in AF, and the risk of recurrent venous

	Total Participants		Participants ≥75		Mean Age (SD)		Men	. %	CHADS	, (SD)	Previous VTE (%)		
Study	DOAC	VKA	DOAC	VKA	DOAC	VKA	DOAC	VKA	DOAC	VKA	DOAC	VKA	
Dabigatran													
Bibr 1048, 2005 ²⁴	104	62	NA	NA	69.0 (8.4)	67.4 (8.8)	85.6	91.9	NA	NA	NA	NA	
Petro, 2007 ³⁰	169	70	NA	NA	70.0 (8.1)	69.0 (8.3)	81.3	84.3	NA	NA	NA	NA	
Re-ly, 200927	12 091	6022	4815	2423	71.4 (8.7)	71.6 (8.6)	63.7	63.3	2.1 (1.1)	2.1 (1.1)	NA	NA	
Recover I, 2010 ²⁸	1274	1265	NA	NA	55.0 (15.8)	54.4 (16.2)	58.0	58.9	NA	NA	327 (25.7)	322 (25.4)	
Recover II, 2013 ²⁹	1279	1289	NA	NA	54.7 (16.2)	55.1 (16.3)	61.0	60.2	NA	NA	247 (19.3)	203 (15.8)	
Apixaban													
Aristotle, 2011 ²⁶	9120	9081	2850	2828	69.1 (9.6)	69.0 (9.7)	64.5	65.0	2.1 (1.1)	2.1 (1.1)	NA	NA	
Aristotle-J, 201132	74	74	45	23	70.0 (8.1)	71.7 (7.0)	82.4	81.1	2.1	1.9	NA	NA	
Botticelli-DVT,200833	130	128	NA	NA	56.0 (14.0)	59.0 (16.0)	64.0	63.0	NA	NA	37 (28.5)	31 (24.2)	
Amplify, 2013 ³¹	2691	2704	398	370	57.2 (16.0)	56.7 (16.0)	58.3	59.1	NA	NA	463 (17.2)	409 (15.1)	
Rivaroxaban													
Rocket-AF, 2011 ²²	7131	7133	3082	3082	71.2 (9.4)	71.2 (9.4)	60.3	60.3	3.5 (0.9)	3.5 (0.9)	NA	NA	
J-Rocket AF, 2011 ²¹	640	640	252	246	71.0 (8.3)	71.2 (7.9)	82.9	78.2	3.3	3.2	NA	NA	
Einstein-DVT Dose Study, 2008 ²³	136	137	NA	NA	58.0	57.0	47.0	53.0	NA	NA	28 (21.0)	40 (29.0)	
Einstein-DVT, 201019	1731	1718	215	225	55.8 (16.4)	56.4 (16.3)	57.4	56.3	NA	NA	336 (19.4)	330 (19.2)	
Einstein-PE, 2012 ²⁰	2419	2413	441	402	57.9 (7.3)	57.5 (7.2)	54.1	51.7	NA	NA	455 (18.8)	489 (20.3)	
Edoxaban													
Edox-P2, 201036	470	251	NA	NA	65.0 (8.6)	66.0 (8.5)	63.0	60.4	NA	NA	NA	NA	
Edox-P2A, 2010 ²⁵	159	76	21	10	65.4 (8.4)	64.5 (9.5)	66.6	62.7	1.9 (1.1)	1.8 (1.1)	NA	NA	
Edox-J, 201237	267	134	77	35	68.9	68.8	73.2	82.9	2.0	2.2	NA	NA	
Engage-AF-Timi 48, 2013 ³⁵	14 069	7036	5654	2820	70.6 (9.4)	70.5 (9.4)	61.6	62.5	2.8 (1.0)	2.8 (1.0)	NA	NA	
Hokusai-VTE, 201334	4143	4149	560	544	55.7 (16.3)	55.9 (16.2)	57.3	57.2	NA	NA	784 (19.0)	736 (17.9)	

Table 2. Patient Characteristics in Included Studies for DOACs in Atrial Fibrillation and Venous Thromboembolism

DOAC indicates direct oral anticoagulants; NA, not available; SD, standard deviation; VKA, vitamin K antagonist; and VTE, venous thromboembolism.

thromboembolism in VTE. Efficacy observed was also similar to that seen in the total population (all ages).

In AF studies, a significant reduction in the risk of stroke or systemic embolism in comparison with VKA was observed for dabigatran 150 mg (odds ratio [OR], 0.66; 95% confidence interval [CI], 0.49–0.90; *P*=0.009) and apixaban (OR, 0.70; 95% CI, 0.52–0.93; *P*=0.01). This significant risk reduction was also maintained in the total population for both DOACs (Figure 3).

Results in the elderly for all 4 DOACs in reducing risk of recurrent VTE are shown in Figure 4. These estimates were limited by low event rates, but did not indicate inferiority in comparison with VKA. Results from the total population also supported noninferiority to VKA.

Primary Safety Outcome

Major Bleeding

In the elderly, a significant reduction in the risk of major bleeding in comparison with VKA was observed for apixaban (OR, 0.63; 95% CI, 0.51–0.77; P<0.0001), edoxaban 60 mg (OR, 0.81; 95% CI, 0.67–0.98; P=0.03) and 30 mg (OR, 0.46; 95% CI, 0.38–0.57; P<0.0001). The superiority to VKA

for these DOACs was also observed in the total population (Figure 5).

Dabigatran 150 mg showed a nonsignificant, higher risk of major bleeding in comparison with VKA in elderly patients (OR, 1.18; 95% CI, 0.97–1.44; P=0.10), although risk was similar to VKA with the 110-mg dose. In contrast in the total population, a nonsignificant lower risk than VKA was observed with the 150-mg dose, whereas a significantly lower risk was observed with the 110-mg dose.

Secondary Outcomes

Gastrointestinal Bleeding

In elderly patients, gastrointestinal bleeding was significantly increased in comparison with VKA with dabigatran 150 mg (OR, 1.78; 95% CI, 1.35–2.35; P<0.0001) and 110 mg (OR, 1.40; 95% CI, 1.04–1.90; P=0.03) (Figure 6). Data regarding the risk of gastrointestinal bleeding in the elderly for the other DOACs was not published or made available.

For the total population: the significantly increased risk of gastrointestinal bleeding in comparison with VKA was sustained with dabigatran 150 mg, but not with the 110-mg dose. In the total population, rivaroxaban and edoxaban 60 mg also

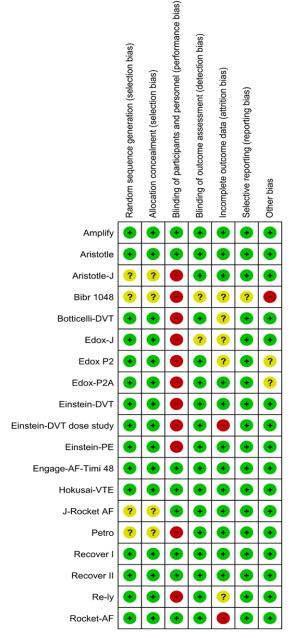


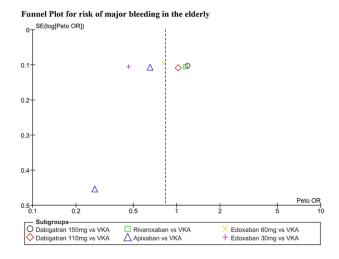
Figure 1. Summary of the risk of bias assessment. Green(+) indicates low-bias risk; red (-), high-bias risk; and yellow(?), unclear bias risk.

showed a significantly higher risk of gastrointestinal bleeding than VKA.

Intracranial Bleeding

In the elderly, a significant reduction in the risk of intracranial bleeding in comparison with VKA was observed for dabigatran 150 mg (OR, 0.43; 95% CI, 0.26–0.72; P=0.001), dabigatran 110 mg (OR, 0.36; 95% CI, 0.22–0.61; P=0.0001), and apixaban (OR, 0.38; 95% CI, 0.24–0.59; P<0.0001). A nonsignificant reduction was also observed for rivaroxaban, whereas data were not available for edoxaban in the elderly.

In the total population, all DOACs showed a significantly lower risk of intracranial bleeding in comparison with VKA as shown in Figure 6.



Funnel Plot for risk of major bleeding in the total population

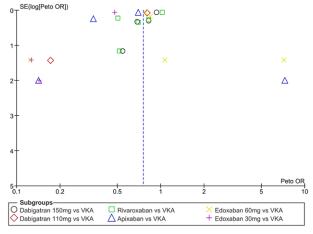


Figure 2. Funnel plot comparison for the risk of major bleeding in the elderly and the total population. OR indicates odds ratio; SE, standard error; and VKA, vitamin K antagonist. *Note: *y* axis scales differ between plots above.

Clinically Relevant Bleeding

In the elderly, the risk of clinically relevant bleeding where reported was not significantly different for DOACs than for VKA, with the exception of apixaban, which demonstrated superiority to VKA (OR, 0.64; 95% CI, 0.54–0.76; P<0.0001; random effects).

In the total population, apixaban, dabigatran 150 mg, and edoxaban 60 mg and 30 mg demonstrated superiority to VKA in reducing this risk (Figure 6).

Fatal Bleeding

In the elderly, the risk of fatal bleeding where reported was not significantly different for DOACs than for VKA, with the exception of rivaroxaban, which showed superiority (OR, 0.53; 95% CI, 0.30–0.93; P=0.03). Data for this outcome were limited by the low number of fatal bleeding events in the studies. No data were available for edoxaban.

In the total population, a significantly reduced risk of fatal bleeding in comparison with VKA was observed for dabigatran 110 mg, rivaroxaban, edoxaban 60 mg, and edoxaban 30 mg (Figure 6).

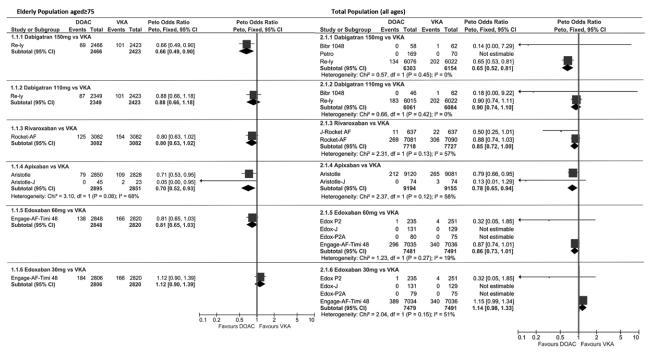


Figure 3. Risk of stroke or systemic embolism in atrial fibrillation studies in the elderly (left) and the total population (right). Cl indicates confidence interval; DOAC, direct oral anticoagulants; and VKA, vitamin K antagonist. *Event numbers for Engage-AF-Timi 48 in the elderly have been estimated from published confidence intervals.

Heterogeneity Assessment and Sensitivity Analysis

Significant heterogeneity ($l^2>75\%$) was found when all 4 DOACs were pooled together and compared with VKA for major bleeding, gastrointestinal bleeding, and fatal bleeding. Moderate heterogeneity ($l^2=50\%-75\%$) was found for the risk of stroke or systemic embolism and intracranial bleeding. Sensitivity analysis undertaken by removing the only direct thrombin inhibitor, dabigatran, and leaving in the 3 factor Xa inhibitors showed similar high heterogeneity across outcomes. Investigation indicated that this high heterogeneity may be

attributable to either differing baseline bleeding risks in the studies or true differences between each DOAC, which, when pooled, were masked. This is why results for all 4 DOACs pooled together in comparison with VKA are not presented.

There was evidence of statistical heterogeneity in the estimate for risk of major bleeding for rivaroxaban in comparison to VKA in the elderly (l^2 =82%). This was largely attributable to the unusually high number of bleeding events in the VKA arm in Einstein PE in comparison with the other 3 rivaroxaban AF and VTE studies. Heterogeneity was also present for the estimate for the risk of clinically relevant bleeding for

Elderly Population	ı aged≥	75									
	DOA	С	VKA		Peto Odds Ratio	Peto Odds Ratio		DOAC	VKA	Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events	Total	Events	Total	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI	Study or Subgroup	Events Tota	I Events Total	Peto, Fixed, 95% CI	Peto, Fixed, 95% Cl
1.2.1 Dabigatran 150mg vs	s VKA						2.2.1 Dabigatran 150mg v	vs VKA			
Pooled Recover Studies	3	253	5	276	0.66 [0.16, 2.66]		Recover I	30 1274	4 27 1265	1.11 [0.65, 1.87]	_
Subtotal (95% CI)		253		276	0.66 [0.16, 2.66]		Recover II	30 1279	28 1289	1.08 [0.64, 1.82]	_
							Subtotal (95% CI)	2553	2554	1.09 [0.76, 1.58]	
							Heterogeneity: Chi ² = 0.0	0, df = 1 (P = 0.9	95); I² = 0%		
1.2.2 Apixaban vs VKA							2.2.2 Apixaban vs VKA				
Amplify	7	389	13	360	0.50 [0.21, 1.21]		Amplify	59 2609	9 71 2635	0.84 [0.59, 1.18]	
Subtotal (95% CI)	'	389	13	360	0.50 [0.21, 1.21]		Botticelli-DVT	3 117	7 3 118		
		000		000	0.00 [0.2.1, 1.2.1]		Subtotal (95% CI)	2726	5 2753	0.84 [0.60, 1.18]	▲
							Heterogeneity: Chi ² = 0.0	5, df = 1 (P = 0.8	32); I ² = 0%		
1.2.3 Rivaroxaban vs VKA							2.2.3 Rivaroxaban vs VK	A			
Einstein-DVT	4	215	10	225	0.43 [0.15, 1.25]		Einstein-DVT	36 173	1 51 1718	0.70 [0.46, 1.07]	
Einstein-PE	11	441	13	402	0.77 [0.34, 1.72]		Einstein-DVT dose study	3 11	5 7 101	0.38 [0.11, 1.34]	
Subtotal (95% CI)		656		627	0.62 [0.33, 1.18]		Einstein-PE	50 241	9 44 2413	1.14 [0.76, 1.71]	
Heterogeneity: Chi ² = 0.70,	df = 1 (F	P = 0.40	0); I² = 0%				Subtotal (95% CI)	4265	5 4232	0.86 [0.65, 1.15]	
							Heterogeneity: Chi ² = 4.3	4, df = 2 (P = 0.1	11); I² = 54%		
1.2.4 Edoxaban 60mg vs V	KA						2.2.4 Edoxaban 60mg vs	VKA			
Hokusai-VTE	14	560	27	544	0.50 [0.27, 0.94]		Hokusai-VTE	130 411	8 146 4122	0.89 [0.70, 1.13]	
Subtotal (95% CI)	14	560	2.1	544	0.50 [0.27, 0.94]		Subtotal (95% CI)	4118			
					F						
					0.	1 0.2 0.5 1 2 5 10					0.1 0.2 0.5 1 2 5
						Favours DOAC Favours VKA					Favours DOAC Favours VKA

Figure 4. Risk of recurrent venous thromboembolism in venous thromboembolism studies in the elderly (left) and the total population (right). Cl indicates confidence interval; DOAC, direct oral anticoagulants; and VKA, vitamin K antagonist.

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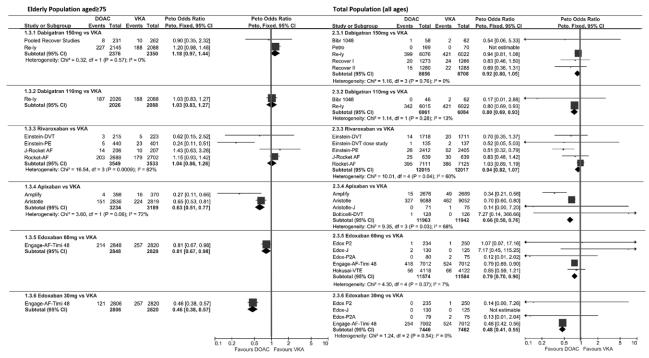


Figure 5. Risk of major bleeding in the elderly (left) and the total population (right). Cl indicates confidence interval; DOAC, direct oral anticoagulants; and VKA, vitamin K antagonist. *Event numbers for Engage-AF-Timi-48 and J-Rocket AF in the elderly have been estimated from published confidence intervals.

apixaban in the total population (P=81%). Sensitivity analysis did not yield a satisfactory source for this heterogeneity. Hence, a random-effects model was applied.¹⁶ No other outcome estimate produced significant heterogeneity.

Additional sensitivity analysis by indication and mean duration of patient follow-up did not significantly alter the interpretation of findings in the elderly, with the exception of the case of rivaroxaban for major bleeding. For rivaroxaban, in AF, the major bleeding risk was OR, 1.17; 95% CI, 0.95 to 1.43, and, in VTE, the major bleeding risk was OR, 0.30; 95% CI, 0.15 to 0.58.

Discussion

This systematic review and meta-analysis investigating the use of DOACs in AF and VTE has shown that they are at least as effective as VKA in the elderly aged \geq 75 years. Similar efficacy was also seen in the elderly and total trial populations (all ages). The meta-analysis of bleeding risks with DOACs has shown them to be distinct from VKA. For the direct thrombin inhibitor, dabigatran, risks also appeared to differ for bleeding between the elderly and total trial populations. Dabigatran 150 mg showed a nonsignificantly higher risk of major bleeding than VKA in the elderly. However, in the total population, a reduction in major bleeding was observed with dabigatran in comparison with VKA which was significant for the 110-mg dose. Two of the direct factor Xa inhibitors (apixaban and edoxaban) showed a lower major bleeding risk than VKA in both the elderly and total population, whereas rivaroxaban showed a similar risk to VKA.

Elderly patients taking either dose of dabigatran were at a higher risk of gastrointestinal bleeding than those on VKA; this higher risk was also present in the total populations but with the 150-mg dose only. Use of DOACs provided a protective effect in comparison with VKA against intracranial bleeding in the elderly that was consistent with the total population. Results where available for clinically relevant bleeding or fatal bleeding for DOACs did not suggest higher risks than with VKA in the elderly. However, interpretation of these secondary bleeding outcomes in the elderly was limited by the low numbers of elderly patients with bleeding events in the studies. This was compounded by the fact that all data requested from pharmaceutical manufacturers and regulatory authorities we approached was not made available.

The intention from our protocol was to provide pooled outcome data for all 4 DOACs together versus VKA as well. However, we found significant heterogeneity when the drugs were combined for several outcomes. This appeared to be attributable to either differing baseline bleeding risks in the studies or true differences between each drug. Hence, this result was not deemed appropriate to present.

Our choice of the total trial population as our reference group for contextualizing the results in the elderly was based on guidance in the Cochrane handbook on conducting subgroup meta-analysis in trials.¹⁴ Comparing 2 subgroup metaanalyses, with subjects aged \geq 75 to <75, for example, based purely on statistical significance of subgroup results, would have been misleading because both analyses are likely to have different abilities to detect effects. Hence, we did not choose the <75 population as our main reference, although we have included the meta-analysis for the <75 population in the Appendix in the online-only Data Supplement.

The subgroup analysis of the dabigatran phase III, Re-ly study, suggested that major bleeding risk may increase with age for dabigatran.³⁹ Our study has suggested, however, that this risk increase is not significantly greater than for VKA.

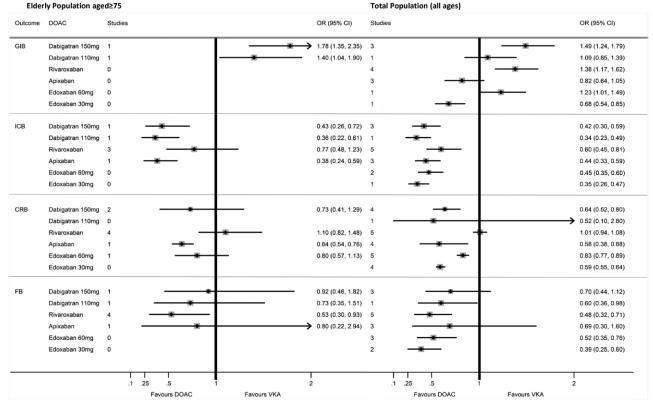


Figure 6. Risk of secondary outcomes in the elderly (**left**) and the total population (**right**). *CRB estimate was only estimate derived by using a random-effects model. **Note: Full Forest plots for each estimate above are available in the online-only Data Supplement. Cl indicates confidence interval; CRB, clinically relevant bleeding; FB, fatal bleeding; GIB, gastrointestinal bleeding; ICB, intracranial bleeding; and OR, odds ratio.

Dabigatran relies more on renal excretion for elimination than the other 3 DOACs. Given that renal function declines with age, this may be a factor for greater bleeding risk.⁴⁰ However, renal function alone cannot fully explain this variation in bleeding risk, which is likely to be influenced by other unverified age-related factors as well.

The increased risk of gastrointestinal bleeding and associated mortality with age has been well established.⁴¹ The use of anticoagulant medication is known to increase this risk further.⁴² Gastrointestinal bleeding was found to significantly increase with rivaroxaban, edoxaban 60 mg and dabigatran 150 mg in comparison with VKA in the total population. This risk increased further for dabigatran in the elderly. Gastrointestinal bleeding risks with other DOACs in the elderly could not be examined owing to the lack of the availability of data. This was a serious concern given that gastrointestinal bleeding has been shown both in this study and previous work to be a significant risk with the usage of DOACs.

The use of VKA and advanced age are both strong predictive factors for intracranial bleeding.⁴³ The protective benefit against intracranial bleeding that the DOACs confer over VKA in the general population did not appear to be lost in the elderly. Given that intracranial bleeding is one of the major factors responsible for mortality resulting from complications of VKA usage, this finding was significant.⁴³

It is worth noting that the pooled bleeding results in this study are heavily weighted toward the large pivotal phase III AF study for each of the 4 DOACs.^{22,26,27,35} As a result, the

respective trial populations in these studies should be considered. Notably, the population in the edoxaban study (Engage-AF-Timi48),35 and rivaroxaban study (Rocket-AF),22 both had higher mean CHADS, risk scores of 2.8 and 3.5, respectively, in comparison with 2.1 in both the dabigatran (Re-ly)²⁷ and apixaban (Aristotle)²⁶ studies. The CHADS, risk assessment tool can help predict the risk of stroke in patients with AF,44 and indicated the inclusion of a lower-risk population in the Re-ly and Aristotle studies. Mean time in therapeutic range on VKA did vary across the 4 studies (55.0%-64.9%); and Rocket-AF had the lowest time in therapeutic range with 55%. Such deviations in time in therapeutic range are, however, also common in clinical practice.⁴⁵ These differences in the trial populations mean comparisons between DOACs can be misleading and were not undertaken here. Until head-to-head clinical trials comparing the DOACs against one another are conducted, it will not be possible to know which DOAC has the best efficacy and harm profile in the elderly or total populations.

Research in Context

This is the first study that has attained and assessed all available evidence for dabigatran, apixaban, rivaroxaban, and edoxaban in AF and VTE treatment in the elderly from the literature, regulatory bodies, and drug manufacturers. The DOACs have been tested for other indications such as thromboprophylaxis following hip and knee replacements. However, these studies used different doses and comparators and, hence, were not eligible for inclusion.⁴⁶

Real-world data are gradually emerging for the DOACs, although such observational data can be subject to confounding.⁴⁷⁻⁴⁹ Studies investigating the risks of dabigatran thus far have produced conflicting results.^{48,49} A Danish cohort study, for example, found significantly worse bleeding patterns with dabigatran 110 mg in the total population than seen in this analysis.⁴⁹ Two small studies also highlighted how bleeding risks, in particular, in the elderly, remain a significant concern with dabigatran.^{50,51} As further information emerges from larger studies such as the prospective DOAC register in Dresden, the harms and benefits for DOACs in the elderly will become clearer.⁵²

Limitations of This Study

Interpretation of subgroup data from clinical trials for elderly patients aged ≥75 years requires caution because trials were not initially powered to detect these differences. Randomization in studies was not stratified by age; hence, it was not possible to ensure that all confounders such as concomitant aspirin usage or impaired renal function were balanced across arms. Population sizes for primary outcomes, however, were reasonably large. Our data were also limited by the lack of published results in the public domain or available from regulatory authorities and manufacturers. This meant that several summary estimates in the elderly were based on only 1 or 2 studies. Because of the lack of patient level data, we were unable to ascertain the age distribution of our elderly participants and the number of frail elderly patients aged over 80 and 85 years that had actually been included.

Outcome data on cardiovascular events were not reported. A signal for increased risk of myocardial infarction with dabigatran in comparison with VKA has been previously raised.⁵³ However, a large postmarketing surveillance study completed by the US Food and Drug Administration has not found this risk to be significant.⁵⁴

In the VTE studies, it was common for patients to receive several days (median, 2–9 days) of a heparin before beginning treatment with either a DOAC or VKA.^{28,29,34} In the Amplify, Einstein-DVT, and Einstein-PE, they received a higher dose of DOAC for a short period prior to initiation of a standard dose.^{19,20,31} Also, because bleeding definitions were not mutually exclusive within trials, some estimates of risk by bleeding classification were difficult to interpret. These factors could ultimately affect the precision of bleeding estimates. Follow-up did vary between studies, but all had at least 3 months and covered the initial period during which harm has been found to be highest with the use of anticoagulants.⁵⁵

Conclusion

DOACs showed at least equal efficacy to VKA in the elderly for acute VTE and AF. However, bleeding patterns seen with DOACs were different. Dabigatran, in particular, showed a significantly higher risk of gastrointestinal bleeding and a nonsignificantly higher major bleeding risk than VKA. This suggests that caution is required in prescribing where there may be concomitant risk factors for gastrointestinal bleeding in the elderly. A benefit of reduced intracranial bleeding was seen with dabigatran, apixaban, and rivaroxaban. Insufficient published data for apixaban, edoxaban, and rivaroxaban meant that all bleeding risks, particularly gastrointestinal risks, could not be fully explored in the elderly. Better availability of unpublished trial data and more research is needed to elucidate risks further.

Sources of Funding

This research was supported by the National Institute for Health Research (NIHR) Biomedical Research Center at Guy's and St Thomas' NHS Foundation Trust and King's College London. The views expressed are those of the authors and not necessarily those of the NHS, the NIHR, or the Department of Health.

Disclosures

Dr Patel has received research funding through an investigator-initiated grant from Bayer. Dr Molokhia has received previous grants from AstraZeneca, Pfizer, and the Serious Adverse Events Consortium for drug safety studies unrelated to this work. The other authors report no conflicts.

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CLINICAL PERSPECTIVE

Elderly patients are at a higher risk of developing atrial fibrillation and venous thromboembolism and are frequently prescribed anticoagulant therapy. Historically, vitamin K antagonists (VKA) were prescribed, but the direct oral anticoagulants (DOACs) dabigatran, apixaban, rivaroxaban, and edoxaban now provide alternatives to clinicians. This study presents the first comprehensive evaluation of the use of DOACs in the elderly. We found DOACs to be at least as effective as VKA in managing the thrombotic risks in atrial fibrillation and acute venous thromboembolism. However, bleeding risks with DOACs were different than with VKA. Dabigatran, apixaban, and rivaroxaban provided a protective effect in comparison with VKA against intracranial bleeding in the elderly. This was consistent with the benefit seen across all ages. Dabigatran, however, was associated with a higher risk of gastrointestinal bleeding than VKA in the elderly; this risk was also evident across all ages but with the higher (150 mg) dose only. Full interpretation of bleeding outcomes in the elderly was limited by accessible trial data (particularly for apixaban, rivaroxaban, and edoxaban), the low numbers of bleeding events, and the lack of data characterizing the older age groups. Our study has added to the current evidence for the prescribing safety of DOACs, in particular, relating to bleeding risks. The results have most significance for prescribers of DOACs in elderly populations who may be at a higher risk of bleeding from concomitant comorbidities and medications. Better availability of unpublished trial data and more research is needed to further elucidate risks and understand the optimal use of DOACs in the elderly.

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Efficacy and Harms of Direct Oral Anticoagulants in the Elderly for Stroke Prevention in Atrial Fibrillation and Secondary Prevention of Venous Thromboembolism: Systematic Review and Meta-Analysis

Manuj Sharma, Victoria R. Cornelius, Jignesh P. Patel, J. Graham Davies and Mariam Molokhia

Circulation. 2015;132:194-204; originally published online May 20, 2015; doi: 10.1161/CIRCULATIONAHA.114.013267 Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231 Copyright © 2015 American Heart Association, Inc. All rights reserved. Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at: http://circ.ahajournals.org/content/132/3/194

Data Supplement (unedited) at: http://circ.ahajournals.org/content/suppl/2015/05/18/CIRCULATIONAHA.114.013267.DC1.html

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Supplemental Methods

Supplemental Methods 1a. Additional Information.

Additional information gathered on the role of funders in the individual studies and characteristics of included studies are detailed in Supplemental Table S3 and Table S4 respectively.

Original forest plots for all outcomes presented in the main manuscript are detailed in Supplemental Figures S2-S8. Additional forest plots detailing data on risks of all death can be found in Figure S9-S10. Forest plots containing data from the <75 and ≥75 populations can be found in Figures S11-S18.

Additional funnel plots for risk of stroke or systemic embolism and venous thromboembolism in the elderly and total population are presented in Supplemental Figure S19-S20.

Supplemental Methods 2a. Search Strategy in EMBASE.

Ovid Technologies, Inc. Search limit to english language Database: Embase Classic+Embase <1947 to 2013 November 21> Search Strategy:

- 1 exp dabigatran etexilate/ or exp dabigatran/ or dabigatran.mp. (4628)
- 2 rivaroxaban.mp. or exp rivaroxaban/ (3840)
- 3 apixaban.mp. or exp apixaban/ (2350)
- 4 edoxaban.mp. or exp edoxaban/ (558)
- 5 exp thrombin inhibitor/ (35324)

6 ((direct adj3 thrombin adj3 inhib\$) or DTI).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (10140)

- 7 xaban\$.mp. (12)
- 8 exp blood clotting factor 10a inhibitor/ (9874)

9 ((factor Xa or factor 10a or fXa) adj3 inhib\$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (4755)

10 (factor 2a inhib\$ or factor IIa inhib\$ or f2a inhib\$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (59)

11 (Pra?ax\$ or Xarelto or Eliqu?s or Lixiana).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (795)

12 (NOAC or (anticoagulant\$ adj3 oral adj3 new) or (anticoagulant\$ adj3 oral adj3 novel)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (1435)

- 13 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 (48838)
- 14 deep vein thrombosis.mp. or exp deep vein thrombosis/ (41442)
- 15 (DVT or thromboembolism or venous thromboembolism or VTE).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (89387)

16 exp lung embolism/ (64280)

17 (lung embol\$ or pulmonary embol\$ or PE).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (100305)

- 18 exp heart atrium fibrillation/ (77878)
- 19 exp heart atrium flutter/ (9788)

20 ((atrial or auricular) adj5 (fibrillation\$ or flutter\$)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (66474)

21 (AF or NVAF).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (51520)

- 22 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 (296005)
- 23 13 and 22 (12898)
- 24 Clinical trial/ (898699)
- 25 randomized controlled trial/ (362954)
- 26 Randomization/ (64197)
- 27 Single blind procedure/ (18566)
- 28 Double blind procedure/ (123454)
- 29 Crossover procedure/ (39339)
- 30 Placebo/ (246077)

- 31 Randomi?ed controlled trial\$.tw. (96717)
- 32 Rct.tw. (13134)
- 33 Random allocation.tw. (1390)
- 34 Randomly allocated.tw. (20328)
- 35 Allocated randomly.tw. (1973)
- 36 (allocated adj2 random).tw. (892)
- 37 Single blind\$.tw. (14467)
- 38 Double blind\$.tw. (151887)
- 39 ((treble or triple) adj blind\$).tw. (383)
- 40 Placebo\$.tw. (207389)
- 41 Prospective study/ (256675)
- 42 or/24-41 (1422876)
- 43 Case study/ (31643)
- 44 Case report.tw. (282476)
- 45 Abstract report/ or letter/ (912074)
- 46 or/43-45 (1220663)
- 47 42 not 46 (1384928)
- 48 23 and 47 (4115)
- 49 limit 48 to last 20 years (4092)
- 50 limit 49 to human (3978)
- 51 limit 50 to english language (3615)

Supplemental Methods 2b. Search Strategy in MEDLINE.

Ovid Technologies, Inc. Search limit to english language

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present> Search Strategy:

1 dabigatran.mp. (1957)

- 2 rivaroxaban.mp. (1283)
- 3 apixaban.mp. (758)
- 4 edoxaban.mp. (161)

5 (NOAC or (anticoagulant\$ adj3 oral adj3 new) or (anticoagulant\$ adj3 oral adj3 novel)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (999)

6 exp Thrombin/ad, ai, tu, th [Administration & Dosage, Antagonists & Inhibitors, Therapeutic Use, Therapy] (5064)

7 ((direct adj3 thrombin adj3 inhib\$) or DTI).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (7055)

8 xaban\$.mp. (7)

9 exp Factor Xa/ad, ai, tu [Administration & Dosage, Antagonists & Inhibitors, Therapeutic Use] (2291)

10 ((factor Xa or factor 10a or fXa) adj3 inhib\$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (2486)

11 ((factor 2a or factor IIa or f2a) adj3 inhib\$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (61)

12 (Pra?ax\$ or Xarelto or Eliqu?s or Lixiana).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (150)

13 exp Venous Thrombosis/ (44632)

14 ("deep vein thrombosis" or DVT or thromboembolism or venous thromboembolism or VTE).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (48776)

15 exp Pulmonary Embolism/ (31309)

16 exp Venous Thromboembolism/ (4499)

17 (lung embol\$ or pulmonary embol\$ or PE).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (62301)

18 exp Atrial Fibrillation/ (34118)

19 exp Atrial Flutter/ (4965)

20 ((atrial or auricular) adj5 (fibrillation\$ or flutter\$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (50348)

21 (AF or NVAF).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (35889)

22 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 (16237)

23 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 (196699)

24 22 and 23 (3363)

- 25 Randomized Controlled Trials as Topic/ (102694)
- 26 randomized controlled trial/ (390641)
- 27 Random Allocation/ (81795)
- 28 Double Blind Method/ (131907)
- 29 Single Blind Method/ (19625)
- 30 clinical trial/ (505248)
- 31 clinical trial, phase i.pt. (16223)
- 32 clinical trial, phase ii.pt. (26928)
- 33 clinical trial, phase iii.pt. (10191)
- 34 clinical trial, phase iv.pt. (998)
- 35 controlled clinical trial.pt. (89952)
- 36 randomized controlled trial.pt. (390641)
- 37 multicenter study.pt. (182921)
- 38 clinical trial.pt. (505248)
- 39 exp Clinical Trials as topic/ (296601)
- 40 or/25-39 (1076886)
- 41 (clinical adj trial\$).tw. (226862)
- 42 ((singl\$ or doubl\$ or treb\$ or tripl\$) adj (blind\$3 or mask\$3)).tw. (134979)
- 43 PLACEBOS/ (33783)
- 44 placebo\$.tw. (169202)
- 45 randomly allocated.tw. (17264)
- 46 (allocated adj2 random\$).tw. (19861)
- 47 or/41-46 (441961)
- 48 40 or 47 (1227780)
- 49 case report.tw. (203598)
- 50 letter/ (832571)
- 51 historical article/ (300469)
- 52 or/49-51 (1325116)
- 53 48 not 52 (1197461)
- 54 24 and 53 (1334)
- 55 limit 54 to humans (1231)
- 56 limit 55 to last 20 years (1211)
- 57 limit 56 to english language (1086)

Supplemental Methods 2c. Search Strategy in CENTRAL.

- ID Search
- #1 dabigatran
- #2 rivaroxaban
- #3 apixaban
- #4 edoxaban
- #5 ((direct adj3 thrombin adj3 inhib\$) or DTI)
- #6 MeSH descriptor: [Antithrombins] explode all trees
- #7 xaban\$
- #8 MeSH descriptor: [Blood Coagulation Factor Inhibitors] explode all trees
- #9 ((factor Xa or factor 10a or fXa or autoprothrombin c or thrombokinase) adj5 inhib\$)
- #10 (factor 2a inhib\$ or factor IIa inhib\$ or f2a inhib\$)
- #11 Pra?ax\$ or Xarelto or Eliqu?s or Lixiana
- #12 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11
- #13 (NOAC or (anticoagulant\$ adj3 oral adj3 new) or (anticoagulant\$ adj3 oral adj3 novel))
- #14 #12 or #13
- #15 MeSH descriptor: [Embolism and Thrombosis] explode all trees
- #16 MeSH descriptor: [Anticoagulants] explode all trees
- #17 #14 or #16
- #18 ("deep vein thrombosis OR DVT" or thromboembolism or venous thromboembolism or VTE)
- #19 (lung embol\$ or pulmonary embol\$ or PE)
- #20 MeSH descriptor: [Atrial Fibrillation] explode all trees
- #21 MeSH descriptor: [Atrial Flutter] explode all trees
- #22 ((atrial or auricular) adj5 (fibrillation\$ or flutter\$))
- #23 (AF or NVAF)
- #24 #15 or #18 or #19 or #20 or #21 or #22 or #23
- #25 #17 and #24

Studies excluded	DOAC	Rationale for exclusion
Re-lyable ¹	Dabigatran	Extension of completed phase III Re-ly study for additional follow up only. Observational study.
Re-medy ²	Dabigatran	Extension study of completed phase III Recover I and Recover II studies in patients who had already received 3 months treatment for acute VTE.
Re-sonate ²	Dabigatran	Extension study as per Re-medy. VKA was not the comparator.
Einstein-Ext ³	Rivaroxaban	Extension study for phase III Einstein DVT and PE studies in patients who had already received 6 months of treatment for acute VTE. VKA was not the comparator.
Odixa DVT ⁴	Rivaroxaban	Phase II study with no arm that used a dose of rivaroxaban that was subsequently used in phase III studies.
NCT00973245 ⁵	Rivaroxaban	Study was less than 3 months in duration.
NCT00973323 ⁶	Rivaroxaban	Study was less than 3 months in duration.
Averroes ⁷	Apixaban	VKA was not the comparator.
Amplify-Ext ⁸	Apixaban	Extension study of previously completed phase III Amplify study. VKA was not used as comparator.

Table S1 Rationale for exclusion of studies following review of full publications.

Study	Mean TTR on VKA (%)	Concomitant aspirin use during study %						
		DOAC	VKA					
DABIGATRAN								
Bibr 1048, 2005	NA	NA	NA					
Petro, 2007	57.2	40.8	0					
Re-ly, 2009	64	20.3	20.8					
Recover I, 2010	60	NA	NA					
Recover II, 2013	56.9	10.2	8.7					
APIXABAN								
Aristotle, 2011	62.2	NA	NA					
Aristotle-J, 2011	NA	28.2	25.3					
Botticelli-DVT,2008	57	NA	NA					
Amplify, 2013	61	NA	NA					
RIVAROXABAN								
Rocket-AF, 2011	55	NA	NA					
J-Rocket AF, 2011	65	NA	NA					
Einstein-DVT Dose Study, 2008	50.3	NA	NA					
Einstein-DVT, 2010	57.7	NA	NA					
Einstein-PE, 2012	62.7	NA	NA					
EDOXABAN								
Edox-P2, 2010	49.7	NA	NA					
Edox-P2A, 2010	45.1	41.9	34.7					
Edox-J, 2012	73 IF <70 years 83 IF ≥70 years	27	23					
Engage-AF-Timi 48, 2013	64.9	NA	NA					
Hokusai-VTE, 2013	63.5	NA	NA					
NA=Not available TTR=Time in therapeutic	range							

Table S2 Mean time in therapeutic range (TTR) on vitamin k antagonist and concomitant aspirin usage for included studies.

Table S3 Role of Funder in individual studies.	•
--	---

Study	Funded by Manufacturer	Role in Design	Role in Analysis	Control over Publication
DABIGATRAN				
Bibr 1048, 2005	Y	NR	NR	NR
Petro, 2007	Y	Υ	Y	NR
Re-ly, 2009	Y	Υ	Y	Y
Recover I, 2010	Υ	Υ	Y	NR
Recover II, 2013	Υ	Y	Y	NR
APIXABAN				
Aristotle, 2011	Υ	Y	Y	NR
Aristotle-J, 2011	Υ	NR	NR	NR
Botticelli- DVT,2008	Y	NR	NR	NR
Amplify, 2013	Υ	Y	Y	Υ
RIVAROXABAN				
Rocket-AF, 2011	Y	NR	Ν	Ν
J-Rocket AF, 2011	Y	Ν	Y	NR
Einstein-DVT Dose Study, 2008	Y	Y	Y	Y
Einstein-DVT, 2010	Y	NR	NR	Y
Einstein-PE, 2012	Y	NR	NR	Υ
EDOXABAN				
Edox-P2, 2010	Y	Y	Y	NR
Edox-P2A, 2010	Y	NR	NR	NR
Edox-J, 2012	Y	Y	Y	Y
Engage-AF-Timi 48, 2013	Y	Y	Υ	Ν
Hokusai-VTE, 2013	Y	Y	NR	NR
Y=Yes N=No				

N=No

NR=Not Reported

Study	Standard Dose	Phase	Inclusion Criteria	Target INR range	Duration/Median Follow up* (months)	Heparin ≥5 days permitted prior to DOAC/VKA
DABIGATRAN						
Bibr 1048, 2005	110mg BD or 150mg BD	II	Aged≥20, NVAF and CHADS₂ of ≥1 or CAD	2-3	3	N
Petro, 2007	150mg BD extracted	II	Aged≥18, NVAF and CHADS₂ of ≥1 or CAD	2-3	3	N
Re-ly, 2009	110mg or 150mg BD	111	Aged≥18, NVAF and CHADS₂ of ≥1 or CAD	2-3	24*	N
Recover I, 2010	150mg BD	III	Aged≥18 and confirmed VTE	2-3	6	Y
Recover II, 2013	150mg BD	III	Aged≥18 and confirmed VTE	2-3	6	Y
APIXABAN						
Aristotle, 2011	5mg BD	Ш	Aged≥18, NVAF and CHADS₂ of ≥1	2-3	21.6*	Ν
Aristotle-J, 2011	5mg BD extracted	II	Aged \geq 20, NVAF and CHADS ₂ of \geq 1	2-3 and 1.6–2.6 if aged≥70	3	N
Botticelli-DVT, 2008	5mg BD	II	Aged≥18 and confirmed DVT without PE	2-3	3	N
Amplify, 2013	10mg BD for 7 days then 5mg BD	111	Aged≥18 and confirmed VTE	2-3	6	N
RIVAROXABAN						
Rocket-AF, 2011	20mg OD	III	Aged≥18, NVAF and CHADS ₂ of ≥2	2-3	23.2*	Ν
J-Rocket AF, 2011	15mg OD	III	Japanese, Aged≥20, NVAF and CHADS₂ of ≥2	2-3 and 1.6–2.6 if aged≥70	30	Ν
Einstein-DVT Dose Study, 2008	20mg OD extracted	II	Aged≥18 and confirmed DVT	2-3	3	Ν
Einstein-DVT, 2010	15mg BD for 21 days then 20mg OD	111	Aged≥18 and confirmed DVT without PE	2-3	3,6 or 12	N
Einstein-PE, 2012	15mg BD for 21 days then 20mg OD	111	Aged≥18 and confirmed PE with/without DVT	2-3	3,6 or 12	Ν
EDOXABAN						
Edox-P2, 2010	30mg and 60mg OD extracted	II	Aged≥18, NVAF and CHADS₂ of ≥2	2-3	3	Ν
Edox-P2A, 2010	30mg OD and 60mg OD	II	Aged≥20, NVAF and CHADS₂ of ≥1	2-3	3	Ν

Table S4 Characteristics of included studies for DOACs in AF and VTE (expanded table).

Study	Standard Dose	Phase	Inclusion Criteria	Target INR range	Duration/Median Follow up* (months)	Heparin ≥5 days permitted prior to DOAC/VKA
Edox-J, 2012	30mg and 60mg OD extracted	II	Aged≥20, NVAF and CHADS₂ of ≥1	2-3 and 1.6–2.6 if aged≥70	3	N
Engage-AF- Timi 48, 2013	30mg OD or 60mg OD	111	Aged \geq 21, NVAF and CHADS ₂ of \geq 2	2-3	33.6*	Ν
Hokusai-VTE, 2013	60mg OD	III	Aged≥18 and confirmed VTE	2-3	3 to 12	Y
OD= Once daily BD=Twice daily NVAF=Non-valvula VTE=Venous Thron DVT=Deep-vein thr PE= Pulmonary Em CAD= Coronary Art	nboembolism ombosis bolism					

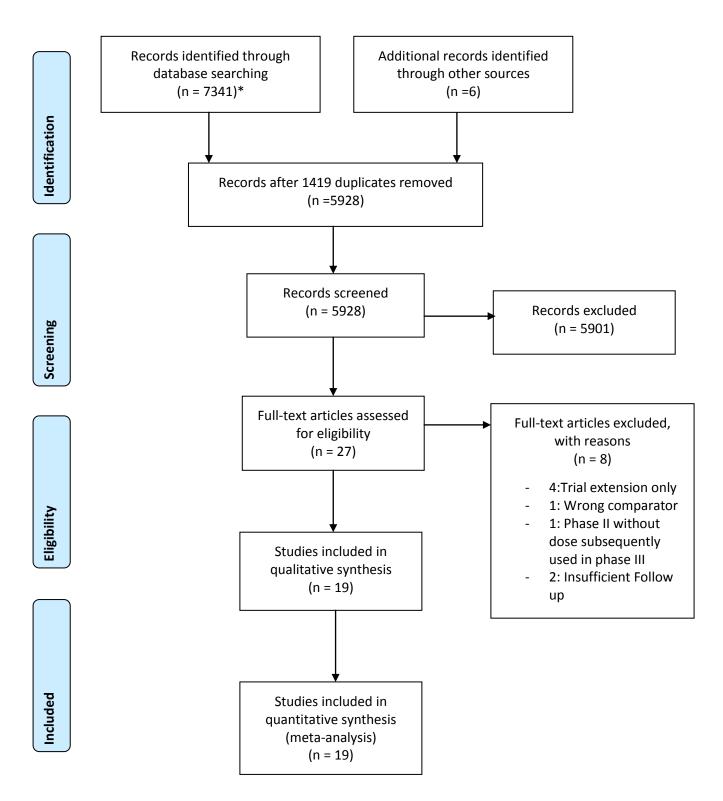


Figure S1. PRISMA Flow Diagram – Study Identification, Selection and Exclusions.

*Monthly automated alerts from 01/12/13 to 01/06/14 consisting of updates to the search strategy identified an additional 429 articles in Embase, Medline and CENTRAL that have been included in flow diagram above. Two eligible studies for inclusion of the total 19 identified were obtained through these updates.

	DOAC	VK			Peto Odds Ratio	Peto Odds Ratio		DOA	-	VKA	-		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup		Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% Cl	Study or Subgroup			Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI
1.1.1 Dabigatran 150r							2.1.1 Dabigatran 150	mg vs VK						
Re-ly	69 2466			100.0%	0.66 [0.49, 0.90]		Bibr 1048	0		1	62	0.3%		•
Subtotal (95% CI)	2466		2423	100.0%	0.66 [0.49, 0.90]	•	Petro	0		0	2		Not estimable	
otal events	69	101					Re-ly	134	6076	202	6022		0.65 [0.53, 0.81]	
leterogeneity: Not app							Subtotal (95% CI)		6303		6154	100.0%	0.65 [0.52, 0.81]	•
est for overall effect: 2	Z = 2.61 (P = 0.)	009)					Total events	134		203				
							Heterogeneity: Chi ² =				= 0%			
1.2 Dabigatran 110r							Test for overall effect:	Z = 3.89 ((P < 0.0)	001)				
te-ly	87 2349			100.0%					21					
ubtotal (95% CI)	2349		2423	100.0%	0.88 [0.66, 1.18]	•	2.1.2 Dabigatran 110	-						·····
otal events	87	101					Bibr 1048	0		1	62			•
leterogeneity: Not app	plicable						Re-ly	183	6015	202	6022			
est for overall effect: 2	Z = 0.82 (P = 0.	41)					Subtotal (95% CI)		6061		6084	100.0%	0.90 [0.74, 1.10]	•
							Total events	183		203				
1.3 Rivaroxaban vs	VKA						Heterogeneity: Chi ² =				= 0%			
ocket-AF	125 3082			100.0%			Test for overall effect:	Z = 1.02 ((P = 0.3)	1)				
ubtotal (95% CI)	3082	2	3082	100.0%	0.80 [0.63, 1.02]	•	67715323 00	1000						
otal events	125	154					2.1.3 Rivaroxaban vs							
leterogeneity: Not app	plicable						J-Rocket AF		637		637	5.5%		
est for overall effect: 2	Z = 1.78 (P = 0.	08)					Rocket-AF	269	7081	306	7090			
							Subtotal (95% CI)		7718		7727	100.0%	0.85 [0.72, 1.00]	•
1.4 Apixaban vs VK	A						Total events	280		328				
istotle	79 2850	109	2828	99.0%	0.71 [0.53, 0.95]		Heterogeneity: Chi ² =				= 57%			
ristotle-J	0 45		23	1.0%	0.05 [0.00, 0.95]	•	Test for overall effect:	Z = 1.97 ((P = 0.0)	5)				
ubtotal (95% CI)	2895	5	2851	100.0%	0.70 [0.52, 0.93]	•	201000000000000000000000000000000000000							
otal events	79	111					2.1.4 Apixaban vs VK							-
eterogeneity: Chi ² = 3	3.10, df = 1 (P =	= 0.08); F	= 68%				Aristotle	212	9120	265	9081		0.79 [0.66, 0.95]	
est for overall effect: 2	Z = 2.46 (P = 0.	01)					Aristotle-J	0		3		0.6%		4.
	S STRUCTURE STO	51.532					Subtotal (95% CI)		9194		9155	100.0%	0.78 [0.65, 0.94]	•
						0.1 0.2 0.5 1 2 5 10	Total events	212		268				
						Favours DOAC Favours VKA	Heterogeneity: Chi ² = Test for overall effect:		10.07.000		= 58%			
														0.1 0.2 0.5 1 2
														Favours DOAC Favours VK

Favours DOAC Favours VKA

Figure S2. Forest Plots for risk of Stroke or Systemic Embolism in AF in Elderly (left) and Total Population (right).

*Event numbers for Engage-AF-Timi 48 in elderly have been estimated from published confidence intervals.

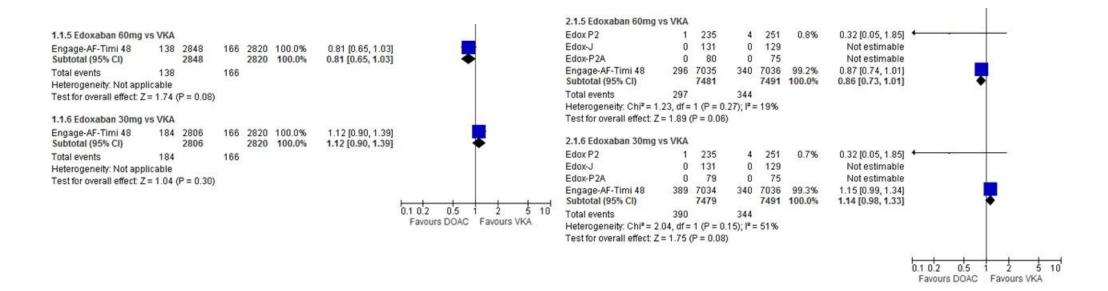


Figure S2. (contd) Forest Plots for risk of Stroke or Systemic Embolism in AF in Elderly (left) and Total Population (right).

*Event numbers for Engage-AF-Timi 48 in elderly have been estimated from published confidence intervals.

Study or Subgroup	DO/ Events		VKA		Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% Cl	Study or Subgroup	DOA	17.1	VKA		Moight	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% Cl
1.2.1 Dabigatran 150mg v	and the second sec	Total	Evento	Total	reight	reto, rixed, solver	100,11,00,00,00	2.2.1 Dabigatran 150mg v		TUtal	Events	Total	weight	Felo, Fixed, 55% CI	Peto, Fixed, 35% CI
Pooled Recover Studies Subtotal (95% CI)	3	253 253	5		100.0%	0.66 [0.16, 2.66]		Recover I Recover II	30	1274 1279		1265 1289	49.6% 50.4%	1.11 [0.65, 1.87] 1.08 [0.64, 1.82]	
Total events	3		5					Subtotal (95% CI)	100	2553			100.0%	1.09 [0.76, 1.58]	+
Heterogeneity: Not applica Test for overall effect: Z = 0		0.56)						Total events Heterogeneity: Chi² = 0.00, Test for overall effect: Z = 0			55 ² = 0%				
1.2.2 Apixaban vs VKA															
Amplify	7	389	13		100.0%	0.50 [0.21, 1.21]		2.2.2 Apixaban vs VKA							_
Subtotal (95% CI)	<u></u>	389		360	100.0%	0.50 [0.21, 1.21]		Amplify Botticelli-DVT		2609 117		2635 118	95.6% 4.4%	0.84 [0.59, 1.18]	
Total events Heterogeneity: Not applica	/		13					Subtotal (95% CI)	3	2726	3		100.0%	1.01 [0.20, 5.09] 0.84 [0.60, 1.18]	+
Test for overall effect: Z = 1		0 1 2)						Total events	62		74				
1.2.3 Rivaroxaban vs VKA								Heterogeneity: Chi² = 0.05, Test for overall effect: Z = 0			I ² = 0%				
Einstein-DVT	4	215	10		36.8%	0.43 [0.15, 1.25]		2.2.3 Rivaroxaban vs VKA							
Einstein-PE	11	441	13		63.2%	0.77 [0.34, 1.72]		Einstein-DVT		1731	51	1718	45.5%	0.70 (0.46, 1.07)	
Subtotal (95% CI)		656		627	100.0%	0.62 [0.33, 1.18]		Einstein-DVT dose study		115		101	45.5%	0.38 [0.11, 1.34]	
Total events Heterogeneity: Chi ² = 0.70.	15	- 0.40	23					Einstein-PE		2419		2413	49.4%	1.14 [0.76, 1.71]	
Test for overall effect: Z = 1); 1~= 0%					Subtotal (95% CI)		4265			100.0%	0.86 [0.65, 1.15]	•
restion overall enect. Z = 1	1.45 (F = 1	0.13)						Total events	89		102				
1.2.4 Edoxaban 60mg vs \	VKA							Heterogeneity: Chi ² = 4.34,			I ² = 54%				
Hokusai-VTE	14	560	27		100.0%	0.50 [0.27, 0.94]		Test for overall effect: Z = 1	.03 (P = 0	.30)					
Subtotal (95% CI)		560	1000	544	100.0%	0.50 [0.27, 0.94]	-	2.2.4 Edoxaban 60mg vs V	/KA						
Total events Heterogeneity: Not applica			27					Hokusai-VTE Subtotal (95% CI)	130	4118 4118	146		100.0%	0.89 [0.70, 1.13] 0.89 [0.70, 1.13]	-
Test for overall effect: Z = 2	2.16 (P = 0	0.03)						Total events Heterogeneity: Not applicat	130		146				
							0.1 0.2 0.5 1 2 5 10	Test for overall effect: Z = 0		.33)					
							Favours DOAC Favours VKA								
															0.1 0.2 0.5 1 2 5 10 Favours DOAC Favours VKA

Figure S3. Forest Plots for risk of Recurrent Venous Thromboembolism in VTE in Elderly (left) and Total Population (right).

Study or Subgroup E	DOAC Events Total	VKA Events Total		Peto Odds Ratio Peto, Fixed, 95% Cl		ds Ratio ed, 95% Cl	Study or Subgroup	DOAC Events Tota	VK al Events		Peto Odds Ratio ght Peto, Fixed, 95% (Peto Odds Ratio	
1.3.1 Dabigatran 150mg vs \							2.3.1 Dabigatran 150mg vs				<u>, , , , , , , , , , , , , , , , , , , </u>		
Pooled Recover Studies	8 231	10 262	4.4%	0.90 [0.35, 2.32]	+		Bibr 1048	1 5	8 2	62 0.	3% 0.54 [0.06, 5.33	3] 4	-
Re-ly	227 2145	188 2088		1.20 [0.98, 1.46]		-	Petro	0 16			Not estimabl		
Subtotal (95% CI)	2376		100.0%	1.18 [0.97, 1.44]		•	Re-lv	399 607	6 421				
Total events	235	198				-	Recoverl	20 127			1% 0.83 [0.46, 1.50	·	
Heterogeneity: Chi ² = 0.32, dt	f = 1 (P = 0.57);	I ² = 0%					Recover II	15 128			3% 0.69 [0.36, 1.31		
Test for overall effect: Z = 1.6							Subtotal (95% CI)	885	6	8708 100			
							Total events	435	469				
1.3.2 Dabigatran 110mg vs \	VKA				_		Heterogeneity: Chi ² = 1.16, d	lf = 3 (P = 0.76); I ^z = 0%				
Re-ly	187 2026	188 2088	100.0%	1.03 [0.83, 1.27]	-	-	Test for overall effect: Z = 1.2	9 (P = 0.20)					
Subtotal (95% CI)	2026	2088	100.0%	1.03 [0.83, 1.27]	₹								
Total events	187	188					2.3.2 Dabigatran 110mg vs	VKA					
Heterogeneity: Not applicable	e						Bibr 1048	0 4	6 2	62 0.	3% 0.17 [0.01, 2.88	3] • • • • • • • • • • • • • • • • • • •	
Test for overall effect: Z = 0.2	5 (P = 0.80)						Re-ly	342 601		6022 99			
							Subtotal (95% CI)	606		6084 100	0% 0.80 [0.69, 0.93	5] •	
1.3.3 Rivaroxaban vs VKA							Total events	342	423				
Einstein-DVT	3 215	5 223	1.9%	0.62 [0.15, 2.52]			Heterogeneity: Chi ² = 1.14, d); I² = 13%				
Einstein-PE	5 440	23 401	6.6%	0.24 [0.11, 0.51]			Test for overall effect: Z = 3.0	10 (P = 0.003)					
J-Rocket AF	14 206	10 207	5.5%	1.43 [0.63, 3.26]									
Rocket-AF	203 2688	179 2702		1.15 [0.93, 1.42]		-	2.3.3 Rivaroxaban vs VKA						
Subtotal (95% CI)	3549	3533	100.0%	1.04 [0.86, 1.26]			Einstein-DVT	14 171			7% 0.70 [0.35, 1.37		
Total events	225	217					Einstein-DVT dose study	1 13			3% 0.52 [0.05, 5.03		-
Heterogeneity: Chi ² = 16.54,		09); I * = 82%					Einstein-PE	26 241			5% 0.51 [0.32, 0.79		
Test for overall effect: Z = 0.3	9 (P = 0.70)						J-Rocket AF Rocket-AF	25 63 395 711			8% 0.83 [0.48, 1.42	•	
1.3.4 Apixaban vs VKA							Subtotal (95% CI)	395 711 1201		7125 81. 12017 100			
-	4 398	16 370	5 200	0.07 (0.44, 0.66)			Total events	461	490	12017 100	0.04 [0.02, 1.07	· · · · · · · · · · · · · · · · · · ·	
Amplify Aristotle	4 398 151 2836	16 370 224 2819	5.3% 94.7%	0.27 [0.11, 0.66] 0.65 [0.53, 0.81]	·		Heterogeneity: Chi ² = 10.01,						
Subtotal (95% CI)	3234		100.0%	0.63 [0.51, 0.77]			Test for overall effect: Z = 0.9		47,1 = 00 X	,			
Total events	155	240	1001070		•			.+ (i = 0.00)					
Heterogeneity: Chi ² = 3.60, dt							2.3.4 Apixaban vs VKA						
Test for overall effect: Z = 4.5							Amplify	15 267	6 49	2689 7.	7% 0.34 [0.21, 0.58	31 	
	- ,,						Aristotle	327 908	8 462	9052 92.			
1.3.5 Edoxaban 60mg vs VK	A						Aristotle-J	0 7	1 1	75 0.	1% 0.14 [0.00, 7.20	j ←	
Engage-AF-Timi 48	214 2848	257 2820	100.0%	0.81 [0.67, 0.98]			Botticelli-DVT	1 12	8 0	126 0.	1% 7.27 [0.14, 366.68	5]	 →
Subtotal (95% CI)	2848		100.0%	0.81 [0.67, 0.98]			Subtotal (95% CI)	1196	3	11942 100	0% 0.66 [0.58, 0.76	5] 🔶	
Total events	214	257					Total events	343	512				
Heterogeneity: Not applicable	e						Heterogeneity: Chi ² = 9.35, d	lf = 3 (P = 0.03); I ² = 68%				
Test for overall effect: Z = 2.13	8 (P = 0.03)						Test for overall effect: Z = 5.9	15 (P < 0.0000)	1)				
												0.1 0.2 0.5 1 2 5	5 10
1.3.6 Edoxaban 30mg vs VK	A				_							Favours DOAC Favours VKA	
Engage-AF-Timi 48	121 2806	257 2820		0.46 [0.38, 0.57]									
Subtotal (95% CI)	2806		100.0%	0.46 [0.38, 0.57]	•								
Total events	121	257											
Heterogeneity: Not applicable													
Test for overall effect: Z = 7.1	9 (P < 0.00001)												
					0.1 0.2 0.5 ⁻	1 2 5 10							
					Favours DOAC	Favours VKA							

Figure S4. Forest Plots for risk of Major Bleeding in Elderly (left) and Total Population (right). *Event numbers for Engage-AF-Timi-48 and J-Rocket AF in the elderly have been estimated from published confidence intervals.

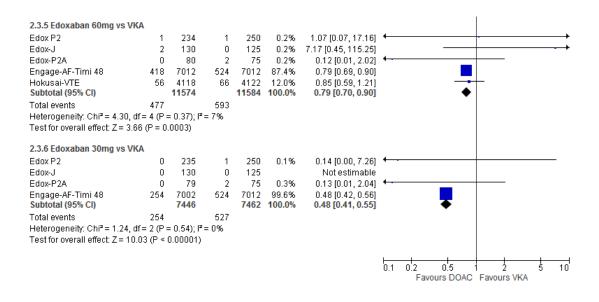


Figure S4. (contd) Forest Plots for risk of Major Bleeding in Total Population (right).

*Event numbers for Engage-AF-Timi-48 and J-Rocket AF in the elderly have been estimated from published confidence intervals.

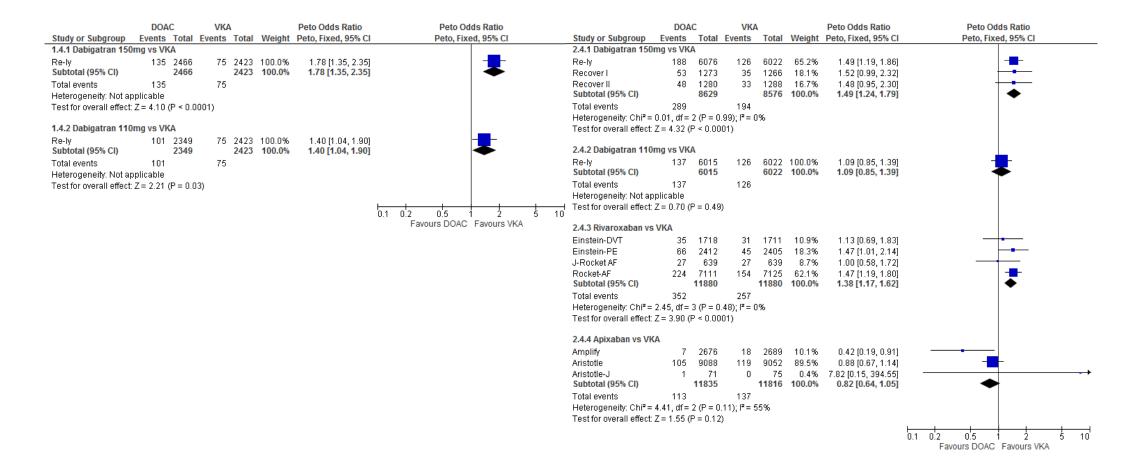


Figure S5. Forest Plots for risk of Gastrointestinal Bleeding in Elderly (left) and Total Population (right).

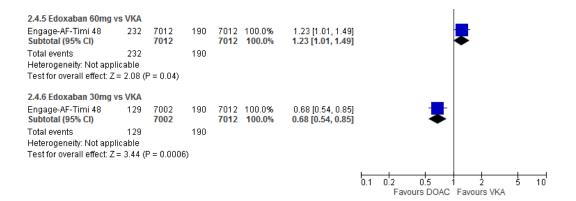


Figure S5. (contd) Forest Plots for risk of Gastrointestinal Bleeding in Total Population (right).

Study or Subgroup	DOAC	VKA	Weight	Peto Odds Ratio	Peto Odds Ratio Peto, Fixed, 95% Cl	Study of Subgroup	DOAG		VKA		Weight	Peto Odds Ratio Peto, Fixed, 95% Cl	Peto Odds Ratio Peto, Fixed, 95% Cl
Study or Subgroup 1.5.1 Dabigatran 150m		Events Total	weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI	Study or Subgroup 2.5.1 Dabigatran 150mg vs		Total	Events	Total	weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI
Re-ly	19 2145	44 2088	100.0%	0.43 [0.26, 0.72]		Re-ly		6076	90	6022	92.0%	0.44 [0.31, 0.62]	
Subtotal (95% CI)	2145		100.0%	0.43 [0.26, 0.72]	→	Recoverl	0	1273		1266	2.2%	0.13 [0.01, 1.29]	
Total events	19	44			-	Recover II	2	1280		1288	5.8%	0.37 [0.09, 1.48]	• • • • • • • • • • • • • • • • • • •
Heterogeneity: Not app	licable					Subtotal (95% CI)		8629		8576	100.0%	0.42 [0.30, 0.59]	◆
Test for overall effect: Z	= 3.28 (P = 0.00	1)				Total events	40		99				
						Heterogeneity: Chi ² = 1.05, d	df = 2 (P =	0.59); P	²=0%				
1.5.2 Dabigatran 110m	-				_	Test for overall effect: Z = 5.0	08 (P < 0.0	00001)					
Re-ly	14 2026		100.0%	0.36 [0.22, 0.61]			1.074						
Subtotal (95% CI)	2026		100.0%	0.36 [0.22, 0.61]		2.5.2 Dabigatran 110mg vs		0045			400.000		
Total events	14	44				Re-ly Subtotal (95% CI)	27	6015 6015	90		100.0% 100.0%	0.34 [0.23, 0.49] 0.34 [0.23, 0.49]	
Heterogeneity: Not app Test for overall effect: Z		043				Total events	27	0015	90	0022	100.070	0.54 [0.25, 0.45]	•
restior overall ellect. Z	.= 3.85 (F = 0.00	01)				Heterogeneity: Not applicabl			30				
1.5.3 Rivaroxaban vs V	/KA					Test for overall effect: Z = 5.8		00001)					
Einstein-DVT	0 215	1 223	1.4%	0.14 [0.00, 7.07]	←			,					
Einstein-PE	2 475	6 448	11.3%	0.34 [0.09, 1.38]	←	2.5.3 Rivaroxaban vs VKA							
Rocket-AF	29 2688	33 2702	87.3%	0.88 [0.53, 1.46]		Einstein-DVT	2	1718	2	1711	2.3%	1.00 [0.14, 7.08]	
Subtotal (95% CI)	3378	3373	100.0%	0.77 [0.48, 1.23]	-	Einstein-DVT dose study	0	135	1	137	0.6%	0.14 [0.00, 6.92]	←
Total events	31	40				Einstein-PE	3	2412		2405	8.7%	0.30 [0.11, 0.82]	
Heterogeneity: Chi ² = 2						J-Rocket AF	5	639	10	639	8.6%	0.51 [0.18, 1.41]	
Test for overall effect: Z	= 1.08 (P = 0.28)				Rocket-AF	55	7111		7125		0.66 [0.47, 0.92]	
						Subtotal (95% CI)		12015		12017	100.0%	0.60 [0.45, 0.81]	-
1.5.4 Apixaban vs VKA					_	Total events	65		109				
Aristotle	20 2836	57 2819		0.38 [0.24, 0.59]		Heterogeneity: Chi ² = 3.00, d			*= 0%				
Subtotal (95% CI)	2836		100.0%	0.38 [0.24, 0.59]		Test for overall effect: Z = 3.3	34 (P = 0.0	0008)					
Total events	20 Variation	57				2.5.4 Apixaban vs VKA							
Heterogeneity: Not app Test for overall effect: Z		043				Amplify	3	2676	Б	2689	4.9%	0.52 [0.14, 1.91]	
Testior overall ellect. Z	- 4.27 (F < 0.00	01)				Aristotle	52	9088		9052	94.5%	0.44 [0.33, 0.60]	
						Aristotle-J	0	71	1	75	0.5%	0.14 [0.00, 7.20]	←
					0.1 0.2 0.5 i 2 5 10	Subtotal (95% CI)	_	11835			100.0%	0.44 [0.33, 0.59]	◆
					Favours DOAC Favours VKA	Total events	55		129				
						Heterogeneity: Chi ² = 0.37, d	df = 2 (P =	0.83); l ^a	²=0%				
						Test for overall effect: Z = 5.5	50 (P < 0.0	00001)					
												ł	
													Eavours DOAC Eavours VKA

Favours DOAC Favours VKA

Figure S6. Forest Plots for risk of Intracranial Bleeding in in Elderly (left) and Total Population (right).

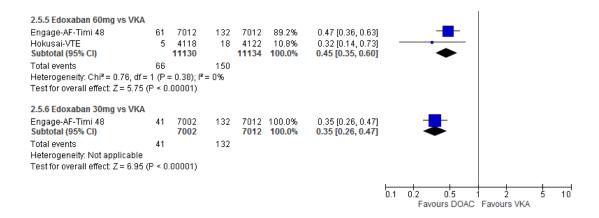


Figure S6. (contd) Forest Plots for risk of Intracranial Bleeding in Total Population (right).

	DOAC	VKA		Odds Ratio	Odds Ratio		DOAC	VKA	Odds Ratio	Odds Ratio			
Study or Subgroup		Events T	otal We	eight IV, Random, 95% Cl	IV, Random, 95% Cl			Events Total W	leight IV, Random, 95% C	I IV, Random, 95% CI			
1.6.1 Dabigatran 150mg					_	2.6.1 Dabigatran 150mg vs VKA							
Pooled Recover Studies	22 231 231		262 100			Bibr 1048	5 58		2.8% 1.08 [0.29, 3.93]				
Subtotal (95% CI)			262 100	0.0% 0.73 [0.41, 1.29]		Petro	13 169		3.5% 1.38 [0.43, 4.37]				
Total events	22	33				Recover I	71 1273		8.9% 0.61 [0.45, 0.84]				
Heterogeneity: Not applica Test for overall effect: Z = 1						Recover II Subtotal (95% CI)	64 1280 2780	102 1288 4 2686 10	4.8% 0.61 [0.44, 0.84] 0.0% 0.64 [0.52, 0.80]				
Testilor overall ellect. Z =	1.00 (F = 0.20)					Total events	153	2000 10	0.04 [0.52, 0.80]				
1.6.3 Rivaroxaban vs VK	4					Heterogeneity: Tau ² = 0.00; (
Einstein-DVT	19 215	20	223 13	0.98 [0.51, 1.90]		Test for overall effect: Z = 4.0		5 (F = 0.48), T = 0.%					
Einstein-PE	58 440	67		0.76 [0.52, 1.11]	— — —	restion overall effect. Z = 4.0	14 (i ~ 0.0001)						
J-Rocket AF	58 205	38		1.8% 1.75 [1.10, 2.79]	_	2.6.2 Dabigatran 110mg vs	VKA						
Rocket-AF	693 2688	633 2	702 40	1.3% 1.14 [1.00, 1.29]	-	Bibr 1048	2 46	5 62 10	0.0% 0.52 (0.10, 2.80				
Subtotal (95% CI)	3548	3	533 100	0.0% 1.10 [0.82, 1.48]	*	Subtotal (95% CI)	46	62 10					
Total events	828	758				Total events	2	5					
Heterogeneity: Tau ² = 0.05		3 (P = 0.0	5); I² = 62	%		Heterogeneity: Not applicabl	le						
Test for overall effect: Z = I	0.64 (P = 0.52)					Test for overall effect: Z = 0.7	76 (P = 0.44)						
1.6.4 Apixaban vs VKA					_	2.6.3 Rivaroxaban vs VKA							
Aristotle Subtotal (95% CI)	257 2836 2836		819 100			Einstein-DVT	139 1718		7.8% 1.00 [0.78, 1.28]				
			819 100	0.04 [0.34, 0.76]	•	Einstein-DVT dose study	8 135		0.5% 0.66 [0.26, 1.66]				
Total events	257	379				Einstein-PE	249 2412		4.2% 0.90 [0.75, 1.07]				
Heterogeneity: Not applica Test for overall effect: Z = 9						J-Rocket AF	138 639		6.4% 1.14 [0.87, 1.50]				
Test for overall effect. $Z = $	5.19 (P < 0.00001)					Rocket-AF	1475 7111		1.1% 1.03 [0.95, 1.11]				
1.6.5 Edoxaban 60mg vs	VKA					Subtotal (95% CI)	12015	12017 10	00.0% 1.01 [0.94, 1.08]	1 T			
Hokusai-VTE	70 560	82	544 100	0.80 [0.57, 1.13]		Total events	2009	1997					
Subtotal (95% CI)	560		544 100			Heterogeneity: Tau ² = 0.00; (1 (P = 0.48); P = 0%					
Total events	70	82			-	Test for overall effect: Z = 0.2	24 (P = 0.81)						
Heterogeneity: Not applica	able					2.6.4 Apixaban vs VKA							
Test for overall effect: Z =	1.24 (P = 0.22)					Amplify	115 2676	261 2689 3	9.2% 0.42 [0.33, 0.52				
						Aristotle	613 9088		3.1% 0.67 [0.61, 0.75]				
							1 71		3.2% 0.25 [0.03, 2.33				
					Favours DOAC Favours VKA	Botticelli-DVT	11 128		4.4% 1.09 [0.45, 2.67]				
						Subtotal (95% CI)	11963	11942 10					
						Total events	740	1152	- / ·	-			
						Heterogeneity: Tau ² = 0.10; (%				
						Test for overall effect: Z = 2.5							
										0.1 0.2 0.5 1 2 5 10			
1										Favours DOAC Favours VKA			

Figure S7. Forest Plots for risk of Clinically Relevant Bleeding in Elderly (left) and Total Population (right) - Random Effects Model

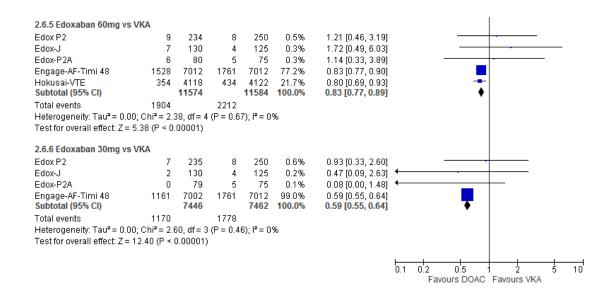


Figure S7. (contd) Forest Plots for risk of Clinically Relevant Bleeding in Total Population (right)- Random Effects Model

DOAC VKA Study or Subgroup Events Total Events Tot	al Moight	Peto Odds Ratio	Peto Odds Ratio Peto, Fixed, 95% Cl	Study of Subgroup	DOAC		VKA	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% Cl	Peto Odds Ratio Peto, Fixed, 95% Cl
1.7.1 Dabigatran 150mg vs VKA	ai weiyin	Peto, Fixed, 95% CI	Peto, Fixed, 95% Ci	Study or Subgroup E 2.7.1 Dabigatran 150mg vs V		TOTAL	vents	Total	weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI
Re-ly 16 2145 17 208	8 100.0%	0.92 [0.46, 1.82]		Re-ly		6076	39	6022	95.7%	0.71 [0.44, 1.15]	
Subtotal (95% CI) 2145 208		0.92 [0.46, 1.82]		Recover I		1273		1266	2.9%	0.99 [0.06, 15.91]	←
Total events 16 17				Recover II		1280		1288	1.4%	0.14 [0.00, 6.86]	←
Heterogeneity: Not applicable				Subtotal (95% CI)		8629			100.0%	0.70 [0.44, 1.12]	
Test for overall effect: Z = 0.25 (P = 0.80)				Total events	29		41				
				Heterogeneity: Chi ² = 0.74, df	= 2 (P = 0).69); I ² =	:0%				
1.7.2 Dabigatran 110mg vs VKA				Test for overall effect: Z = 1.47	7 (P = 0.14	4)					
	8 100.0%	0.73 [0.35, 1.51]									
	8 100.0%	0.73 [0.35, 1.51]		2.7.2 Dabigatran 110mg vs V	/KA						_
Total events 12 17				Re-ly		6015			100.0%	0.60 [0.36, 0.98]	
Heterogeneity: Not applicable				Subtotal (95% CI)		6015		6022	100.0%	0.60 [0.36, 0.98]	
Test for overall effect: Z = 0.85 (P = 0.40)				Total events	23		39				
1.7.3 Rivaroxaban vs VKA				Heterogeneity: Not applicable							
		0447004.000		Test for overall effect: Z = 2.03	3 (P = 0.04	4)					
Einstein-DVT 0 215 2 22 Einstein-PE 2 475 2 44		0.14 [0.01, 2.24]		2.7.3 Rivaroxaban vs VKA							
J-Rocket AF 1 206 2 20		0.51 [0.05, 4.97]		Einstein-DVT	4	1718	E	1711	6.1%	0.26 [0.05, 1.30]	•
Rocket-AF 13 2688 25 270		0.53 [0.28, 1.01]		Einstein-DVT dose study		135	2	137	1.0%	0.28 [0.05, 1.30]	
Subtotal (95% CI) 3584 358		0.53 [0.30, 0.93]		Einstein-PE		2412	3	2405	5.1%	0.67 [0.12, 3.86]	·
Total events 16 31				J-Rocket AF	1	639	3	639	4.1%	0.37 [0.05, 2.61]	←
Heterogeneity: Chi ² = 1.22, df = 3 (P = 0.75); l ² = 0%				Rocket-AF	27	7111	-	7125	83.6%	0.50 [0.33, 0.78]	
Test for overall effect: Z = 2.19 (P = 0.03)				Subtotal (95% CI)		2015			100.0%	0.48 [0.32, 0.71]	
·····,				Total events	31		67				
1.7.4 Apixaban vs VKA				Heterogeneity: Chi ² = 1.20, df	= 4 (P = 0).88); I ² =	:0%				
Aristotle 4 2836 5 281	9 100.0%	0.80 [0.22, 2.94]		Test for overall effect: Z = 3.64	4 (P = 0.00	003)					
Subtotal (95% CI) 2836 281	9 100.0%	0.80 [0.22, 2.94]									
Total events 4 5				2.7.4 Apixaban vs VKA							
Heterogeneity: Not applicable				Amplify		2676		2689	13.6%	0.52 [0.05, 4.96]	•
Test for overall effect: Z = 0.34 (P = 0.73)				Aristotle	8	9088		9052	86.4%	0.73 [0.30, 1.79]	
				Aristotle-J	0	71	0	75		Not estimable	
		0.1 0.2	0.5 1 2 5 10	Subtotal (95% CI)		1835		1816	100.0%	0.69 [0.30, 1.60]	
			vours DOAC Favours VKA	Total events	9		13				
											Favours DOAC Favours VKA
											Favours DOAC Favours VKA

Figure S8. Forest Plots for risk of Fatal Bleeding in Elderly (left) and Total Population (right).

2.7.5 Edoxaban 60mg vs VK	(A)								
Edox-J	1	130	0	125	1.0%	7.11 [0.14, 358.60]			→
Engage-AF-Timi 48	32	7012	59	7012	87.4%	0.55 [0.36, 0.83]			
Hokusai-VTE Subtotal (95% CI)	2	4118 11260	10	4122 11259	11.6% 100.0%	0.26 [0.08, 0.82] 0.52 [0.35, 0.76]	•	•	
Total events	35		69						
Heterogeneity: Chi ² = 3.17, d	f= 2 (P =	0.21); I ^z =	37%						
Test for overall effect: Z = 3.3	84 (P = 0.0	0008)							
2.7.6 Edoxaban 30mg vs VK	(A								
Edox-J	0	130	0	125		Not estimable		_	
Engage-AF-Timi 48 Subtotal (95% CI)	21	7002 7132	59	7012 7137	100.0% 100.0%	0.39 [0.25, 0.60] 0.39 [0.25, 0.60]			
Total events Heterogeneity: Not applicabl	21 le		59						
Test for overall effect: Z = 4.2		0001)							
							0.1	0.2 0.5 1 2 5	10
								Favours DOAC Favours VKA	

Figure S8. (contd) Forest Plots for risk of Fatal Bleeding in Elderly (left) and Total Population (right).

DOAC VKA Study or Subgroup Events Total Events		Peto Odds Ratio Peto, Fixed, 95% Cl	Peto Odds Ratio Peto, Fixed, 95% Cl	DOAC VKA Peto Odds Ratio Peto Odds Ratio Study or Subgroup Events Total Events Total Weight Peto, Fixed, 95% Cl Peto, Fixed, 95% Cl
1.8.1 Dabigatran 150mg vs VKA Re-ly 230 2145 215	2088 100.0%	1.05 [0.86, 1.27]		2.8.1 Dabigatran 150mg vs VKA Bibr 1048 0 58 0 62 Not estimable
Subtotal (95% CI) 2145 Total events 230 215 Heterogeneity: Not applicable	2088 100.0%	1.05 [0.86, 1.27]	Ť	Petro 0 169 0 70 Not estimable Re-ly 438 6076 487 6022 100.0% 0.88 [0.77, 1.01] Subtotal (95% CI) 6303 6154 100.0% 0.88 [0.77, 1.01]
Test for overall effect: Z = 0.45 (P = 0.65)				Total events 438 487 Heterogeneity: Not applicable
1.8.2 Dabigatran 110mg vs VKA Re-ly 211 2026 215	2088 100.0%	1.01 [0.83, 1.24]	.	Test for overall effect: Z = 1.82 (P = 0.07)
Subtotal (95% CI) 2026	2088 100.0%	1.01 [0.83, 1.24]		2.8.2 Dabigatran 110mg vs VKA
Total events 211 215 Heterogeneity: Not applicable Test for overall effect: Z = 0.12 (P = 0.90)				Bibr 1048 0 46 0 62 Not estimable Re-ly 446 6015 487 6022 100.0% 0.91 [0.80, 1.04] Subtotal (95% CI) 6061 6084 100.0% 0.91 [0.80, 1.04] Image: Comparison of the second
1.8.3 Rivaroxaban vs VKA			_	Total events 446 487 Heterogeneity: Not applicable
Rocket-AF 106 2652 127 Subtotal (95% CI) 2652	2678 100.0% 2678 100.0%	0.84 [0.64, 1.09] 0.84 [0.64, 1.09]	-	Test for overall effect: Z = 1.38 (P = 0.17)
Total events 106 127 Heterogeneity: Not applicable Test for overall effect: Z = 1.33 (P = 0.18)				2.8.3 Rivaroxaban vs VKA J-Rocket AF 7 637 5 637 1.1% 1.40 [0.45, 4.36] Rocket AF 582 7131 632 7133 98.9% 0.91 [0.81, 1.03]
		<u> </u>		Subtotal (95% CI) 7768 7770 100.0% 0.92 [0.82, 1.03] Total events 589 637
		0.1 0.2 Fav	0.5 1 2 5 10 vours DOAC Favours VKA	Heterogeneity: Chi² = 0.53, df = 1 (P = 0.46); l² = 0% Test for overall effect: Z = 1.43 (P = 0.15)
				2.8.4 Apixaban vs VKA Aristotle 603 9120 669 9081 100.0% 0.89 [0.79, 1.00]
				Aristotle-J 0 74 0 74 Not estimable Subtotal (95% CI) 9194 9155 100.0% 0.89 [0.79, 1.00]
				Total events 603 669 Heterogeneity: Not applicable
				Test for overall effect: $Z = 2.00$ (P = 0.05)
				2.8.5 Edoxaban 60mg vs VKA
				Edox-J 1 131 1 129 0.1% 0.98 [0.06, 15.83] Engage-AF-Timi 48 773 7035 839 7036 99.9% 0.91 [0.82, 1.01]
				Subtotal (95% Cl) 7166 7165 100.0% 0.91 [0.82, 1.01] ♦ Total events 774 840
				Heterogeneity: Chi ² = 0.00, df = 1 (P = 0.96); i ² = 0% Test for overall effect: Z = 1.74 (P = 0.08)
				2.8.6 Edoxaban 30mg vs VKA Edox-J 0 131 1 129 0.1% 0.13 [0.00, 6.72] ←
				Engage-AF-Timi 48 737 7034 839 7036 99.9% 0.86 [0.78 0.96] Subtotal (95% CI) 7155 7165 100.0% 0.86 [0.78 0.96]
				Subtotal (95% Cl) 7165 7165 100.0% 0.86 [0.78, 0.96] Total events 737 840 Heterogeneity: Chi² = 0.87, df = 1 (P = 0.35); l² = 0% Test for overall effect: Z = 2.75 (P = 0.006)
				0.1 0.2 0.5 1 2 5 10 Favours DOAC Favours VKA

Figure S9. Forest Plots for risk of All Cause Death in Atrial Fibrillation in Elderly (left) and Total Population (right).

*Event numbers for Rocket-AF in elderly have been estimated from published confidence intervals

	DOA	С	VK/	4		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup		Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% Cl
2.9.1 Dabigatran 150mg v	s VKA						
Recover I	21	1274	21	1265	45.7%	0.99 [0.54, 1.83]	_
Recover II	25	1279	25	1289	54.3%	1.01 [0.58, 1.76]	
Subtotal (95% CI)		2553		2554	100.0%	1.00 [0.66, 1.51]	-
Total events	46		46				
Heterogeneity: Chi² = 0.00,		-	; ² = 0%				
Test for overall effect: Z = 0	.00 (P = 1	.00)					
2.9.3 Rivaroxaban vs VKA							
Einstein-DVT	38	1718	49	1711	42.6%	0.77 [0.50, 1.18]	
Einstein-DVT dose study	4	136	5	137	4.4%	0.80 [0.21, 3.02]	
Einstein-PE	58	2412	50	2405	53.0%	1.16 [0.79, 1.70]	
Subtotal (95% CI)		4266		4253	100.0%	0.96 [0.73, 1.26]	•
Total events	100		104				
Heterogeneity: Chi ² = 2.07,	df = 2 (P	= 0.36)	2 = 3%				
Test for overall effect: Z = 0	.30 (P = 0	.76)					
2.9.4 Apixaban vs VKA							
Amplify	41	2676	52	2689	96.8%	0.79 [0.52, 1.19]	
Botticelli-DVT	3	128	0	126	3.2%	7.39 [0.76, 71.70]	
Subtotal (95% CI)		2804		2815	100.0%	0.85 [0.57, 1.27]	
Total events	44		52				
Heterogeneity: Chi ² = 3.60,	df = 1 (P	= 0.06)	; I² = 72%	,			
Test for overall effect: Z = 0	.80 (P = 0	.42)					
2.9.5 Edoxaban 60mg vs \	/KA						\perp
Hokusai-VTE	132	4118	126		100.0%	1.05 [0.82, 1.35]	
Subtotal (95% CI)		4118		4122	100.0%	1.05 [0.82, 1.35]	•
Total events	132		126				
Heterogeneity: Not applica	ble						
Test for overall effect: Z = 0	.39 (P = 0	.70)					
							0.1 0.2 0.5 1 2 5 10
							Favours DOAC Favours VKA

Figure S10. Forest Plots for risk of All Cause Death in Venous thromboembolism in Total Population (right).

*No results available for the elderly for this outcome

DOAC Study or Subgroup Events Total	VKA Events Tota	Peto Odds Ratio I Peto, Fixed, 95% Cl	Peto Odds Ratio Peto, Fixed, 95% Cl	Study or Subgroup	DOAC Events Total	VKA Events Tota	Peto Odds Ratio	Peto Odds Ratio Peto, Fixed, 95% Cl
1.1.1 Dabigatran 150mg vs VKA				3.1.1 Dabigatran 150n				
Re-ly 69 2466				Re-ly	65 3610	101 3599		
Subtotal (95% CI) 2466	2423	0.66 [0.49, 0.90]	◆	Subtotal (95% CI)	3610	3599	0.64 [0.47, 0.87]	▲
Fotal events 69	101			Total events	65	101		
Heterogeneity: Not applicable Fest for overall effect: Z = 2.61 (P = 0.1	009)			Heterogeneity: Not app Test for overall effect: 2		04)		
1.1.2 Dabigatran 110mg vs VKA				3.1.2 Dabigatran 110n	ng vs VKA			
Re-ly 87 2349	101 2423			Re-ly	96 3666	101 3599		
Subtotal (95% CI) 2349		0.88 [0.66, 1.18]	-	Subtotal (95% CI)	3666	3599	0.93 [0.70, 1.24]	↓ ←
Fotal events 87	101			Total events	96	101		
Heterogeneity: Not applicable	(A)			Heterogeneity: Not app				
Fest for overall effect: Z = 0.82 (P = 0.4	+1)			Test for overall effect: 2	2 = 0.49 (P = 0.6.	2)		
1.1.3 Rivaroxaban vs VKA			_	3.1.3 Rivaroxaban vs	VKA			
Rocket-AF 125 3082				Rocket-AF	144 3999	152 4008		
Subtotal (95% CI) 3082		2 0.80 [0.63, 1.02]	◆	Subtotal (95% CI)	3999	4008	3 0.95 [0.75, 1 .20]	•
Fotal events 125	154			Total events	144	152		
Heterogeneity: Not applicable Fest for overall effect: Z = 1.78 (P = 0.0	101			Heterogeneity: Not app Test for overall effect: 2		5)		
$\frac{1}{1} = \frac{1}{1} = \frac{1}$	JO)			Testior overall ellect. 2	2 - 0.40 (F - 0.0	5)		
1.1.4 Apixaban vs VKA				3.1.4 Apixaban vs VK/	Α			
Aristotle 79 2850				Aristotle	133 6270	156 6253	3 0.85 [0.67, 1.07]	
Aristotle-J 0 45	2 23			Aristotle-J	0 103	1 51		
Subtotal (95% CI) 2895 Fotal events 79	2851 111	0.70 [0.52, 0.93]	-	Subtotal (95% CI) Total events	6373 133	6304 157	0.84 [0.67, 1.06]	
Heterogeneity: Chi ^z = 3.10, df = 1 (P =				Heterogeneity: Chi ² = 1				
Fest for overall effect: Z = 2.46 (P = 0.1				Test for overall effect: 2				
	,				(,	.,		
1.1.5 Edoxaban 60mg vs VKA			_	3.1.5 Edoxaban 60mg				
Engage-AF-Timi 48 138 2848	166 2820			Engage-AF-Timi 48	165 4187	179 4216		
Subtotal (95% CI) 2848		0.81 [0.65, 1.03]	-	Subtotal (95% CI)	4187	4216	6 0.93 [0.75, 1.15]	•
Fotal events 138 Heterogeneity: Not applicable	166			Total events Heterogeneity: Not app	165 olicoble	179		
Fest for overall effect: Z = 1.74 (P = 0.0	18)			Test for overall effect: 2		8)		
	,					-,		
1.1.6 Edoxaban 30mg vs VKA			<u> </u>	3.1.6 Edoxaban 30mg				
Engage-AF-Timi 48 184 2806				Engage-AF-Timi 48	208 4228	179 4216		
Subtotal (95% CI) 2806) 1.12 [0.90, 1.39]	-	Subtotal (95% CI)	4228	4216	5 1.17 [0.95, 1.43]	
Fotal events 184 Heterogeneity: Not applicable	166			Total events Heterogeneity: Not app	208 Dicable	179		
Fest for overall effect: Z = 1.04 (P = 0.3	30)			Test for overall effect: 2		4)		
		⊢ 0.1	0.2 0.5 1 2 5 10					
			Favours DOAC Favours VKA					Favours DOAC Favours VKA

Figure S11. Forest Plots for risk of Stroke or Systemic Embolism in AF in Elderly (left) and <75 Population (right).

*Event numbers for Engage-AF-Timi 48 in elderly have been estimated from published confidence intervals.

Study or Subgroup E	DOA Events	-	VKA Events		Peto Odds Ratio Peto, Fixed, 95% Cl	Peto Od Peto, Fixe		Study or Subgroup	DOAC Events Total E	VKA Events Total	Peto Odds Ratio Peto, Fixed, 95% Cl	Peto Odds Ratio Peto, Fixed, 95% Cl
1.2.1 Dabigatran 150mg vs \	VKA							3.2.1 Dabigatran 150mg v	vs VKA			
Pooled Recover Studies Subtotal (95% CI)	3	253 253	5	276 276	0.66 [0.16, 2.66] 0.66 [0.16, 2.66]			Pooled Recover Studies Subtotal (95% CI)	57 2300 2300	50 2278 2278	1.13 [0.77, 1.66] 1.13 [0.77, 1.66]	
Total events Heterogeneity: Not applicable	3 e		5					Total events Heterogeneity: Not applica	57 able	50		
Test for overall effect: Z = 0.5	9 (P = 0	.56)						Test for overall effect: Z = 0				
1.2.2 Apixaban vs VKA						_		3.2.2 Apixaban vs VKA				
Amplify Subtotal (95% CI)	7	389 389	13	360 360	0.50 [0.21, 1.21] 0.50 [0.21, 1.21]		-	Amplify Subtotal (95% CI)	52 2220 2220	58 2275 2275	0.92 [0.63, 1.34] 0.92 [0.63, 1.34]	
Total events	7		13					Total events	52	58		
Heterogeneity: Not applicable Test for overall effect: Z = 1.5		.12)						Heterogeneity: Not applica Test for overall effect: Z = 0				
1.2.3 Rivaroxaban vs VKA								3.2.3 Rivaroxaban vs VKA	N N			
Einstein-DVT	4	215		225	0.43 [0.15, 1.25]	· · · ·	_	Einstein-DVT	32 1516	41 1493	0.76 [0.48, 1.22]	
Einstein-PE Subtotal (95% CI)	11	441 656	13	402 627	0.77 [0.34, 1.72] 0.62 [0.33, 1.18]		-	Einstein-PE Subtotal (95% CI)	39 1978 3494	31 2011 3504	1.28 [0.80, 2.06] 0.99 [0.71, 1.37]	•
Total events	15		23					Total events	71	72		
Heterogeneity: $Chi^2 = 0.70$, dt Test for overall effect: $Z = 1.43$; ² = 0%					Heterogeneity: Chi ² = 2.35, Test for overall effect: Z = 0		I² = 57%		
1.2.4 Edoxaban 60mg vs VK	A					_		3.2.4 Edoxaban 60mg vs	VKA			
Hokusai-VTE Subtotal (95% CI)	14	560 560	27	544 <mark>544</mark>	0.50 [0.27, 0.94] 0.50 [0.27, 0.94]			Hokusai-VTE Subtotal (95% CI)	116 3558 3558	119 3578 3578	0.98 [0.76, 1.27] 0.98 [0.76, 1.27]	
Total events	14		27					Total events	116	119		
Heterogeneity: Not applicable Test for overall effect: $Z = 2.1$		1.03)						Heterogeneity: Not applica Test for overall effect: Z = 0				
						0.1 0.2 0.5 1	2 5 10				F	
						Favours DOAC					-	Favours DOAC Favours VKA

Figure S12. Forest Plots for risk of Venous Thromboembolism in VTE in Elderly (left) and <75 Population (right).

Study or Subgroup	DOAC Events Total E	VKA Events Total	Peto Odds Ratio Peto, Fixed, 95% CI		lds Ratio ed, 95% Cl	Study or Subgroup	DOAC Events Tot	VK/ al Events		Peto Odds Ratio Peto, Fixed, 95% Cl		dds Ratio ed, 95% Cl
1.3.1 Dabigatran 150mg v				,,		3.3.1 Dabigatran 150mg v					,,	
Pooled Recover Studies	8 231	10 262	0.90 [0.35, 2.32]			Pooled Recover Studies	16 222	5 30	2200	0.53 [0.30, 0.96]		-
Re-ly	227 2145	188 2088	1.20 [0.98, 1.46]			Re-ly	172 393		3934	0.73 [0.60, 0.89]		
Subtotal (95% CI)	2376	2350	1.18 [0.97, 1.44]		•	Subtotal (95% CI)	615	120	6134	0.71 [0.58, 0.85]	•	
Total events	235	198				Total events	188	263				
Heterogeneity: Chi² = 0.32		P ² = 0%				Heterogeneity: Chi ² = 0.98,						
Test for overall effect: Z = 1	1.64 (P = 0.10)					Test for overall effect: Z = 3	.62 (P = 0.000	13)				
1.3.2 Dabigatran 110mg v	s VKA					3.3.2 Dabigatran 110mg v					_	
Re-ly	187 2026	188 2088	1.03 [0.83, 1.27]			Re-ly	155 398		3934	0.65 [0.53, 0.79]		
Subtotal (95% CI)	2026	2088	1.03 [0.83, 1.27]			Subtotal (95% CI)	398	101	3934	0.65 [0.53, 0.79]	•	
Total events	187	188				Total events	155	233				
Heterogeneity: Not applica Test for overall effect: Z = 0						Heterogeneity: Not applica Test for overall effect: Z = 4		43				
Test for overall effect. $Z = t$	J.25 (P = 0.80)					restior overall ellect. Z = 4	.20 (F < 0.000	(1)				
1.3.3 Rivaroxaban vs VKA	1					3.3.3 Rivaroxaban vs VKA						
Einstein-DVT	3 215	5 223	0.62 [0.15, 2.52]	10 and		Einstein-DVT	11 150		1488	0.73 [0.34, 1.57]		
Einstein-PE	5 440	23 401	0.24 [0.11, 0.51]		-64	Einstein-PE	21 196		2004	0.74 [0.42, 1.29]		<u></u>
J-Rocket AF	14 206	10 207	1.43 [0.63, 3.26]	×1		J-Rocket AF	12 43			0.59 [0.29, 1.20]		- 10
Rocket-AF	203 2688	179 2702	1.15 [0.93, 1.42]			Rocket-AF	192 442		4423	0.92 [0.76, 1.13]		1
Subtotal (95% CI)	3549	3533	1.04 [0.86, 1.26]			Subtotal (95% CI)	832		8347	0.87 [0.73, 1.04]	•	
Total events	225	217				Total events	236	271				
Heterogeneity: Chi² = 16.5 Test for overall effect: Z = 0		19); if = 82%				Heterogeneity: Chi ² = 2.03, Test for overall effect: Z = 1		57), 17 = 0%				
restion overall ellect. Z = t	0.59 (F = 0.70)					restion overall ellect. Z = 1	.57 (F = 0.12)					
1.3.4 Apixaban vs VKA						3.3.4 Apixaban vs VKA						
Amplify	4 398	16 370	0.27 [0.11, 0.66]	· · · · · · · · · · · · · · · · · · ·		Amplify	11 227		2319	0.37 [0.20, 0.67]	· · · · · · · · · · · · · · · · · · ·	
Aristotle	151 2836	224 2819	0.65 [0.53, 0.81]			Aristotle	176 625		6233	0.73 [0.60, 0.89]		
Subtotal (95% CI)	3234	3189	0.63 [0.51, 0.77]	•		Subtotal (95% CI)	853		8552	0.68 [0.57, 0.82]	•	
Total events	155	240				Total events	187 	271	v			
Heterogeneity: Chi² = 3.60 Test for overall effect: Z = 4		1~= 7.2%				Heterogeneity: Chi ² = 4.53, Test for overall effect: Z = 4			Xo			
restion overall ellect. Z = 4	4.52 (F < 0.00001)					restior overall ellect. Z = 4	.00 (F < 0.000	(1)				
1.3.5 Edoxaban 60mg vs V	VKA					3.3.5 Edoxaban 60mg vs \	/KA					
Engage-AF-Timi 48	214 2848	257 2820	0.81 [0.67, 0.98]		-	Engage-AF-Timi 48	204 418		4216	0.76 [0.63, 0.91]		
Subtotal (95% CI)	2848	2820	0.81 [0.67, 0.98]	•	2	Subtotal (95% CI)	418	and a second second	4216	0.76 [0.63, 0.91]	•	
Total events	214	257				Total events	204	267				
Heterogeneity: Not applica						Heterogeneity: Not applica		20				
Test for overall effect: Z = 2	2.18 (P = 0.03)					Test for overall effect: Z = 2	91 (P = 0.004)				
1.3.6 Edoxaban 30mg vs	VKA					3.3.6 Edoxaban 30mg vs \	/KA					
Engage-AF-Timi 48	121 2806	257 2820	0.46 [0.38, 0.57]			Engage-AF-Timi 48	133 422		4216	0.49 [0.40, 0.60]	-	
Subtotal (95% CI)	2806	2820	0.46 [0.38, 0.57]	-		Subtotal (95% CI)	422		4216	0.49 [0.40, 0.60]	-	
Total events	121	257				Total events	133	267				
Heterogeneity: Not applica						Heterogeneity: Not applica		12103				
Test for overall effect: Z = 7	7.19 (P < 0.00001)					Test for overall effect: Z = 6	.89 (P < 0.000	101)				
												<u> </u>
				0.1 0.2 0.5	1 2 5 10 [°]						0.1 0.2 0.5	1 2 5
				Favours DOAC	Favours VKA						Favours DOAC	Favours VKA

Figure S13. Forest Plots for risk of Major Bleeding in Elderly (left) and <75 Population (right).

*Event numbers for Engage-AF-Timi-48 and J-Rocket AF in the elderly have been estimated from published confidence intervals.

	DOAC	VKA	Peto Odds Ratio	Peto Odds Ratio		DOAC	VKA	Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events Total	Events Tot	al Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl	Study or Subgroup	Events Total	Events Total	Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl
1.4.1 Dabigatran 150n	ng vs VKA				3.4.1 Dabigatran 150	Omg vs VKA			
Re-ly Subtotal (95% CI)	135 2466 2466	75 242 242			Re-ly Subtotal (95% CI)	88 3666 3666			-
Total events Heterogeneity: Not app Test for overall effect: 2		75 001)			Total events Heterogeneity: Not a Test for overall effect	• •	73 28)		
1.4.2 Dabigatran 110n	ng vs VKA				3.4.2 Dabigatran 110	Omg vs VKA			
Re-ly Subtotal (95% CI)	101 2349 2349	75 242 242			Re-ly Subtotal (95% CI)	61 3610 3610			
Total events Heterogeneity: Not app Test for overall effect: 2		75 3)			Total events Heterogeneity: Not a Test for overall effect	• •	73 29)		
				0.1 0.2 0.5 1 2 5 10 Favours DOAC Favours VKA					0.1 0.2 0.5 1 2 5 10 Favours DOAC Favours VKA

Figure S14. Forest Plots for risk of Gastrointestinal Bleeding in Elderly (left) and <75 Population (right).

	DOAC	VKA	Peto Odds Ratio	Peto Odds Ratio		DOAC	VKA	Peto Odds Ratio	Peto Odds Ratio
		Events Total	Peto, Fixed, 95% CI	Peto, Fixed, 95% Cl			Events Total	Peto, Fixed, 95% CI	Peto, Fixed, 95% Cl
.5.1 Dabigatran 150	South Shattire 26			_	3.5.1 Dabigatran 150	and a second second			_
'e-ly	19 21 4 5	44 2088	0.43 [0.26, 0.72]		Re-ly	19 3931	46 3934	0.43 [0.27, 0.71]	
ubtotal (95% CI)	2145	2088	0.43 [0.26, 0.72]		Subtotal (95% CI)	3931	3934	0.43 [0.27, 0.71]	
otal events	19	44			Total events	19	46		
leterogeneity: Not ap					Heterogeneity: Not ap				
est for overall effect:	Z = 3.28 (P = 0.00	11)			Test for overall effect:	Z = 3.36 (P = 0.0)008)		
.5.2 Dabigatran 110	mg vs VKA				3.5.2 Dabigatran 110	mg vs VKA			
'e-ly	14 2026	44 2088	0.36 [0.22, 0.61]		Re-ly	13 3989	46 3934	0.32 [0.19, 0.53]	
ubtotal (95% CI)	2026	2088	0.36 [0.22, 0.61]		Subtotal (95% CI)	3989	3934	0.32 [0.19, 0.53]	
otal events	14	44			Total events	13	46		
leterogeneity: Not ap	plicable				Heterogeneity: Not ap	plicable			
est for overall effect:	Z = 3.85 (P = 0.00	101)			Test for overall effect:	Z = 4.37 (P < 0.0)001)		
.5.3 Rivaroxaban vs	VKA				3.5.3 Rivaroxaban vs	VKA			
instein-DVT	0 215	1 223	0.14 [0.00, 7.07]		Einstein-DVT	2 1503	1 1488	1.93 [0.20, 18.56]	
instein-PE	2 475	6 448	0.34 [0.09, 1.38]		Einstein-PE	1 1944	6 1957	0.24 [0.05, 1.06] +	
ocket-AF	29 2688	33 2702	0.88 [0.53, 1.46]		Rocket-AF	26 4423	51 4423	0.52 [0.33, 0.81]	
ubtotal (95% CI)	3378	3373	0.77 [0.48, 1.23]	-	Subtotal (95% CI)	7870	7868	0.51 [0.34, 0.78]	-
otal events	31	40			Total events	29	58		
leterogeneity: Chi ^z =	2.30, df = 2 (P = 0	.32); I ^z = 13%			Heterogeneity: Chi ² =	2.32, df = 2 (P =	0.31); I ^z = 14%		
est for overall effect:	Z = 1.08 (P = 0.28)			Test for overall effect:	Z = 3.12 (P = 0.0)02)		
.5.4 Apixaban vs VK	A				3.5.4 Apixaban vs Vk	A			
ristotle	20 2836	57 2819	0.38 [0.24, 0.59]		Aristotle	32 6252	65 6233	0.50 [0.34, 0.75]	
ubtotal (95% CI)	2836	2819	0.38 [0.24, 0.59]		Subtotal (95% CI)	6252	6233	0.50 [0.34, 0.75]	•
otal events	20	57			Total events	32	65		
leterogeneity: Not ap					Heterogeneity: Not ap				
est for overall effect:	Z = 4.27 (P < 0.00	101)			Test for overall effect:	Z = 3.38 (P = 0.0)007)		
								Ē	
			0.1	D.2 D.5 1 2 5 Favours DOAC Favours VKA	10			0	.1 0.2 0.5 1 2 5 1 Favours DOAC Favours VKA

Figure S15. Forest Plots for risk of Intracranial Bleeding in Elderly (left) and <75 Population (right).

Study or Subgroup E 1.6.1 Dabigatran 150mg vs V Pooled Recover Studies		Total					The board of the second s						Odds Ratio
Contraction of the second s		Totui	Events	Total I	V, Random, 95% Cl	IV, Random, 95% CI	Study or Subgroup		Total E	vents	Total	IV, Random, 95% CI	IV, Random, 95% Cl
Dealed Deseuse Ofusion	VKA						3.6.1 Dabigatran 150mg v	s VKA					
Subtotal (95% CI)	22	231 231	33	262 262	0.73 [0.41, 1.29] 0.73 [0.41, 1.29]		Pooled Recover Studies Subtotal (95% CI)		2225 2225	156	2200 2200	0.53 [0.41, 0.70] 0.53 [0.41, 0.70]	1
Total events	22		33				Total events	87		156			
Heterogeneity: Not applicable	le						Heterogeneity: Not applica	ble					
Test for overall effect: Z = 1.0		.28)					Test for overall effect: Z = 4	.58 (P < 0	.00001)				
1.6.3 Rivaroxaban vs VKA							3.6.3 Rivaroxaban vs VKA						
Einstein-DVT	19	215	20	223	0.98 [0.51, 1.90]		Einstein-DVT	120	1503	118	1488	1.01 [0.77, 1.31]	
Einstein-PE	58	440	67	401	0.76 [0.52, 1.11]		Einstein-PE	191	1972	207	2004	0.93 [0.76, 1.15]	
J-Rocket AF	58	205	38	207	1.75 [1.10, 2.79]		J-Rocket AF	78	432	86	430	0.88 [0.63, 1.24]	2
Rocket-AF	693	2688	633	2702	1.14 [1.00, 1.29]	-	Rocket-AF	782	4423	816	4423	0.95 [0.85, 1.06]	
Subtotal (95% CI)		3548		3533	1.10 [0.82, 1.48]	-	Subtotal (95% CI)		8330		8345	0.95 [0.87, 1.03]	•
Total events	828		758				Total events	1171		1227			
Heterogeneity: Tau ² = 0.05; C	Chi ² = 7.	84, df =	3 (P = 0	.05); I ² =	62%		Heterogeneity: Tau ² = 0.00	; Chi ² = 0	41, df = 3	B (P = 0)	.94); l²∶	= 0%	
Test for overall effect: Z = 0.6	64 (P = 0	.52)					Test for overall effect: Z = 1	.21 (P = 0	.23)				
1.6.4 Apixaban vs VKA							3.6.4 Apixaban vs VKA						
Aristotle Subtotal (95% CI)		2836 2836		2819 2819	0.64 [0.54, 0.76] 0.64 [0.54, 0.76]		Aristotle Subtotal (95% CI)		6252 6252	498	6233 6233	0.70 [0.60, 0.80] 0.70 [0.60, 0.80]	■
Total events	257		379				Total events	356		498			
Heterogeneity: Not applicable	le						Heterogeneity: Not applica	ble					
Test for overall effect: Z = 5.1	9 (P < 0	.00001))				Test for overall effect: Z = 5	i.06 (P < 0	.00001)				
1.6.5 Edoxaban 60mg vs VK	A						3.6.5 Edoxaban 60mg vs \	/KA					
Hokusai-VTE Subtotal (95% CI)	70	560 560	82	544 544	0.80 [0.57, 1.13] 0.80 [0.57, 1.13]	-	Hokusai-VTE Subtotal (95% CI)	279	3558 3558	341	3578 3578	0.81 [0.68, 0.95] 0.81 [0.68, 0.95]	
Total events	70	(2,2,2)	82		max. Extended to the second of a		Total events	279		341	110000	SALES AND AND AND A CONTRACT	
Heterogeneity: Not applicable							Heterogeneity: Not applica	10.000		0.11			
Test for overall effect: $Z = 1.2$.22)					Test for overall effect: Z = 2		.01)				
					0.1		10						
					0.1	Favours DOAC Favours VKA	TU:						Favours DOAC Favours VKA

Figure S16. Forest Plots for risk of Clinically Relevant Bleeding in Elderly (left) and <75 Population (right) - Random Effects Model.

	DOAC	VK	A	Peto Odds Ratio	Peto Odds Ratio		DOAC	VKA	Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup		Events	Total	Peto, Fixed, 95% CI	Peto, Fixed, 95% Cl	Study or Subgroup	Events To	tal Events Tota	Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl
.7.1 Dabigatran 150	mg vs VKA					3.7.1 Dabigatran 150)mg vs VKA			
Re-ly	16 2145		2088	0.92 [0.46, 1.82]		Re-ly	12 39			
Subtotal (95% CI)	2145		2088	0.92 [0.46, 1.82]		Subtotal (95% CI)	39	31 3934	0.55 [0.28, 1.09]	
Fotal events	16	17				Total events	12	22		
Heterogeneity: Not ap	(1) [1] [2] [2] [2] [2] [2] [2] [2] [2] [2] [2					Heterogeneity: Not a				
est for overall effect:	Z = 0.25 (P = 0.)	30)				Test for overall effect	: Z = 1.72 (P =	0.09)		
.7.2 Dabigatran 110	mg vs VKA					3.7.2 Dabigatran 110)mg vs VKA			
Re-ly	12 2026		2088	0.73 [0.35, 1.51]		Re-ly	11 39	89 22 3934	0.50 [0.25, 1.00]	
Subtotal (95% CI)	2026		2088	0.73 [0.35, 1.51]		Subtotal (95% CI)	39	89 3934	0.50 [0.25, 1.00]	
Total events	12	17				Total events	11	22		
Heterogeneity: Not ap						Heterogeneity: Not a	pplicable			
Fest for overall effect:	Z = 0.85 (P = 0.4	40)				Test for overall effect	: Z = 1.96 (P =	0.05)		
1.7.3 Rivaroxaban vs	VKA					3.7.3 Rivaroxaban v	s VKA			
Einstein-DVT	0 215	2	223	0.14 [0.01, 2.24] 🔶		Einstein-DVT	1 15	03 3 1488	0.36 [0.05, 2.59]	←
Einstein-PE	2 475	2	448	0.94 [0.13, 6.72]		Einstein-PE	0 19	44 1 1957	0.14 [0.00, 6.87]	<
I-Rocket AF	1 206		207	0.51 [0.05, 4.97] 🔶		J-Rocket AF	04	33 1 432	0.14 [0.00, 6.80]	·
Rocket-AF	13 2688		2702	0.53 [0.28, 1.01]		Rocket-AF	14 44			
Subtotal (95% CI)	3584		3580	0.53 [0.30, 0.93]		Subtotal (95% CI)	83	03 8300	0.45 [0.26, 0.78]	
Fotal events	16	31				Total events	15	35		
Heterogeneity: Chi² =			= 0%			Heterogeneity: Chi ² =		~		
est for overall effect:	Z = 2.19 (P = 0.1	33)				Test for overall effect	: Z = 2.84 (P =	0.005)		
.7.4 Apixaban vs VK	A				_	3.7.4 Apixaban vs VI	KA			_
Aristotle	4 2836		2819	0.80 [0.22, 2.94]		Aristotle	4 62			
Subtotal (95% CI)	2836		2819	0.80 [0.22, 2.94]		Subtotal (95% CI)	62	52 6233	0.67 [0.19, 2.31]	
Fotal events	4	5				Total events	4	6		
leterogeneity: Not ap		19230				Heterogeneity: Not a				
est for overall effect:	Z = 0.34 (P = 0.3	73)				Test for overall effect	: Z = 0.64 (P =	0.52)		
				-		-				
				Ö.1	0.2 0.0 1 2 0 1.) ^{**}				0.1 0.2 0.5 1 2 5
					Favours DOAC Favours VKA					Favours DOAC Favours VKA

Figure S17. Forest Plots for risk of Fatal Bleeding in Elderly (left) and <75 Population (right).

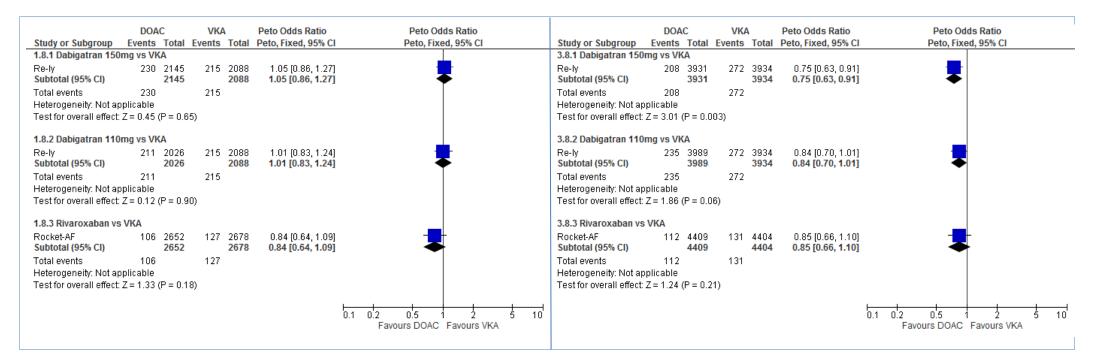


Figure S18. Forest Plots for risk of All Cause Death in AF in Elderly (left) and <75 Population (right).

*Event numbers for Rocket-AF in elderly have been estimated from published confidence intervals.

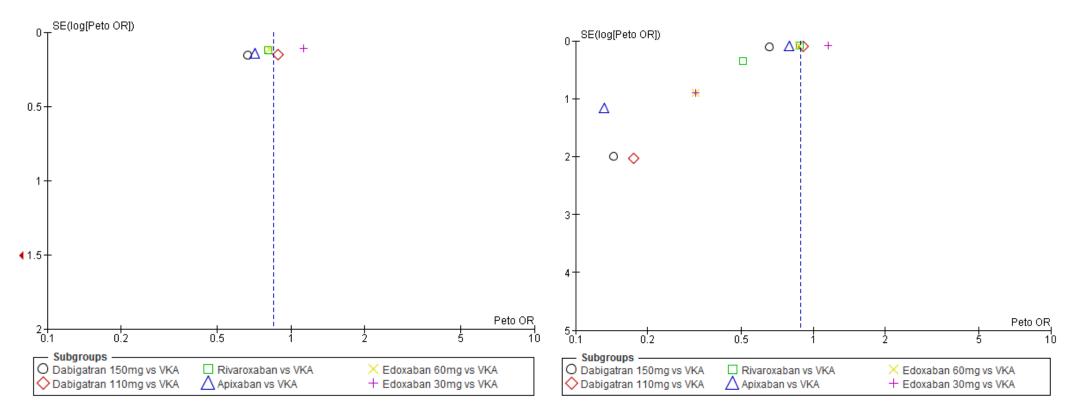


Figure S19. Funnel Plots for Stroke or Systemic Embolism in AF in Elderly (left) and Total population (right).

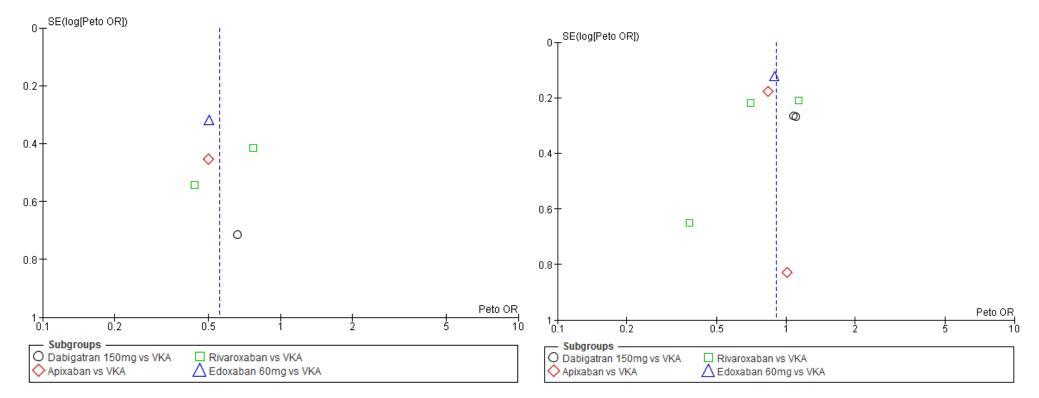


Figure S20. Funnel Plots for risk of Recurrent Venous Thromboembolism in VTE in Elderly (left) and Total population (right).

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Supplemental Methods

Supplemental Methods 1a. Additional Information.

Additional information gathered on the role of funders in the individual studies and characteristics of included studies are detailed in Supplemental Table S3 and Table S4 respectively.

Original forest plots for all outcomes presented in the main manuscript are detailed in Supplemental Figures S2-S8. Additional forest plots detailing data on risks of all death can be found in Figure S9-S10. Forest plots containing data from the <75 and ≥75 populations can be found in Figures S11-S18.

Additional funnel plots for risk of stroke or systemic embolism and venous thromboembolism in the elderly and total population are presented in Supplemental Figure S19-S20.

Supplemental Methods 2a. Search Strategy in EMBASE.

Ovid Technologies, Inc. Search limit to english language Database: Embase Classic+Embase <1947 to 2013 November 21> Search Strategy:

- 1 exp dabigatran etexilate/ or exp dabigatran/ or dabigatran.mp. (4628)
- 2 rivaroxaban.mp. or exp rivaroxaban/ (3840)
- 3 apixaban.mp. or exp apixaban/ (2350)
- 4 edoxaban.mp. or exp edoxaban/ (558)
- 5 exp thrombin inhibitor/ (35324)

6 ((direct adj3 thrombin adj3 inhib\$) or DTI).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (10140)

- 7 xaban\$.mp. (12)
- 8 exp blood clotting factor 10a inhibitor/ (9874)

9 ((factor Xa or factor 10a or fXa) adj3 inhib\$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (4755)

10 (factor 2a inhib\$ or factor IIa inhib\$ or f2a inhib\$).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (59)

11 (Pra?ax\$ or Xarelto or Eliqu?s or Lixiana).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (795)

12 (NOAC or (anticoagulant\$ adj3 oral adj3 new) or (anticoagulant\$ adj3 oral adj3 novel)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (1435)

- 13 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 (48838)
- 14 deep vein thrombosis.mp. or exp deep vein thrombosis/ (41442)
- 15 (DVT or thromboembolism or venous thromboembolism or VTE).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (89387)

16 exp lung embolism/ (64280)

17 (lung embol\$ or pulmonary embol\$ or PE).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (100305)

- 18 exp heart atrium fibrillation/ (77878)
- 19 exp heart atrium flutter/ (9788)

20 ((atrial or auricular) adj5 (fibrillation\$ or flutter\$)).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (66474)

21 (AF or NVAF).mp. [mp=title, abstract, subject headings, heading word, drug trade name, original title, device manufacturer, drug manufacturer, device trade name, keyword] (51520)

- 22 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 (296005)
- 23 13 and 22 (12898)
- 24 Clinical trial/ (898699)
- 25 randomized controlled trial/ (362954)
- 26 Randomization/ (64197)
- 27 Single blind procedure/ (18566)
- 28 Double blind procedure/ (123454)
- 29 Crossover procedure/ (39339)
- 30 Placebo/ (246077)

- 31 Randomi?ed controlled trial\$.tw. (96717)
- 32 Rct.tw. (13134)
- 33 Random allocation.tw. (1390)
- 34 Randomly allocated.tw. (20328)
- 35 Allocated randomly.tw. (1973)
- 36 (allocated adj2 random).tw. (892)
- 37 Single blind\$.tw. (14467)
- 38 Double blind\$.tw. (151887)
- 39 ((treble or triple) adj blind\$).tw. (383)
- 40 Placebo\$.tw. (207389)
- 41 Prospective study/ (256675)
- 42 or/24-41 (1422876)
- 43 Case study/ (31643)
- 44 Case report.tw. (282476)
- 45 Abstract report/ or letter/ (912074)
- 46 or/43-45 (1220663)
- 47 42 not 46 (1384928)
- 48 23 and 47 (4115)
- 49 limit 48 to last 20 years (4092)
- 50 limit 49 to human (3978)
- 51 limit 50 to english language (3615)

Supplemental Methods 2b. Search Strategy in MEDLINE.

Ovid Technologies, Inc. Search limit to english language

Database: Ovid MEDLINE(R) In-Process & Other Non-Indexed Citations and Ovid MEDLINE(R) <1946 to Present> Search Strategy:

1 dabigatran.mp. (1957)

- 2 rivaroxaban.mp. (1283)
- 3 apixaban.mp. (758)
- 4 edoxaban.mp. (161)

5 (NOAC or (anticoagulant\$ adj3 oral adj3 new) or (anticoagulant\$ adj3 oral adj3 novel)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (999)

6 exp Thrombin/ad, ai, tu, th [Administration & Dosage, Antagonists & Inhibitors, Therapeutic Use, Therapy] (5064)

7 ((direct adj3 thrombin adj3 inhib\$) or DTI).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (7055)

8 xaban\$.mp. (7)

9 exp Factor Xa/ad, ai, tu [Administration & Dosage, Antagonists & Inhibitors, Therapeutic Use] (2291)

10 ((factor Xa or factor 10a or fXa) adj3 inhib\$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (2486)

11 ((factor 2a or factor IIa or f2a) adj3 inhib\$).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (61)

12 (Pra?ax\$ or Xarelto or Eliqu?s or Lixiana).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (150)

13 exp Venous Thrombosis/ (44632)

14 ("deep vein thrombosis" or DVT or thromboembolism or venous thromboembolism or VTE).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (48776)

15 exp Pulmonary Embolism/ (31309)

16 exp Venous Thromboembolism/ (4499)

17 (lung embol\$ or pulmonary embol\$ or PE).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (62301)

18 exp Atrial Fibrillation/ (34118)

19 exp Atrial Flutter/ (4965)

20 ((atrial or auricular) adj5 (fibrillation\$ or flutter\$)).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (50348)

21 (AF or NVAF).mp. [mp=title, abstract, original title, name of substance word, subject heading word, keyword heading word, protocol supplementary concept, rare disease supplementary concept, unique identifier] (35889)

22 1 or 2 or 3 or 4 or 5 or 6 or 7 or 8 or 9 or 10 or 11 or 12 (16237)

23 13 or 14 or 15 or 16 or 17 or 18 or 19 or 20 or 21 (196699)

24 22 and 23 (3363)

- 25 Randomized Controlled Trials as Topic/ (102694)
- 26 randomized controlled trial/ (390641)
- 27 Random Allocation/ (81795)
- 28 Double Blind Method/ (131907)
- 29 Single Blind Method/ (19625)
- 30 clinical trial/ (505248)
- 31 clinical trial, phase i.pt. (16223)
- 32 clinical trial, phase ii.pt. (26928)
- 33 clinical trial, phase iii.pt. (10191)
- 34 clinical trial, phase iv.pt. (998)
- 35 controlled clinical trial.pt. (89952)
- 36 randomized controlled trial.pt. (390641)
- 37 multicenter study.pt. (182921)
- 38 clinical trial.pt. (505248)
- 39 exp Clinical Trials as topic/ (296601)
- 40 or/25-39 (1076886)
- 41 (clinical adj trial\$).tw. (226862)
- 42 ((singl\$ or doubl\$ or treb\$ or tripl\$) adj (blind\$3 or mask\$3)).tw. (134979)
- 43 PLACEBOS/ (33783)
- 44 placebo\$.tw. (169202)
- 45 randomly allocated.tw. (17264)
- 46 (allocated adj2 random\$).tw. (19861)
- 47 or/41-46 (441961)
- 48 40 or 47 (1227780)
- 49 case report.tw. (203598)
- 50 letter/ (832571)
- 51 historical article/ (300469)
- 52 or/49-51 (1325116)
- 53 48 not 52 (1197461)
- 54 24 and 53 (1334)
- 55 limit 54 to humans (1231)
- 56 limit 55 to last 20 years (1211)
- 57 limit 56 to english language (1086)

Supplemental Methods 2c. Search Strategy in CENTRAL.

- ID Search
- #1 dabigatran
- #2 rivaroxaban
- #3 apixaban
- #4 edoxaban
- #5 ((direct adj3 thrombin adj3 inhib\$) or DTI)
- #6 MeSH descriptor: [Antithrombins] explode all trees
- #7 xaban\$
- #8 MeSH descriptor: [Blood Coagulation Factor Inhibitors] explode all trees
- #9 ((factor Xa or factor 10a or fXa or autoprothrombin c or thrombokinase) adj5 inhib\$)
- #10 (factor 2a inhib\$ or factor IIa inhib\$ or f2a inhib\$)
- #11 Pra?ax\$ or Xarelto or Eliqu?s or Lixiana
- #12 #1 or #2 or #3 or #4 or #5 or #6 or #7 or #8 or #9 or #10 or #11
- #13 (NOAC or (anticoagulant\$ adj3 oral adj3 new) or (anticoagulant\$ adj3 oral adj3 novel))
- #14 #12 or #13
- #15 MeSH descriptor: [Embolism and Thrombosis] explode all trees
- #16 MeSH descriptor: [Anticoagulants] explode all trees
- #17 #14 or #16
- #18 ("deep vein thrombosis OR DVT" or thromboembolism or venous thromboembolism or VTE)
- #19 (lung embol\$ or pulmonary embol\$ or PE)
- #20 MeSH descriptor: [Atrial Fibrillation] explode all trees
- #21 MeSH descriptor: [Atrial Flutter] explode all trees
- #22 ((atrial or auricular) adj5 (fibrillation\$ or flutter\$))
- #23 (AF or NVAF)
- #24 #15 or #18 or #19 or #20 or #21 or #22 or #23
- #25 #17 and #24

Studies excluded	DOAC	Rationale for exclusion
Re-lyable ¹	Dabigatran	Extension of completed phase III Re-ly study for additional follow up only. Observational study.
Re-medy ²	Dabigatran	Extension study of completed phase III Recover I and Recover II studies in patients who had already received 3 months treatment for acute VTE.
Re-sonate ²	Dabigatran	Extension study as per Re-medy. VKA was not the comparator.
Einstein-Ext ³	Rivaroxaban	Extension study for phase III Einstein DVT and PE studies in patients who had already received 6 months of treatment for acute VTE. VKA was not the comparator.
Odixa DVT ⁴	Rivaroxaban	Phase II study with no arm that used a dose of rivaroxaban that was subsequently used in phase III studies.
NCT00973245 ⁵	Rivaroxaban	Study was less than 3 months in duration.
NCT00973323 ⁶	Rivaroxaban	Study was less than 3 months in duration.
Averroes ⁷	Apixaban	VKA was not the comparator.
Amplify-Ext ⁸	Apixaban	Extension study of previously completed phase III Amplify study. VKA was not used as comparator.

Table S1 Rationale for exclusion of studies following review of full publications.

Study	Mean TTR on VKA (%)	Concomitant aspirin use during study %						
		DOAC	VKA					
DABIGATRAN								
Bibr 1048, 2005	NA	NA	NA					
Petro, 2007	57.2	40.8	0					
Re-ly, 2009	64	20.3	20.8					
Recover I, 2010	60	NA	NA					
Recover II, 2013	56.9	10.2	8.7					
APIXABAN								
Aristotle, 2011	62.2	NA	NA					
Aristotle-J, 2011	NA	28.2	25.3					
Botticelli-DVT,2008	57	NA	NA					
Amplify, 2013	61	NA	NA					
RIVAROXABAN								
Rocket-AF, 2011	55	NA	NA					
J-Rocket AF, 2011	65	NA	NA					
Einstein-DVT Dose	50.3	NA	NA					
Study, 2008	F7 7	NIA						
Einstein-DVT, 2010	57.7	NA	NA					
Einstein-PE, 2012	62.7	NA	NA					
EDOXABAN								
Edox-P2, 2010	49.7	NA	NA					
Edox-P2A, 2010	45.1	41.9	34.7					
Edox-J, 2012	73 IF <70 years 83 IF ≥70 years	27	23					
Engage-AF-Timi 48, 2013	64.9	NA	NA					
Hokusai-VTE, 2013	63.5	NA	NA					
NA=Not available TTR=Time in therapeutic	range							

Table S2 Mean time in therapeutic range (TTR) on vitamin k antagonist and concomitant aspirin usage for included studies.

Table S3 Role of Funder in individual studies.
--

Study	Funded by Manufacturer	Role in Design	Role in Analysis	Control over Publication		
DABIGATRAN						
Bibr 1048, 2005	Y	NR	NR	NR		
Petro, 2007	Y	Υ	Y	NR		
Re-ly, 2009	Y	Υ	Y	Υ		
Recover I, 2010	Υ	Υ	Y	NR		
Recover II, 2013	Υ	Y	Y	NR		
APIXABAN						
Aristotle, 2011	Υ	Y	Y	NR		
Aristotle-J, 2011	Υ	NR	NR	NR		
Botticelli- DVT,2008	Y	NR	NR	NR		
Amplify, 2013	Υ	Y	Υ	Υ		
RIVAROXABAN						
Rocket-AF, 2011	Y	NR	Ν	Ν		
J-Rocket AF, 2011	Y	Ν	Y	NR		
Einstein-DVT Dose Study, 2008	Y	Y	Y	Y		
Einstein-DVT, 2010	Y	NR	NR	Y		
Einstein-PE, 2012	Y	NR	NR	Υ		
EDOXABAN						
Edox-P2, 2010	Y	Y	Y	NR		
Edox-P2A, 2010	Y	NR	NR	NR		
Edox-J, 2012	Y	Y	Y	Y		
Engage-AF-Timi 48, 2013	Y	Y	Y	Ν		
Hokusai-VTE, 2013	Y	Y	NR	NR		
Y=Yes N=No						

N=No

NR=Not Reported

Study	Standard Dose	Phase	Inclusion Criteria	Target INR range	Duration/Median Follow up* (months)	Heparin ≥5 days permitted prior to DOAC/VKA
DABIGATRAN						
Bibr 1048, 2005	110mg BD or 150mg BD	II	Aged≥20, NVAF and CHADS₂ of ≥1 or CAD	2-3	3	N
Petro, 2007	150mg BD extracted	II	Aged≥18, NVAF and CHADS₂ of ≥1 or CAD	2-3	3	N
Re-ly, 2009	110mg or 150mg BD	111	Aged≥18, NVAF and CHADS₂ of ≥1 or CAD	2-3	24*	N
Recover I, 2010	150mg BD	III	Aged≥18 and confirmed VTE	2-3	6	Y
Recover II, 2013	150mg BD	III	Aged≥18 and confirmed VTE	2-3	6	Y
APIXABAN						
Aristotle, 2011	5mg BD	Ш	Aged≥18, NVAF and CHADS₂ of ≥1	2-3	21.6*	Ν
Aristotle-J, 2011	5mg BD extracted	II	Aged \geq 20, NVAF and CHADS ₂ of \geq 1	2-3 and 1.6–2.6 if aged≥70	3	N
Botticelli-DVT, 2008	5mg BD	II	Aged≥18 and confirmed DVT without PE	2-3	3	N
Amplify, 2013	10mg BD for 7 days then 5mg BD	111	Aged≥18 and confirmed VTE	2-3	6	N
RIVAROXABAN						
Rocket-AF, 2011	20mg OD	III	Aged≥18, NVAF and CHADS ₂ of ≥2	2-3	23.2*	Ν
J-Rocket AF, 2011	15mg OD	III	Japanese, Aged≥20, NVAF and CHADS₂ of ≥2	2-3 and 1.6–2.6 if aged≥70	30	Ν
Einstein-DVT Dose Study, 2008	20mg OD extracted	II	Aged≥18 and confirmed DVT	2-3	3	Ν
Einstein-DVT, 2010	15mg BD for 21 days then 20mg OD	111	Aged≥18 and confirmed DVT without PE	2-3	3,6 or 12	N
Einstein-PE, 2012	15mg BD for 21 days then 20mg OD	111	Aged≥18 and confirmed PE with/without DVT	2-3	3,6 or 12	N
EDOXABAN						
Edox-P2, 2010	30mg and 60mg OD extracted	II	Aged≥18, NVAF and CHADS₂ of ≥2	2-3	3	Ν
Edox-P2A, 2010	30mg OD and 60mg OD	II	Aged≥20, NVAF and CHADS₂ of ≥1	2-3	3	Ν

Table S4 Characteristics of included studies for DOACs in AF and VTE (expanded table).

Study	Standard Dose	Phase	Inclusion Criteria	Target INR range	Duration/Median Follow up* (months)	Heparin ≥5 days permitted prior to DOAC/VKA
Edox-J, 2012	30mg and 60mg OD extracted	II	Aged≥20, NVAF and CHADS ₂ of ≥1	2-3 and 1.6–2.6 if aged≥70	3	N
Engage-AF- Timi 48, 2013	30mg OD or 60mg OD	111	Aged \geq 21, NVAF and CHADS ₂ of \geq 2	2-3	33.6*	Ν
Hokusai-VTE, 2013	60mg OD	III	Aged≥18 and confirmed VTE	2-3	3 to 12	Y
OD= Once daily BD=Twice daily NVAF=Non-valvula VTE=Venous Thron DVT=Deep-vein thr PE= Pulmonary Em CAD= Coronary Art	nboembolism ombosis bolism					

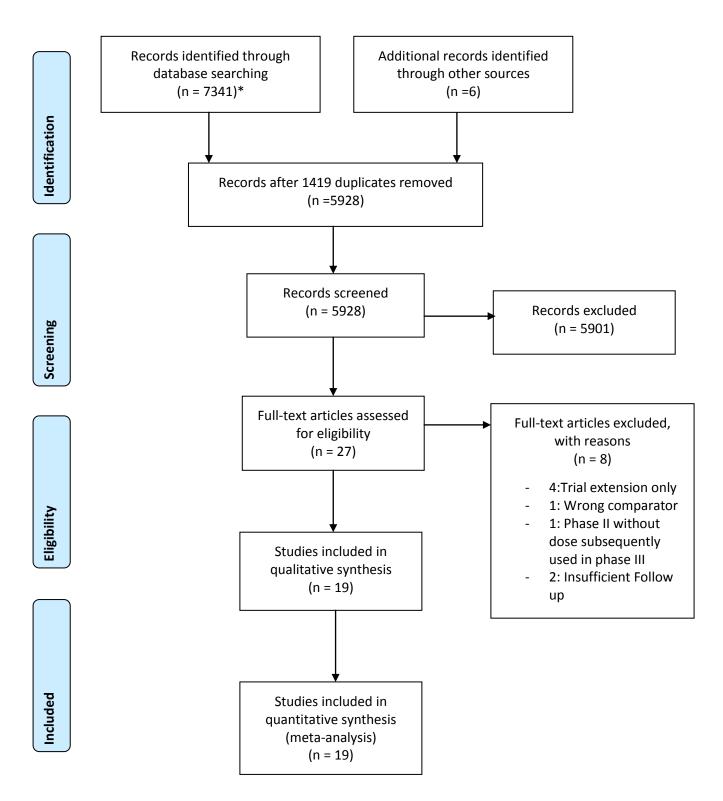


Figure S1. PRISMA Flow Diagram – Study Identification, Selection and Exclusions.

*Monthly automated alerts from 01/12/13 to 01/06/14 consisting of updates to the search strategy identified an additional 429 articles in Embase, Medline and CENTRAL that have been included in flow diagram above. Two eligible studies for inclusion of the total 19 identified were obtained through these updates.

	DOAC	VK			Peto Odds Ratio	Peto Odds Ratio		DOA	-	VKA	-		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup		Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% Cl	Study or Subgroup			Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI
1.1.1 Dabigatran 150r							2.1.1 Dabigatran 150r	mg vs VK						
Re-ly	69 2466			100.0%	0.66 [0.49, 0.90]		Bibr 1048	0		1	62	0.3%		•
Subtotal (95% CI)	2466		2423	100.0%	0.66 [0.49, 0.90]	•	Petro	0		0	2		Not estimable	
otal events	69	101					Re-ly	134	6076	202	6022		0.65 [0.53, 0.81]	
leterogeneity: Not app							Subtotal (95% CI)		6303		6154	100.0%	0.65 [0.52, 0.81]	•
est for overall effect: 2	Z = 2.61 (P = 0.)	009)					Total events	134		203				
							Heterogeneity: Chi ² =				= 0%			
1.2 Dabigatran 110r							Test for overall effect: .	Z = 3.89 ((P < 0.0)	001)				
te-ly	87 2349			100.0%					21					
ubtotal (95% CI)	2349		2423	100.0%	0.88 [0.66, 1.18]	•	2.1.2 Dabigatran 110	-						·····
otal events	87	101					Bibr 1048	0		1	62			•
eterogeneity: Not app	plicable						Re-ly	183	6015	202	6022			
est for overall effect: 2	Z = 0.82 (P = 0.	41)					Subtotal (95% CI)		6061		6084	100.0%	0.90 [0.74, 1.10]	•
							Total events	183		203				
1.3 Rivaroxaban vs	VKA						Heterogeneity: Chi ² =				= 0%			
ocket-AF	125 3082			100.0%			Test for overall effect: .	Z = 1.02 ((P = 0.3)	1)				
ubtotal (95% CI)	3082	2	3082	100.0%	0.80 [0.63, 1.02]	•	69715323 00	1000						
otal events	125	154					2.1.3 Rivaroxaban vs							
eterogeneity: Not app	plicable						J-Rocket AF		637		637	5.5%		
est for overall effect: 2	Z = 1.78 (P = 0.	08)					Rocket-AF	269	7081	306	7090			
							Subtotal (95% CI)		7718		7727	100.0%	0.85 [0.72, 1.00]	•
1.4 Apixaban vs VK	A						Total events	280		328				
istotle	79 2850	109	2828	99.0%	0.71 [0.53, 0.95]		Heterogeneity: Chi ² =	2.31, df =	1 (P=	0.13); F=	= 57%			
ristotle-J	0 45	5 2	23	1.0%	0.05 [0.00, 0.95]	·	Test for overall effect:	Z = 1.97 ((P = 0.0)	5)				
ubtotal (95% CI)	2895	5	2851	100.0%	0.70 [0.52, 0.93]	•	2010/01/02 13							
otal events	79	111					2.1.4 Apixaban vs VK							-
eterogeneity: Chi ² = 3	3.10, df = 1 (P =	= 0.08); F	= 68%				Aristotle	212	9120	265	9081		0.79 [0.66, 0.95]	
est for overall effect: 2	Z = 2.46 (P = 0.	01)					Aristotle-J	0		3		0.6%		•
	S STRUCTURE STO	51.532					Subtotal (95% CI)		9194		9155	100.0%	0.78 [0.65, 0.94]	•
						0.1 0.2 0.5 1 2 5 10	Total events	212		268				
						Favours DOAC Favours VKA	Heterogeneity: Chi ² = Test for overall effect: .		10.07.000		= 58%			
														0.1 0.2 0.5 1 2
														Favours DOAC Favours VK

Favours DOAC Favours VKA

Figure S2. Forest Plots for risk of Stroke or Systemic Embolism in AF in Elderly (left) and Total Population (right).

*Event numbers for Engage-AF-Timi 48 in elderly have been estimated from published confidence intervals.

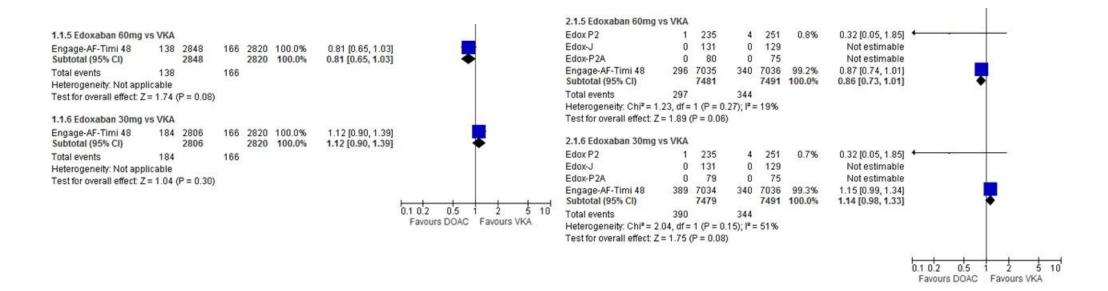


Figure S2. (contd) Forest Plots for risk of Stroke or Systemic Embolism in AF in Elderly (left) and Total Population (right).

*Event numbers for Engage-AF-Timi 48 in elderly have been estimated from published confidence intervals.

Study or Subgroup	DO/		VKA		Weight	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% CI	Study or Subgroup	DOA	-	VKA		Moight	Peto Odds Ratio Peto, Fixed, 95% CI	Peto Odds Ratio Peto, Fixed, 95% Cl
1.2.1 Dabigatran 150mg v	the second division of	Total	Evento	Total	reight	reto, rixed, solver	reto, nace, oon of	2.2.1 Dabigatran 150mg v	and the second se	TUtar	Events	Total	weight	Felo, Fixed, 55% CI	Peto, Fixed, 35% CI
Pooled Recover Studies Subtotal (95% CI)	3	253 253	5		100.0% 100.0%	0.66 [0.16, 2.66]		Recover I Recover II	30	1274 1279		1265 1289	49.6% 50.4%	1.11 [0.65, 1.87] 1.08 [0.64, 1.82]	
Total events	3		5					Subtotal (95% CI)	100	2553				1.09 [0.76, 1.58]	+
Heterogeneity: Not applica Test for overall effect: Z = 0		0.56)						Total events Heterogeneity: Chi² = 0.00, Test for overall effect: Z = 0			55 ² = 0%				
1.2.2 Apixaban vs VKA															
Amplify	7	389	13		100.0%	0.50 [0.21, 1.21]		2.2.2 Apixaban vs VKA							_
Subtotal (95% CI)	<u></u>	389		360	100.0%	0.50 [0.21, 1.21]		Amplify Botticelli-DVT		2609 117		2635 118	95.6% 4.4%	0.84 [0.59, 1.18]	
Total events Heterogeneity: Not applica	/ ble		13					Subtotal (95% CI)	3	2726	3		4.4 %	1.01 [0.20, 5.09] 0.84 [0.60, 1.18]	+
Test for overall effect: Z = 1		112)						Total events	62		74				
1.2.3 Rivaroxaban vs VKA								Heterogeneity: Chi² = 0.05, Test for overall effect: Z = 0			I ² = 0%				
Einstein-DVT	4	215	10		36.8%	0.43 [0.15, 1.25]		2.2.3 Rivaroxaban vs VKA							
Einstein-PE	11	441	13		63.2%	0.77 [0.34, 1.72]		Einstein-DVT		1731	51	1718	45.5%	0.70 (0.46, 1.07)	
Subtotal (95% CI)		656		627	100.0%	0.62 [0.33, 1.18]		Einstein-DVT dose study		115		101	45.5%	0.38 [0.11, 1.34]	
Total events Heterogeneity: Chi ² = 0.70.	15	- 0.40	23					Einstein-PE		2419		2413		1.14 [0.76, 1.71]	
Test for overall effect: Z = 1); 1~= 0%					Subtotal (95% CI)		4265			100.0%	0.86 [0.65, 1.15]	•
restion overall ellect. 2 = 1	.45 (F = 0	5.13)						Total events	89		102				
1.2.4 Edoxaban 60mg vs \	VKA							Heterogeneity: Chi ² = 4.34,			I ² = 54%	•			
Hokusai-VTE	14	560	27		100.0%	0.50 [0.27, 0.94]		Test for overall effect: Z = 1	.03 (P = 0	.30)					
Subtotal (95% CI)		560	1000	544	100.0%	0.50 [0.27, 0.94]	-	2.2.4 Edoxaban 60mg vs V	'KA						
Total events Heterogeneity: Not applica			27					Hokusai-VTE Subtotal (95% CI)	130	4118 4118	146		100.0% 100.0%	0.89 [0.70, 1.13] 0.89 [0.70, 1.13]	-
Test for overall effect: Z = 2	2.16 (P = 0	0.03)						Total events	130		146				
							0.1 0.2 0.5 1 2 5 10	Heterogeneity: Not applicat Test for overall effect: Z = 0		.33)					
							Favours DOAC Favours VKA								
															0.1 0.2 0.5 1 2 5 10 Favours DOAC Favours VKA

Figure S3. Forest Plots for risk of Recurrent Venous Thromboembolism in VTE in Elderly (left) and Total Population (right).

Study or Subgroup	DOAC Events Total	VKA Events Total V	Peto Odd Veight Peto, Fixe		Peto Odo Peto, Fixe		Study or Subgroup	DOAC Events Tot	VK al Events			Peto Odds Ratio Peto, Fixed, 95% Cl		ds Ratio ed, 95% Cl	
1.3.1 Dabigatran 150mg vs			···;···	-,		.,	2.3.1 Dabigatran 150mg vs					,			
Pooled Recover Studies	8 231	10 262	4.4% 0.90 [0	.35, 2.32]			Bibr 1048	1 5	8 2	62	0.3%	0.54 [0.06, 5.33]	• • • • •		_
Re-ly	227 2145			.98, 1.46]		-	Petro	0 16				Not estimable			
Subtotal (95% CI)	2376	2350 1		.97, 1.44]	-	•	Re-lv	399 607	6 421		90.2%	0.94 [0.81, 1.08]	-		
Total events	235	198	-				Recover I	20 127			5.1%	0.83 [0.46, 1.50]		—	
Heterogeneity: Chi ² = 0.32, d	df = 1 (P = 0.57);	I² = 0%					Recover II	15 128			4.3%	0.69 [0.36, 1.31]		<u> </u>	
Test for overall effect: Z = 1.6							Subtotal (95% CI)	885	6	8708 1	00.0%	0.92 [0.80, 1.05]	•		
							Total events	435	469						
1.3.2 Dabigatran 110mg vs	VKA					_	Heterogeneity: Chi ² = 1.16, c	f = 3 (P = 0.76); I² = 0%						
Re-ly	187 2026	188 2088 10		.83, 1.27]	-	-	Test for overall effect: Z = 1.2	29 (P = 0.20)							
Subtotal (95% CI)	2026	2088 1	00.0% 1.03 [0	.83, 1.27]											
Total events	187	188					2.3.2 Dabigatran 110mg vs	VKA							
Heterogeneity: Not applicabl	le						Bibr 1048	0 4	6 2	62	0.3%	0.17 [0.01, 2.88]	·		
Test for overall effect: Z = 0.2	25 (P = 0.80)						Re-ly	342 601			99.7%	0.80 [0.69, 0.93]			
							Subtotal (95% CI)	606		6084 1	00.0%	0.80 [0.69, 0.93]	•		
1.3.3 Rivaroxaban vs VKA							Total events	342	423						
Einstein-DVT	3 215			.15, 2.52]			Heterogeneity: Chi ² = 1.14, c); I z = 13%						
Einstein-PE	5 440			.11,0.51] =			Test for overall effect: Z = 3.0	00 (P = 0.003)							
J-Rocket AF	14 206	10 207	5.5% 1.43 [0	.63, 3.26]											
Rocket-AF	203 2688			.93, 1.42]	-	-	2.3.3 Rivaroxaban vs VKA								
Subtotal (95% CI)	3549		00.0% 1.04 [0	.86, 1.26]	•		Einstein-DVT	14 171			3.7%	0.70 [0.35, 1.37]		<u> </u>	
Total events	225	217					Einstein-DVT dose study	1 13			0.3%	0.52 [0.05, 5.03]	• • • • •		-
Heterogeneity: Chi ² = 16.54,	• •	09); I ² = 82%					Einstein-PE	26 241			8.5%	0.51 [0.32, 0.79]			
Test for overall effect: Z = 0.3	39 (P = 0.70)						J-Rocket AF	25 63			5.8%	0.83 [0.48, 1.42]			
							Rocket-AF	395 711			81.6%	1.03 [0.89, 1.19]			
1.3.4 Apixaban vs VKA							Subtotal (95% CI)	1201		12017 1	00.0%	0.94 [0.82, 1.07]		ſ	
Amplify	4 398			.11, 0.66] =			Total events	461	490						
Aristotle Subtotal (95% CI)	151 2836 3234	224 2819 9 3189 1		.53, 0.81] . 51, 0.77]			Heterogeneity: Chi ² = 10.01, Test for overall effect: Z = 0.9		4), 17 = 60%	0					
			00.0% 0.03 [0	.51, 0.77]	•		Test for overall effect. $Z = 0.5$	94 (F = 0.30)							
Total events Heterogeneity: Chi² = 3.60, c	155 4f = 1 /D = 0.06\;	240 IZ - 700					2.3.4 Apixaban vs VKA								
Test for overall effect: Z = 4.5							Amplify	15 267	6 49	2689	7.7%	0.34 [0.21, 0.56]			
Testilor overall effect. $Z = 4.5$	52 (F < 0.00001)						Aristotle	327 908			92.0%	0.70 [0.60, 0.80]			
1.3.5 Edoxaban 60mg vs Vk	KΔ						Aristotle-J	0 7			0.1%	0.14 [0.00, 7.20]	<		
Engage-AF-Timi 48	214 2848	257 2820 11	0.00% 0.0110	.67, 0.98]			Botticelli-DVT	1 12				7.27 [0.14, 366.66]			→
Subtotal (95% CI)	2848	2820 1		.67, 0.98]			Subtotal (95% CI)	1196		11942 1		0.66 [0.58, 0.76]	•		
Total events	214	257			•		Total events	343	512						
Heterogeneity: Not applicabl		201					Heterogeneity: Chi ² = 9.35, c								
Test for overall effect: Z = 2.1							Test for overall effect: Z = 5.9		~ ~						
1001101 010101 01000.2								•						1	
1.3.6 Edoxaban 30mg vs Vk	KA												0.1 0.2 0.5 Favours DOAC	Eavoure VKA	5 10
Engage-AF-Timi 48	121 2806	257 2820 10	00.0% 0.4610	.38, 0.57]									Favours DUAC	Favours vrvA	
Subtotal (95% CI)	2806	2820 1		.38, 0.57]											
Total events	121	257	-	_	-										
Heterogeneity: Not applicabl	le														
Test for overall effect: Z = 7.1	19 (P < 0.00001)														
				0.1	0.2 0.5 1	2 5 10									
				0.1	Favours DOAC										

Figure S4. Forest Plots for risk of Major Bleeding in Elderly (left) and Total Population (right). *Event numbers for Engage-AF-Timi-48 and J-Rocket AF in the elderly have been estimated from published confidence intervals.

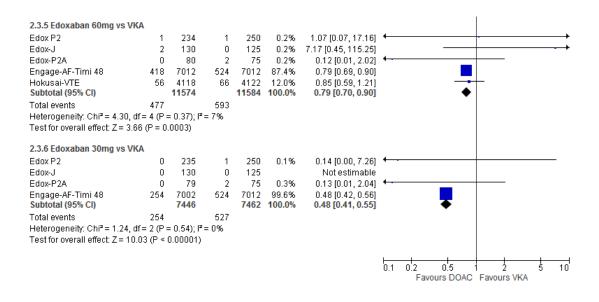


Figure S4. (contd) Forest Plots for risk of Major Bleeding in Total Population (right).

*Event numbers for Engage-AF-Timi-48 and J-Rocket AF in the elderly have been estimated from published confidence intervals.

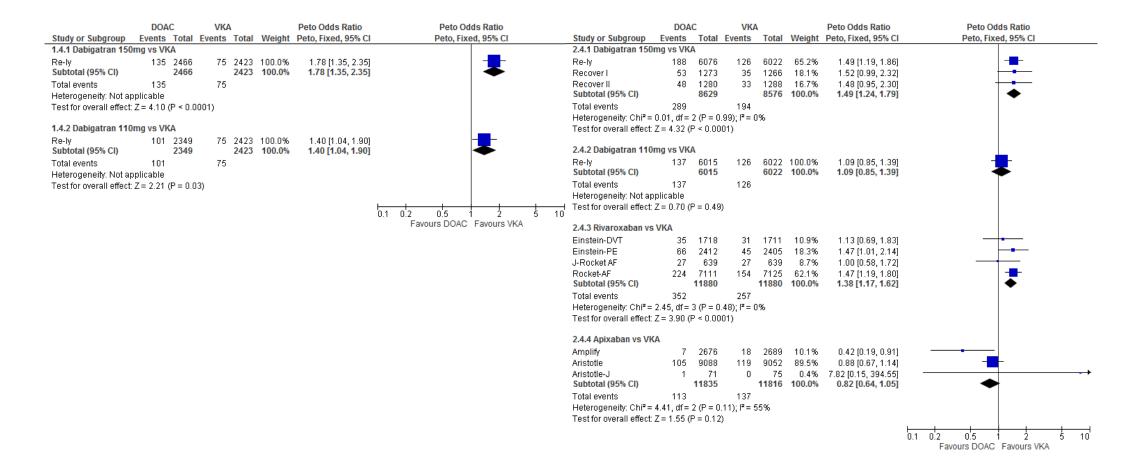


Figure S5. Forest Plots for risk of Gastrointestinal Bleeding in Elderly (left) and Total Population (right).

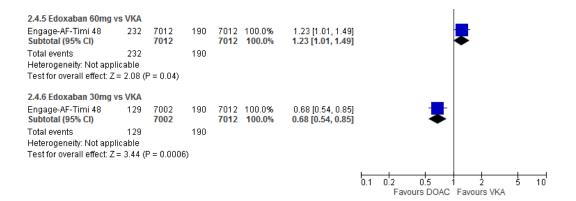


Figure S5. (contd) Forest Plots for risk of Gastrointestinal Bleeding in Total Population (right).

Study or Subgroup	DOAC	VKA	Weight	Peto Odds Ratio	Peto Odds Ratio Peto, Fixed, 95% Cl	Study of Subgroup	DOA		VKA		Weight	Peto Odds Ratio Peto, Fixed, 95% Cl	Peto Odds Ra Peto, Fixed, 95	
Study or Subgroup 1.5.1 Dabigatran 150m		Events Total	weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI	Study or Subgroup 2.5.1 Dabigatran 150mg vs		Total	Events	Total	weight	Peto, Fixed, 95% CI	Peto, Fixed, 955	0 CI
Re-ly	19 2145	44 2088	100.0%	0.43 [0.26, 0.72]		Re-ly		6076	90	6022	92.0%	0.44 [0.31, 0.62]		
Subtotal (95% CI)	2145		100.0%	0.43 [0.26, 0.72]	➡	Recover I	0	1273		1266	2.2%	0.13 [0.01, 1.29]		
Total events	19	44			-	Recover II	2	1280		1288	5.8%	0.37 [0.09, 1.48]	•	
Heterogeneity: Not app	licable					Subtotal (95% CI)		8629		8576	100.0%	0.42 [0.30, 0.59]	•	
Test for overall effect: Z	= 3.28 (P = 0.00	1)				Total events	40		99					
						Heterogeneity: Chi ² = 1.05, d	lf = 2 (P =	0.59); l²	= 0%					
1.5.2 Dabigatran 110m	-				_	Test for overall effect: Z = 5.0	I8 (P ≤ 0.0	00001)						
Re-ly	14 2026		100.0%	0.36 [0.22, 0.61]		2 5 2 D-bi-stere 440								
Subtotal (95% CI)	2026		100.0%	0.36 [0.22, 0.61]	-	2.5.2 Dabigatran 110mg vs		0045			400.000			
Total events	14	44				Re-ly Subtotal (95% CI)	27	6015 6015	90		100.0%	0.34 [0.23, 0.49] 0.34 [0.23, 0.49]		
Heterogeneity: Not app Test for overall effect: Z		043				Total events	27	0015	90	0022	100.070	0.54 [0.25, 0.45]		
restior overall ellect. Z	.= 3.85 (F = 0.00	01)				Heterogeneity: Not applicable			30					
1.5.3 Rivaroxaban vs V	/KA					Test for overall effect: Z = 5.8		10001)						
Einstein-DVT	0 215	1 223	1.4%	0.14 [0.00, 7.07]	←			,						
Einstein-PE	2 475	6 448	11.3%	0.34 [0.09, 1.38]	←	2.5.3 Rivaroxaban vs VKA								
Rocket-AF	29 2688	33 2702	87.3%	0.88 [0.53, 1.46]		Einstein-DVT	2	1718	2	1711	2.3%	1.00 [0.14, 7.08]		
Subtotal (95% CI)	3378	3373	100.0%	0.77 [0.48, 1.23]	-	Einstein-DVT dose study	0	135	1	137	0.6%	0.14 [0.00, 6.92]	•	
Total events	31	40				Einstein-PE	3	2412		2405	8.7%	0.30 [0.11, 0.82]		
Heterogeneity: Chi ² = 2						J-Rocket AF	5	639	10	639	8.6%	0.51 [0.18, 1.41]		
Test for overall effect: Z	= 1.08 (P = 0.28)				Rocket-AF	55	7111		7125	79.8%	0.66 [0.47, 0.92]		
						Subtotal (95% CI)		12015		12017	100.0%	0.60 [0.45, 0.81]	-	
1.5.4 Apixaban vs VKA					_	Total events	65		109					
Aristotle	20 2836	57 2819		0.38 [0.24, 0.59]		Heterogeneity: Chi ² = 3.00, d			= 0%					
Subtotal (95% CI)	2836		100.0%	0.38 [0.24, 0.59]		Test for overall effect: Z = 3.3	14 (P = 0.0	1008)						
Total events	20 Variation	57				2.5.4 Apixaban vs VKA								
Heterogeneity: Not app Test for overall effect: Z		043				Amplify	3	2676	Б	2689	4.9%	0.52 [0.14, 1.91]	•	-
Testior overall ellect. Z	- 4.27 (F < 0.00	01)				Aristotle	52	9088		9052	94.5%	0.44 [0.33, 0.60]		
						Aristotle-J	0	71	1	75	0.5%	0.14 [0.00, 7.20]	· · · · · · · · · · · · · · · · · · ·	
					0.1 0.2 0.5 1 2 5 10	Subtotal (95% CI)	-	11835			100.0%	0.44 [0.33, 0.59]	•	
					Favours DOAC Favours VKA	Total events	55		129					
						Heterogeneity: Chi ² = 0.37, d	lf = 2 (P =	0.83); l ²	= 0%					
						Test for overall effect: Z = 5.5	i0 (P ≤ 0.0	00001)						
												ł	0.1 0.2 0.5 1	$\frac{1}{2}$ $\frac{1}{5}$ $\frac{1}{10}$
													Favours DOAC Favo	2 0 10

Favours DOAC Favours VKA

Figure S6. Forest Plots for risk of Intracranial Bleeding in in Elderly (left) and Total Population (right).

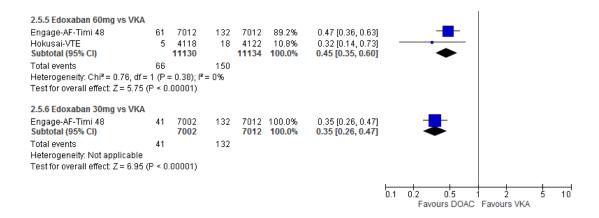


Figure S6. (contd) Forest Plots for risk of Intracranial Bleeding in Total Population (right).

	DOAC	VKA			Odds Ratio	Odds Ratio		DOAC	VK/		Odds Ratio	Odds Ratio
Study or Subgroup		Events	Total	Weight	IV, Random, 95% CI	IV, Random, 95% Cl	Study or Subgroup		Events	Total We	eight IV, Random, 95%	CI IV, Random, 95% CI
1.6.1 Dabigatran 150mg						_	2.6.1 Dabigatran 150mg v					
Pooled Recover Studies	22 231 231	33		100.0%	0.73 [0.41, 1.29]		Bibr 1048	5 58	5		2.8% 1.08 [0.29, 3.9	
Subtotal (95% CI)			202	100.0%	0.73 [0.41, 1.29]		Petro	13 169	4		3.5% 1.38 [0.43, 4.3	
Total events	22	33					Recover I	71 1273	111		3.9% 0.61 [0.45, 0.8	
Heterogeneity: Not applica Test for overall effect: Z = 1							Recover II Subtotal (95% CI)	64 1280 2780	102	1288 44 2686 10	1.8% 0.61 [0.44, 0.8 0.0% 0.64 [0.52, 0.8	-
Testilor overall ellect. Z =	1.00 (F = 0.20)						Total events	153	222	2000 10	0.0% 0.04 [0.52, 0.6	oj 🔶
1.6.3 Rivaroxaban vs VK	4						Heterogeneity: Tau ² = 0.00;			0\·IZ = 000		
Einstein-DVT	19 215	20	223	13.7%	0.98 [0.51, 1.90]		Test for overall effect: Z = 4) (F - 0.4	3),1 - 0 %		
Einstein-PE	58 440		401		0.76 [0.52, 1.11]	_ _	restion overall ellect. Z = 4	.04 (1 < 0.0001)				
J-Rocket AF	58 205		207		1.75 [1.10, 2.79]	_	2.6.2 Dabigatran 110mg vs	s VKA				
Rocket-AF	693 2688	633	2702	40.3%	1.14 [1.00, 1.29]	-	Bibr 1048	2 46	5	62 100	0.0% 0.52 [0.10, 2.8	on +
Subtotal (95% CI)	3548		3533	100.0%	1.10 [0.82, 1.48]	+	Subtotal (95% CI)	46		62 10		
Total events	828	758					Total events	2	5			
Heterogeneity: Tau ² = 0.05		3 (P = 0	.05); I²	= 62%			Heterogeneity: Not applical	ble				
Test for overall effect: Z = I	0.64 (P = 0.52)						Test for overall effect: Z = 0	.76 (P = 0.44)				
1.6.4 Apixaban vs VKA						_	2.6.3 Rivaroxaban vs VKA					
Aristotle Subtotal (95% CI)	257 2836 2836			100.0% 100.0%	0.64 [0.54, 0.76] 0.64 [0.54, 0.76]		Einstein-DVT	139 1718	138		7.8% 1.00 [0.78, 1.2	
			2819	100.0%	0.04 [0.34, 0.70]	•	Einstein-DVT dose study	8 135	12).5% 0.66 [0.26, 1.6	
Total events	257	379					Einstein-PE	249 2412	274		l.2% 0.90 (0.75, 1.0	
Heterogeneity: Not applica Test for overall effect: Z = :							J-Rocket AF	138 639	124		6.4% 1.14 [0.87, 1.5	
Test for overall effect. $Z = $	5.19 (P < 0.00001)						Rocket-AF	1475 7111	1449		.1% 1.03 [0.95, 1.1	
1.6.5 Edoxaban 60mg vs	VKA						Subtotal (95% CI)	12015		12017 10	0.0% 1.01 [0.94, 1.0	8]
Hokusai-VTE	70 560	82	544	100.0%	0.80 [0.57, 1.13]		Total events	2009	1997	0.17 000		
Subtotal (95% CI)	560	02		100.0%	0.80 [0.57, 1.13]		Heterogeneity: Tau ² = 0.00;		F(P = 0.4)	8);1*=0%		
Total events	70	82				-	Test for overall effect: Z = 0	.24 (P = 0.81)				
Heterogeneity: Not applica	able						2.6.4 Apixaban vs VKA					
Test for overall effect: Z =	1.24 (P = 0.22)						Amplify	115 2676	261	2689 39	9.2% 0.42 [0.33, 0.5	21
							Aristotle	613 9088	877		3.1% 0.67 [0.61, 0.7	
								1 71	4		3.2% 0.25 [0.03, 2.3	
						Favours DOAC Favours VKA	Botticelli-DVT	11 128	10		1.09 [0.45, 2.6	
							Subtotal (95% CI)	11963		11942 10		
							Total events	740	1152		- '	-
							Heterogeneity: Tau ² = 0.10;	; Chi ² = 16.19, df =	3 (P = 0.	001); I ² = 819	%	
							Test for overall effect: Z = 2					
												0.1 0.2 0.5 1 2 5 10
1												Favours DOAC Favours VKA

Figure S7. Forest Plots for risk of Clinically Relevant Bleeding in Elderly (left) and Total Population (right) - Random Effects Model

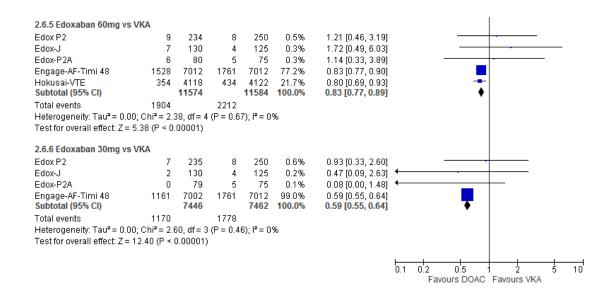


Figure S7. (contd) Forest Plots for risk of Clinically Relevant Bleeding in Total Population (right)- Random Effects Model

DOAC VKA Study or Subgroup Events Total Events Tot	al Moight	Peto Odds Ratio	Peto Odds Ratio Peto, Fixed, 95% Cl	Study of Subgroup	DOAC		VKA	Total	Weight	Peto Odds Ratio Peto, Fixed, 95% Cl	Peto Odds Ratio Peto, Fixed, 95% Cl
1.7.1 Dabigatran 150mg vs VKA	ai weiyin	Peto, Fixed, 95% CI	Peto, Fixed, 95% Ci	Study or Subgroup E 2.7.1 Dabigatran 150mg vs V		TOTAL	vents	Total	weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% CI
Re-ly 16 2145 17 208	8 100.0%	0.92 [0.46, 1.82]		Re-ly		6076	39	6022	95.7%	0.71 [0.44, 1.15]	
Subtotal (95% CI) 2145 208		0.92 [0.46, 1.82]		Recover I		1273		1266	2.9%	0.99 [0.06, 15.91]	←
Total events 16 17				Recover II		1280		1288	1.4%	0.14 [0.00, 6.86]	←
Heterogeneity: Not applicable				Subtotal (95% CI)		8629			100.0%	0.70 [0.44, 1.12]	
Test for overall effect: Z = 0.25 (P = 0.80)				Total events	29		41				
				Heterogeneity: Chi ² = 0.74, df	= 2 (P = 0).69); I ² =	:0%				
1.7.2 Dabigatran 110mg vs VKA				Test for overall effect: Z = 1.47	7 (P = 0.14	4)					
	8 100.0%	0.73 [0.35, 1.51]									
	8 100.0%	0.73 [0.35, 1.51]		2.7.2 Dabigatran 110mg vs V	/KA						_
Total events 12 17				Re-ly		6015			100.0%	0.60 [0.36, 0.98]	
Heterogeneity: Not applicable				Subtotal (95% CI)		6015		6022	100.0%	0.60 [0.36, 0.98]	
Test for overall effect: Z = 0.85 (P = 0.40)				Total events	23		39				
1.7.3 Rivaroxaban vs VKA				Heterogeneity: Not applicable							
		0447004.000		Test for overall effect: Z = 2.03	3 (P = 0.04	4)					
Einstein-DVT 0 215 2 22 Einstein-PE 2 475 2 44		0.14 [0.01, 2.24]		2.7.3 Rivaroxaban vs VKA							
J-Rocket AF 1 206 2 20		0.51 [0.05, 4.97]		Einstein-DVT	4	1718	E	1711	6.1%	0.26 [0.05, 1.30]	•
Rocket-AF 13 2688 25 270		0.53 [0.28, 1.01]		Einstein-DVT dose study		135	2	137	1.0%	0.28 [0.05, 1.30]	
Subtotal (95% CI) 3584 358		0.53 [0.30, 0.93]		Einstein-PE		2412	3	2405	5.1%	0.67 [0.12, 3.86]	·
Total events 16 31				J-Rocket AF	1	639	3	639	4.1%	0.37 [0.05, 2.61]	←
Heterogeneity: Chi ² = 1.22, df = 3 (P = 0.75); l ² = 0%				Rocket-AF	27	7111	-	7125	83.6%	0.50 [0.33, 0.78]	
Test for overall effect: Z = 2.19 (P = 0.03)				Subtotal (95% CI)		2015			100.0%	0.48 [0.32, 0.71]	
·····,				Total events	31		67				
1.7.4 Apixaban vs VKA				Heterogeneity: Chi ² = 1.20, df	= 4 (P = 0).88); I ² =	:0%				
Aristotle 4 2836 5 281	9 100.0%	0.80 [0.22, 2.94]		Test for overall effect: Z = 3.64	4 (P = 0.00	003)					
Subtotal (95% CI) 2836 281	9 100.0%	0.80 [0.22, 2.94]									
Total events 4 5				2.7.4 Apixaban vs VKA							
Heterogeneity: Not applicable				Amplify		2676		2689	13.6%	0.52 [0.05, 4.96]	•
Test for overall effect: Z = 0.34 (P = 0.73)				Aristotle	8	9088		9052	86.4%	0.73 [0.30, 1.79]	
				Aristotle-J	0	71	0	75		Not estimable	
		0.1 0.2	0.5 1 2 5 10	Subtotal (95% CI)		1835		1816	100.0%	0.69 [0.30, 1.60]	
			vours DOAC Favours VKA	Total events	9		13				
											Favours DOAC Favours VKA
											Favours DOAC Favours VKA

Figure S8. Forest Plots for risk of Fatal Bleeding in Elderly (left) and Total Population (right).

2.7.5 Edoxaban 60mg vs VK	(A)								
Edox-J	1	130	0	125	1.0%	7.11 [0.14, 358.60]			→
Engage-AF-Timi 48	32	7012	59	7012	87.4%	0.55 [0.36, 0.83]			
Hokusai-VTE Subtotal (95% CI)	2	4118 11260	10	4122 11259	11.6% 100.0%	0.26 [0.08, 0.82] 0.52 [0.35, 0.76]	•	•	
Total events	35		69						
Heterogeneity: Chi ² = 3.17, d	f= 2 (P =	0.21); I ^z =	37%						
Test for overall effect: Z = 3.3	84 (P = 0.0	0008)							
2.7.6 Edoxaban 30mg vs VK	(A								
Edox-J	0	130	0	125		Not estimable		_	
Engage-AF-Timi 48 Subtotal (95% CI)	21	7002 7132	59	7012 7137	100.0% 100.0%	0.39 [0.25, 0.60] 0.39 [0.25, 0.60]			
Total events Heterogeneity: Not applicabl	21 le		59						
Test for overall effect: Z = 4.2		0001)							
							0.1	0.2 0.5 1 2 5	10
								Favours DOAC Favours VKA	

Figure S8. (contd) Forest Plots for risk of Fatal Bleeding in Elderly (left) and Total Population (right).

DOAC VKA Study or Subgroup Events Total Events		Peto Odds Ratio Peto, Fixed, 95% Cl	Peto Odds Ratio Peto, Fixed, 95% Cl	DOAC VKA Peto Odds Ratio Peto Odds Ratio Study or Subgroup Events Total Events Total Weight Peto, Fixed, 95% Cl Peto, Fixed, 95% Cl
1.8.1 Dabigatran 150mg vs VKA Re-ly 230 2145 215	2088 100.0%	1.05 [0.86, 1.27]		2.8.1 Dabigatran 150mg vs VKA Bibr 1048 0 58 0 62 Not estimable
Subtotal (95% CI) 2145 Total events 230 215 Heterogeneity: Not applicable	2088 100.0%	1.05 [0.86, 1.27]	Ť	Petro 0 169 0 70 Not estimable Re-ly 438 6076 487 6022 100.0% 0.88 [0.77, 1.01] Subtotal (95% CI) 6303 6154 100.0% 0.88 [0.77, 1.01]
Test for overall effect: Z = 0.45 (P = 0.65)				Total events 438 487 Heterogeneity: Not applicable
1.8.2 Dabigatran 110mg vs VKA Re-ly 211 2026 215	2088 100.0%	1.01 [0.83, 1.24]	.	Test for overall effect: Z = 1.82 (P = 0.07)
Subtotal (95% CI) 2026	2088 100.0%	1.01 [0.83, 1.24]		2.8.2 Dabigatran 110mg vs VKA
Total events 211 215 Heterogeneity: Not applicable Test for overall effect: Z = 0.12 (P = 0.90)				Bibr 1048 0 46 0 62 Not estimable Re-ly 446 6015 487 6022 100.0% 0.91 [0.80, 1.04] Subtotal (95% CI) 6061 6084 100.0% 0.91 [0.80, 1.04] Image: Comparison of the second
1.8.3 Rivaroxaban vs VKA			_	Total events 446 487 Heterogeneity: Not applicable
Rocket-AF 106 2652 127 Subtotal (95% CI) 2652	2678 100.0% 2678 100.0%	0.84 [0.64, 1.09] 0.84 [0.64, 1.09]		Test for overall effect: Z = 1.38 (P = 0.17)
Total events 106 127 Heterogeneity: Not applicable Test for overall effect: Z = 1.33 (P = 0.18)				2.8.3 Rivaroxaban vs VKA J-Rocket AF 7 637 5 637 1.1% 1.40 [0.45, 4.36] Rocket AF 582 7131 632 7133 98.9% 0.91 [0.81, 1.03]
		<u> </u>		Subtotal (95% CI) 7768 7770 100.0% 0.92 [0.82, 1.03] Total events 589 637
		0.1 0.2 Fav	0.5 1 2 5 10 vours DOAC Favours VKA	Heterogeneity: Chi² = 0.53, df = 1 (P = 0.46); l² = 0% Test for overall effect: Z = 1.43 (P = 0.15)
				2.8.4 Apixaban vs VKA Aristotle 603 9120 669 9081 100.0% 0.89 [0.79, 1.00]
				Aristotle-J 0 74 0 74 Not estimable Subtotal (95% CI) 9194 9155 100.0% 0.89 [0.79, 1.00]
				Total events 603 669 Heterogeneity: Not applicable
				Test for overall effect: $Z = 2.00$ (P = 0.05)
				2.8.5 Edoxaban 60mg vs VKA
				Edox-J 1 131 1 129 0.1% 0.98 [0.06, 15.83] Engage-AF-Timi 48 773 7035 839 7036 99.9% 0.91 [0.82, 1.01]
				Subtotal (95% Cl) 7166 7165 100.0% 0.91 [0.82, 1.01] ♦ Total events 774 840
				Heterogeneity: Chi ² = 0.00, df = 1 (P = 0.96); i ² = 0% Test for overall effect: Z = 1.74 (P = 0.08)
				2.8.6 Edoxaban 30mg vs VKA Edox-J 0 131 1 129 0.1% 0.13 [0.00, 6.72] ←
				Engage-AF-Timi 48 737 7034 839 7036 99.9% 0.86 [0.78 0.96] Subtotal (95% CI) 7155 7165 100.0% 0.86 [0.78 0.96]
				Subtotal (95% Cl) 7165 7165 100.0% 0.86 [0.78, 0.96] Total events 737 840 Heterogeneity: Chi² = 0.87, df = 1 (P = 0.35); l² = 0% Test for overall effect: Z = 2.75 (P = 0.006)
				0.1 0.2 0.5 1 2 5 10 Favours DOAC Favours VKA

Figure S9. Forest Plots for risk of All Cause Death in Atrial Fibrillation in Elderly (left) and Total Population (right).

*Event numbers for Rocket-AF in elderly have been estimated from published confidence intervals

	DOA	С	VK/	4		Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup		Total	Events	Total	Weight	Peto, Fixed, 95% CI	Peto, Fixed, 95% Cl
2.9.1 Dabigatran 150mg v	s VKA						
Recover I	21	1274	21	1265	45.7%	0.99 [0.54, 1.83]	_
Recover II	25	1279	25	1289	54.3%	1.01 [0.58, 1.76]	
Subtotal (95% CI)		2553		2554	100.0%	1.00 [0.66, 1.51]	-
Total events	46		46				
Heterogeneity: Chi² = 0.00,		-	; ² = 0%				
Test for overall effect: Z = 0	.00 (P = 1	.00)					
2.9.3 Rivaroxaban vs VKA							
Einstein-DVT	38	1718	49	1711	42.6%	0.77 [0.50, 1.18]	
Einstein-DVT dose study	4	136	5	137	4.4%	0.80 [0.21, 3.02]	
Einstein-PE	58	2412	50	2405	53.0%	1.16 [0.79, 1.70]	
Subtotal (95% CI)		4266		4253	100.0%	0.96 [0.73, 1.26]	•
Total events	100		104				
Heterogeneity: Chi ² = 2.07,	df = 2 (P	= 0.36)	2 = 3%				
Test for overall effect: Z = 0	.30 (P = 0	.76)					
2.9.4 Apixaban vs VKA							
Amplify	41	2676	52	2689	96.8%	0.79 [0.52, 1.19]	
Botticelli-DVT	3	128	0	126	3.2%	7.39 [0.76, 71.70]	
Subtotal (95% CI)		2804		2815	100.0%	0.85 [0.57, 1.27]	
Total events	44		52				
Heterogeneity: Chi ² = 3.60,	df = 1 (P	= 0.06)	; I² = 72%	,			
Test for overall effect: Z = 0	.80 (P = 0	.42)					
2.9.5 Edoxaban 60mg vs \	/KA						\perp
Hokusai-VTE	132	4118	126		100.0%	1.05 [0.82, 1.35]	
Subtotal (95% CI)		4118		4122	100.0%	1.05 [0.82, 1.35]	•
Total events	132		126				
Heterogeneity: Not applica	ble						
Test for overall effect: Z = 0	.39 (P = 0	.70)					
							0.1 0.2 0.5 1 2 5 10
							Favours DOAC Favours VKA

Figure S10. Forest Plots for risk of All Cause Death in Venous thromboembolism in Total Population (right).

*No results available for the elderly for this outcome

DOAC Study or Subgroup Events Total	VKA Events Tota	Peto Odds Ratio I Peto, Fixed, 95% Cl	Peto Odds Ratio Peto, Fixed, 95% Cl	Study or Subgroup	DOAC Events Total	VKA Events Tota	Peto Odds Ratio	Peto Odds Ratio Peto, Fixed, 95% Cl
1.1.1 Dabigatran 150mg vs VKA				3.1.1 Dabigatran 150n				
Re-ly 69 2466				Re-ly	65 3610	101 3599		
Subtotal (95% CI) 2466	2423	0.66 [0.49, 0.90]	◆	Subtotal (95% CI)	3610	3599	0.64 [0.47, 0.87]	▲
Fotal events 69	101			Total events	65	101		
Heterogeneity: Not applicable Fest for overall effect: Z = 2.61 (P = 0.1	009)			Heterogeneity: Not app Test for overall effect: 2		04)		
1.1.2 Dabigatran 110mg vs VKA				3.1.2 Dabigatran 110n	ng vs VKA			
Re-ly 87 2349	101 2423			Re-ly	96 3666	101 3599		
Subtotal (95% CI) 2349		0.88 [0.66, 1.18]	-	Subtotal (95% CI)	3666	3599	0.93 [0.70, 1.24]	↓ ←
Fotal events 87	101			Total events	96	101		
Heterogeneity: Not applicable	(A)			Heterogeneity: Not app				
Fest for overall effect: Z = 0.82 (P = 0.4	+1)			Test for overall effect: 2	2 = 0.49 (P = 0.6.	2)		
1.1.3 Rivaroxaban vs VKA			_	3.1.3 Rivaroxaban vs	VKA			
Rocket-AF 125 3082				Rocket-AF	144 3999	152 4008		
Subtotal (95% CI) 3082		2 0.80 [0.63, 1.02]	◆	Subtotal (95% CI)	3999	4008	3 0.95 [0.75, 1 .20]	•
Fotal events 125	154			Total events	144	152		
Heterogeneity: Not applicable Fest for overall effect: Z = 1.78 (P = 0.0	101			Heterogeneity: Not app Test for overall effect: 2		5)		
$\frac{1}{1} = \frac{1}{1} = \frac{1}$	JO)			Testior overall ellect. 2	2 - 0.40 (F - 0.0	5)		
1.1.4 Apixaban vs VKA				3.1.4 Apixaban vs VK/	Α			
Aristotle 79 2850				Aristotle	133 6270	156 6253	3 0.85 [0.67, 1.07]	
Aristotle-J 0 45	2 23			Aristotle-J	0 103	1 51		
Subtotal (95% CI) 2895 Fotal events 79	2851 111	0.70 [0.52, 0.93]	-	Subtotal (95% CI) Total events	6373 133	6304 157	0.84 [0.67, 1.06]	
rotarevents 79 Heterogeneity: Chi² = 3.10, df = 1 (P =				Heterogeneity: Chi ² = 1				
Fest for overall effect: Z = 2.46 (P = 0.1				Test for overall effect: 2				
	,				(,	.,		
1.1.5 Edoxaban 60mg vs VKA			_	3.1.5 Edoxaban 60mg				
Engage-AF-Timi 48 138 2848	166 2820			Engage-AF-Timi 48	165 4187	179 4216		
Subtotal (95% CI) 2848		0.81 [0.65, 1.03]	-	Subtotal (95% CI)	4187	4216	6 0.93 [0.75, 1.15]	•
Fotal events 138 Heterogeneity: Not applicable	166			Total events Heterogeneity: Not app	165 olicoble	179		
Fest for overall effect: Z = 1.74 (P = 0.0	18)			Test for overall effect: 2		8)		
	,					-,		
1.1.6 Edoxaban 30mg vs VKA			<u> </u>	3.1.6 Edoxaban 30mg				
Engage-AF-Timi 48 184 2806				Engage-AF-Timi 48	208 4228	179 4216		
Subtotal (95% CI) 2806) 1.12 [0.90, 1.39]	-	Subtotal (95% CI)	4228	4216	5 1.17 [0.95, 1.43]	
Fotal events 184 Heterogeneity: Not applicable	166			Total events Heterogeneity: Not app	208 Dicable	179		
Fest for overall effect: Z = 1.04 (P = 0.3	30)			Test for overall effect: 2		4)		
		⊢ 0.1	0.2 0.5 1 2 5 10					
			Favours DOAC Favours VKA					Favours DOAC Favours VKA

Figure S11. Forest Plots for risk of Stroke or Systemic Embolism in AF in Elderly (left) and <75 Population (right).

*Event numbers for Engage-AF-Timi 48 in elderly have been estimated from published confidence intervals.

Study or Subgroup E	DOA Events	-	VKA Events		Peto Odds Ratio Peto, Fixed, 95% Cl	Peto Od Peto, Fixe		Study or Subgroup	DOAC Events Total E	VKA Events Total	Peto Odds Ratio Peto, Fixed, 95% Cl	Peto Odds Ratio Peto, Fixed, 95% Cl
1.2.1 Dabigatran 150mg vs \	VKA							3.2.1 Dabigatran 150mg v	vs VKA			
Pooled Recover Studies Subtotal (95% CI)	3	253 253	5	276 276	0.66 [0.16, 2.66] 0.66 [0.16, 2.66]			Pooled Recover Studies Subtotal (95% CI)	57 2300 2300	50 2278 2278	1.13 [0.77, 1.66] 1.13 [0.77, 1.66]	
Total events Heterogeneity: Not applicable	3 e		5					Total events Heterogeneity: Not applica	57 able	50		
Test for overall effect: Z = 0.5	9 (P = 0	.56)						Test for overall effect: Z = 0				
1.2.2 Apixaban vs VKA						_		3.2.2 Apixaban vs VKA				
Amplify Subtotal (95% CI)	7	389 389	13	360 360	0.50 [0.21, 1.21] 0.50 [0.21, 1.21]		-	Amplify Subtotal (95% CI)	52 2220 2220	58 2275 2275	0.92 [0.63, 1.34] 0.92 [0.63, 1.34]	
Total events	7		13					Total events	52	58		
Heterogeneity: Not applicable Test for overall effect: Z = 1.5		.12)						Heterogeneity: Not applica Test for overall effect: Z = 0				
1.2.3 Rivaroxaban vs VKA								3.2.3 Rivaroxaban vs VKA	N N			
Einstein-DVT	4	215		225	0.43 [0.15, 1.25]	· · · ·	_	Einstein-DVT	32 1516	41 1493	0.76 [0.48, 1.22]	
Einstein-PE Subtotal (95% CI)	11	441 656	13	402 627	0.77 [0.34, 1.72] 0.62 [0.33, 1.18]		-	Einstein-PE Subtotal (95% CI)	39 1978 3494	31 2011 3504	1.28 [0.80, 2.06] 0.99 [0.71, 1.37]	•
Total events	15		23					Total events	71	72		
Heterogeneity: $Chi^2 = 0.70$, dt Test for overall effect: $Z = 1.43$; ² = 0%					Heterogeneity: Chi ² = 2.35, Test for overall effect: Z = 0		I² = 57%		
1.2.4 Edoxaban 60mg vs VK	A					_		3.2.4 Edoxaban 60mg vs	VKA			
Hokusai-VTE Subtotal (95% CI)	14	560 560	27	544 <mark>544</mark>	0.50 [0.27, 0.94] 0.50 [0.27, 0.94]			Hokusai-VTE Subtotal (95% CI)	116 3558 3558	119 3578 3578	0.98 [0.76, 1.27] 0.98 [0.76, 1.27]	‡
Total events	14		27					Total events	116	119		
Heterogeneity: Not applicable Test for overall effect: $Z = 2.1$		1.03)						Heterogeneity: Not applica Test for overall effect: Z = 0				
						0.1 0.2 0.5 1	2 5 10				F	
						Favours DOAC					-	Favours DOAC Favours VKA

Figure S12. Forest Plots for risk of Venous Thromboembolism in VTE in Elderly (left) and <75 Population (right).

Study or Subgroup	DOAC Events Total E	VKA Events Total	Peto Odds Ratio Peto, Fixed, 95% CI		lds Ratio ed, 95% Cl	Study or Subgroup	DOAC Events Tot	VK/ al Events		Peto Odds Ratio Peto, Fixed, 95% Cl		dds Ratio ed, 95% Cl
1.3.1 Dabigatran 150mg v				,,		3.3.1 Dabigatran 150mg v					,,	
Pooled Recover Studies	8 231	10 262	0.90 [0.35, 2.32]			Pooled Recover Studies	16 222	5 30	2200	0.53 [0.30, 0.96]		-
Re-ly	227 2145	188 2088	1.20 [0.98, 1.46]			Re-ly	172 393		3934	0.73 [0.60, 0.89]		
Subtotal (95% CI)	2376	2350	1.18 [0.97, 1.44]		•	Subtotal (95% CI)	615	120	6134	0.71 [0.58, 0.85]	•	
Total events	235	198				Total events	188	263				
Heterogeneity: Chi² = 0.32		P ² = 0%				Heterogeneity: Chi ² = 0.98,						
Test for overall effect: Z = 1	1.64 (P = 0.10)					Test for overall effect: Z = 3	.62 (P = 0.000	13)				
1.3.2 Dabigatran 110mg v	s VKA					3.3.2 Dabigatran 110mg v					_	
Re-ly	187 2026	188 2088	1.03 [0.83, 1.27]			Re-ly	155 398		3934	0.65 [0.53, 0.79]		
Subtotal (95% CI)	2026	2088	1.03 [0.83, 1.27]			Subtotal (95% CI)	398	101	3934	0.65 [0.53, 0.79]	•	
Total events	187	188				Total events	155	233				
Heterogeneity: Not applica Test for overall effect: Z = 0						Heterogeneity: Not applica Test for overall effect: Z = 4		43				
Test for overall effect. $Z = t$	J.25 (P = 0.80)					restior overall ellect. Z = 4	.20 (F < 0.000	(1)				
1.3.3 Rivaroxaban vs VKA	1					3.3.3 Rivaroxaban vs VKA						
Einstein-DVT	3 215	5 223	0.62 [0.15, 2.52]	10 and		Einstein-DVT	11 150		1488	0.73 [0.34, 1.57]		
Einstein-PE	5 440	23 401	0.24 [0.11, 0.51]		-64	Einstein-PE	21 196		2004	0.74 [0.42, 1.29]		<u></u>
J-Rocket AF	14 206	10 207	1.43 [0.63, 3.26]	×1		J-Rocket AF	12 43			0.59 [0.29, 1.20]		- 10
Rocket-AF	203 2688	179 2702	1.15 [0.93, 1.42]			Rocket-AF	192 442		4423	0.92 [0.76, 1.13]		1
Subtotal (95% CI)	3549	3533	1.04 [0.86, 1.26]			Subtotal (95% CI)	832		8347	0.87 [0.73, 1.04]	•	
Total events	225	217				Total events	236	271				
Heterogeneity: Chi² = 16.5 Test for overall effect: Z = 0		19); if = 82%				Heterogeneity: Chi ² = 2.03, Test for overall effect: Z = 1		57), 17 = 0%				
restion overall ellect. Z = t	0.59 (F = 0.70)					restion overall ellect. Z = 1	.57 (F = 0.12)					
1.3.4 Apixaban vs VKA						3.3.4 Apixaban vs VKA						
Amplify	4 398	16 370	0.27 [0.11, 0.66]	· · · · · · · · · · · · · · · · · · ·		Amplify	11 227		2319	0.37 [0.20, 0.67]	· · · · · · · · · · · · · · · · · · ·	
Aristotle	151 2836	224 2819	0.65 [0.53, 0.81]			Aristotle	176 625		6233	0.73 [0.60, 0.89]		
Subtotal (95% CI)	3234	3189	0.63 [0.51, 0.77]	•		Subtotal (95% CI)	853		8552	0.68 [0.57, 0.82]	•	
Total events	155	240				Total events	187	271	v			
Heterogeneity: Chi² = 3.60 Test for overall effect: Z = 4		1~= 7.2%				Heterogeneity: Chi ² = 4.53, Test for overall effect: Z = 4			Xo			
restion overall ellect. Z = 4	4.52 (F < 0.00001)					restior overall ellect. Z = 4	.00 (F < 0.000	(1)				
1.3.5 Edoxaban 60mg vs V	VKA					3.3.5 Edoxaban 60mg vs \	/KA					
Engage-AF-Timi 48	214 2848	257 2820	0.81 [0.67, 0.98]		-	Engage-AF-Timi 48	204 418		4216	0.76 [0.63, 0.91]		
Subtotal (95% CI)	2848	2820	0.81 [0.67, 0.98]	•	2	Subtotal (95% CI)	418	and a second second	4216	0.76 [0.63, 0.91]	•	
Total events	214	257				Total events	204	267				
Heterogeneity: Not applica						Heterogeneity: Not applica		20				
Test for overall effect: Z = 2	2.18 (P = 0.03)					Test for overall effect: Z = 2	91 (P = 0.004)				
1.3.6 Edoxaban 30mg vs	VKA					3.3.6 Edoxaban 30mg vs \	/KA					
Engage-AF-Timi 48	121 2806	257 2820	0.46 [0.38, 0.57]			Engage-AF-Timi 48	133 422		4216	0.49 [0.40, 0.60]	-	
Subtotal (95% CI)	2806	2820	0.46 [0.38, 0.57]	-		Subtotal (95% CI)	422		4216	0.49 [0.40, 0.60]	-	
Total events	121	257				Total events	133	267				
Heterogeneity: Not applica						Heterogeneity: Not applica		12103				
Test for overall effect: Z = 7	7.19 (P < 0.00001)					Test for overall effect: Z = 6	.89 (P < 0.000	101)				
												<u> </u>
				0.1 0.2 0.5	1 2 5 10 [°]						0.1 0.2 0.5	1 2 5
				Favours DOAC	Favours VKA						Favours DOAC	Favours VKA

Figure S13. Forest Plots for risk of Major Bleeding in Elderly (left) and <75 Population (right).

*Event numbers for Engage-AF-Timi-48 and J-Rocket AF in the elderly have been estimated from published confidence intervals.

	DOAC	VKA	Peto Odds Ratio	Peto Odds Ratio		DOAC	VKA	Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup	Events Total	Events Tot	al Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl	Study or Subgroup	Events Total	Events Total	Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl
1.4.1 Dabigatran 150n	ng vs VKA				3.4.1 Dabigatran 150	Omg vs VKA			
Re-ly Subtotal (95% CI)	135 2466 2466	75 242 242			Re-ly Subtotal (95% CI)	88 3666 3666			-
Total events Heterogeneity: Not app Test for overall effect: 2		75 001)			Total events Heterogeneity: Not a Test for overall effect		73 28)		
1.4.2 Dabigatran 110n	ng vs VKA				3.4.2 Dabigatran 110	Omg vs VKA			
Re-ly Subtotal (95% CI)	101 2349 2349	75 242 242			Re-ly Subtotal (95% CI)	61 3610 3610			
Total events Heterogeneity: Not app Test for overall effect: 2		75 3)			Total events Heterogeneity: Not a Test for overall effect		73 29)		
				0.1 0.2 0.5 1 2 5 10 Favours DOAC Favours VKA					0.1 0.2 0.5 1 2 5 10 Favours DOAC Favours VKA

Figure S14. Forest Plots for risk of Gastrointestinal Bleeding in Elderly (left) and <75 Population (right).

	DOAC	VKA	Peto Odds Ratio	Peto Odds Ratio		DOAC	VKA	Peto Odds Ratio	Peto Odds Ratio
		Events Total	Peto, Fixed, 95% CI	Peto, Fixed, 95% Cl			Events Total	Peto, Fixed, 95% CI	Peto, Fixed, 95% Cl
.5.1 Dabigatran 150	South Shattire 26			_	3.5.1 Dabigatran 150	and a second second			_
'e-ly	19 21 4 5	44 2088	0.43 [0.26, 0.72]		Re-ly	19 3931	46 3934	0.43 [0.27, 0.71]	
ubtotal (95% CI)	2145	2088	0.43 [0.26, 0.72]		Subtotal (95% CI)	3931	3934	0.43 [0.27, 0.71]	
otal events	19	44			Total events	19	46		
leterogeneity: Not ap					Heterogeneity: Not ap				
est for overall effect:	Z = 3.28 (P = 0.00	11)			Test for overall effect:	Z = 3.36 (P = 0.0)008)		
.5.2 Dabigatran 110	mg vs VKA				3.5.2 Dabigatran 110	mg vs VKA			
'e-ly	14 2026	44 2088	0.36 [0.22, 0.61]		Re-ly	13 3989	46 3934	0.32 [0.19, 0.53]	
ubtotal (95% CI)	2026	2088	0.36 [0.22, 0.61]		Subtotal (95% CI)	3989	3934	0.32 [0.19, 0.53]	
otal events	14	44			Total events	13	46		
leterogeneity: Not ap	plicable				Heterogeneity: Not ap	plicable			
est for overall effect:	Z = 3.85 (P = 0.00	101)			Test for overall effect:	Z = 4.37 (P < 0.0)001)		
.5.3 Rivaroxaban vs	VKA				3.5.3 Rivaroxaban vs	VKA			
instein-DVT	0 215	1 223	0.14 [0.00, 7.07]		Einstein-DVT	2 1503	1 1488	1.93 [0.20, 18.56]	
instein-PE	2 475	6 448	0.34 [0.09, 1.38]		Einstein-PE	1 1944	6 1957	0.24 [0.05, 1.06] +	
ocket-AF	29 2688	33 2702	0.88 [0.53, 1.46]		Rocket-AF	26 4423	51 4423	0.52 [0.33, 0.81]	
ubtotal (95% CI)	3378	3373	0.77 [0.48, 1.23]	-	Subtotal (95% CI)	7870	7868	0.51 [0.34, 0.78]	-
otal events	31	40			Total events	29	58		
leterogeneity: Chi ^z =	2.30, df = 2 (P = 0	.32); I ^z = 13%			Heterogeneity: Chi ² =	2.32, df = 2 (P =	0.31); I ^z = 14%		
est for overall effect:	Z = 1.08 (P = 0.28)			Test for overall effect:	Z = 3.12 (P = 0.0)02)		
.5.4 Apixaban vs VK	A				3.5.4 Apixaban vs Vk	A			
ristotle	20 2836	57 2819	0.38 [0.24, 0.59]		Aristotle	32 6252	65 6233	0.50 [0.34, 0.75]	
ubtotal (95% CI)	2836	2819	0.38 [0.24, 0.59]		Subtotal (95% CI)	6252	6233	0.50 [0.34, 0.75]	•
otal events	20	57			Total events	32	65		
leterogeneity: Not ap					Heterogeneity: Not ap				
est for overall effect:	Z = 4.27 (P < 0.00	101)			Test for overall effect:	Z = 3.38 (P = 0.0)007)		
								Ē	
			0.1	D.2 D.5 1 2 5 Favours DOAC Favours VKA	10			0	.1 0.2 0.5 1 2 5 1 Favours DOAC Favours VKA

Figure S15. Forest Plots for risk of Intracranial Bleeding in Elderly (left) and <75 Population (right).

Study or Subgroup E 1.6.1 Dabigatran 150mg vs V Pooled Recover Studies		Total					The board of the second s						Odds Ratio
Construction of the second s		Totui	Events	Total I	V, Random, 95% Cl	IV, Random, 95% CI	Study or Subgroup		Total E	vents	Total	IV, Random, 95% CI	IV, Random, 95% Cl
Dealed Deseuse Ofusion	VKA						3.6.1 Dabigatran 150mg v	s VKA					
Subtotal (95% CI)	22	231 231	33	262 262	0.73 [0.41, 1.29] 0.73 [0.41, 1.29]		Pooled Recover Studies Subtotal (95% CI)		2225 2225	156	2200 2200	0.53 [0.41, 0.70] 0.53 [0.41, 0.70]	1
Total events	22		33				Total events	87		156			
Heterogeneity: Not applicable	le						Heterogeneity: Not applica	ble					
Test for overall effect: Z = 1.0		.28)					Test for overall effect: Z = 4	.58 (P < 0	.00001)				
1.6.3 Rivaroxaban vs VKA							3.6.3 Rivaroxaban vs VKA						
Einstein-DVT	19	215	20	223	0.98 [0.51, 1.90]		Einstein-DVT	120	1503	118	1488	1.01 [0.77, 1.31]	
Einstein-PE	58	440	67	401	0.76 [0.52, 1.11]		Einstein-PE	191	1972	207	2004	0.93 [0.76, 1.15]	
J-Rocket AF	58	205	38	207	1.75 [1.10, 2.79]		J-Rocket AF	78	432	86	430	0.88 [0.63, 1.24]	2
Rocket-AF	693	2688	633	2702	1.14 [1.00, 1.29]	-	Rocket-AF	782	4423	816	4423	0.95 [0.85, 1.06]	
Subtotal (95% CI)		3548		3533	1.10 [0.82, 1.48]	-	Subtotal (95% CI)		8330		8345	0.95 [0.87, 1.03]	•
Total events	828		758				Total events	1171		1227			
Heterogeneity: Tau ² = 0.05; C	Chi ² = 7.	84, df =	3 (P = 0	.05); I ² =	62%		Heterogeneity: Tau ² = 0.00	; Chi ² = 0	41, df = 3	B(P = 0)	.94); l²∶	= 0%	
Test for overall effect: Z = 0.6	64 (P = 0	.52)					Test for overall effect: Z = 1	.21 (P = 0	.23)				
1.6.4 Apixaban vs VKA							3.6.4 Apixaban vs VKA						
Aristotle Subtotal (95% CI)		2836 2836		2819 2819	0.64 [0.54, 0.76] 0.64 [0.54, 0.76]		Aristotle Subtotal (95% CI)		6252 6252	498	6233 6233	0.70 [0.60, 0.80] 0.70 [0.60, 0.80]	■
Total events	257		379				Total events	356		498			
Heterogeneity: Not applicable	le						Heterogeneity: Not applica	ble					
Test for overall effect: Z = 5.1	9 (P < 0	.00001))				Test for overall effect: Z = 5	i.06 (P < 0	.00001)				
1.6.5 Edoxaban 60mg vs VK	A						3.6.5 Edoxaban 60mg vs \	/KA					
Hokusai-VTE Subtotal (95% CI)	70	560 560	82	544 544	0.80 [0.57, 1.13] 0.80 [0.57, 1.13]		Hokusai-VTE Subtotal (95% CI)	279	3558 3558	341	3578 3578	0.81 [0.68, 0.95] 0.81 [0.68, 0.95]	
Total events	70	(2,2,2)	82		max. Bulk Fattor & Analta		Total events	279		341	110000	SALES AND AND AND A CONTRACT	
Heterogeneity: Not applicable							Heterogeneity: Not applica	10.000		0.11			
Test for overall effect: $Z = 1.2$.22)					Test for overall effect: Z = 2		.01)				
					0.1		10						
					0.1	Favours DOAC Favours VKA	TU:						Favours DOAC Favours VKA

Figure S16. Forest Plots for risk of Clinically Relevant Bleeding in Elderly (left) and <75 Population (right) - Random Effects Model.

	DOAC	VK	A	Peto Odds Ratio	Peto Odds Ratio		DOAC	VKA	Peto Odds Ratio	Peto Odds Ratio
Study or Subgroup		Events	Total	Peto, Fixed, 95% CI	Peto, Fixed, 95% Cl	Study or Subgroup	Events To	tal Events Tota	Peto, Fixed, 95% Cl	Peto, Fixed, 95% Cl
.7.1 Dabigatran 150	mg vs VKA					3.7.1 Dabigatran 150)mg vs VKA			
Re-ly	16 2145		2088	0.92 [0.46, 1.82]		Re-ly	12 39			
Subtotal (95% CI)	2145		2088	0.92 [0.46, 1.82]		Subtotal (95% CI)	39	31 3934	0.55 [0.28, 1.09]	
Fotal events	16	17				Total events	12	22		
Heterogeneity: Not ap	(1) [1] [2] [2] [2] [2] [2] [2] [2] [2] [2] [2					Heterogeneity: Not a				
est for overall effect:	Z = 0.25 (P = 0.)	30)				Test for overall effect	: Z = 1.72 (P =	0.09)		
.7.2 Dabigatran 110	mg vs VKA					3.7.2 Dabigatran 110)mg vs VKA			
Re-ly	12 2026		2088	0.73 [0.35, 1.51]		Re-ly	11 39	89 22 3934	0.50 [0.25, 1.00]	
Subtotal (95% CI)	2026		2088	0.73 [0.35, 1.51]		Subtotal (95% CI)	39	89 3934	0.50 [0.25, 1.00]	
Total events	12	17				Total events	11	22		
Heterogeneity: Not ap						Heterogeneity: Not a	pplicable			
Fest for overall effect:	Z = 0.85 (P = 0.4	40)				Test for overall effect	: Z = 1.96 (P =	0.05)		
1.7.3 Rivaroxaban vs	VKA					3.7.3 Rivaroxaban v	s VKA			
Einstein-DVT	0 215	2	223	0.14 [0.01, 2.24] 🔶		Einstein-DVT	1 15	03 3 1488	0.36 [0.05, 2.59]	←
Einstein-PE	2 475	2	448	0.94 [0.13, 6.72]		Einstein-PE	0 19	44 1 1957	0.14 [0.00, 6.87]	<
I-Rocket AF	1 206		207	0.51 [0.05, 4.97] 🔶		J-Rocket AF	04	33 1 432	0.14 [0.00, 6.80]	·
Rocket-AF	13 2688		2702	0.53 [0.28, 1.01]		Rocket-AF	14 44			
Subtotal (95% CI)	3584		3580	0.53 [0.30, 0.93]		Subtotal (95% CI)	83	03 8300	0.45 [0.26, 0.78]	
Fotal events	16	31				Total events	15	35		
Heterogeneity: Chi² =			= 0%			Heterogeneity: Chi ² =		~		
est for overall effect:	Z = 2.19 (P = 0.1	33)				Test for overall effect	: Z = 2.84 (P =	0.005)		
.7.4 Apixaban vs VK	A				_	3.7.4 Apixaban vs VI	KA			_
Aristotle	4 2836		2819	0.80 [0.22, 2.94]		Aristotle	4 62			
Subtotal (95% CI)	2836		2819	0.80 [0.22, 2.94]		Subtotal (95% CI)	62	52 6233	0.67 [0.19, 2.31]	
Fotal events	4	5				Total events	4	6		
leterogeneity: Not ap		19230				Heterogeneity: Not a				
est for overall effect:	Z = 0.34 (P = 0.3	73)				Test for overall effect	: Z = 0.64 (P =	0.52)		
				-		-				
				Ö.1	0.2 0.0 1 2 0 1.) ^{**}				0.1 0.2 0.5 1 2 5
					Favours DOAC Favours VKA					Favours DOAC Favours VKA

Figure S17. Forest Plots for risk of Fatal Bleeding in Elderly (left) and <75 Population (right).

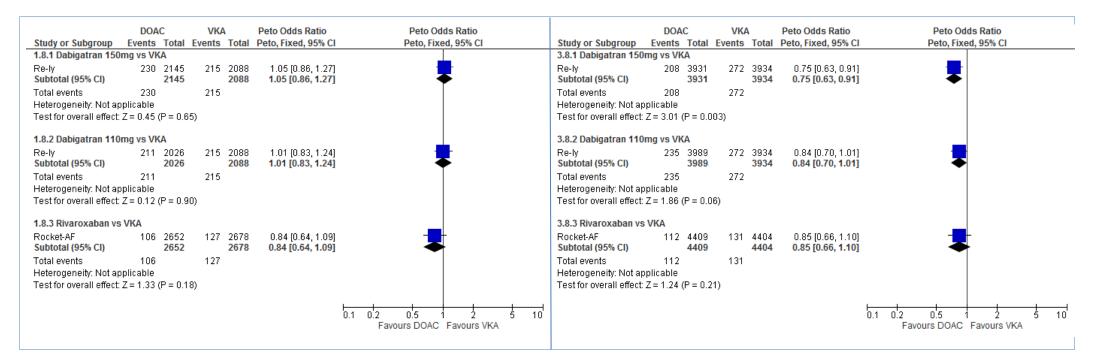


Figure S18. Forest Plots for risk of All Cause Death in AF in Elderly (left) and <75 Population (right).

*Event numbers for Rocket-AF in elderly have been estimated from published confidence intervals.

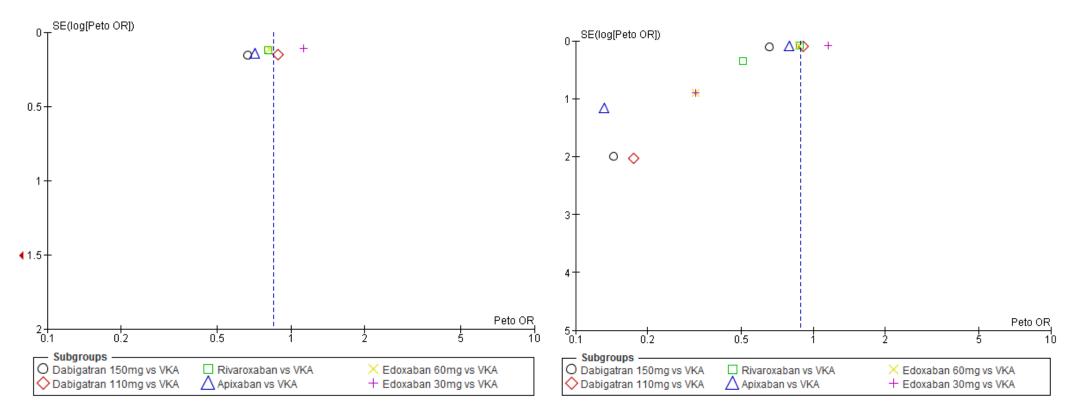


Figure S19. Funnel Plots for Stroke or Systemic Embolism in AF in Elderly (left) and Total population (right).

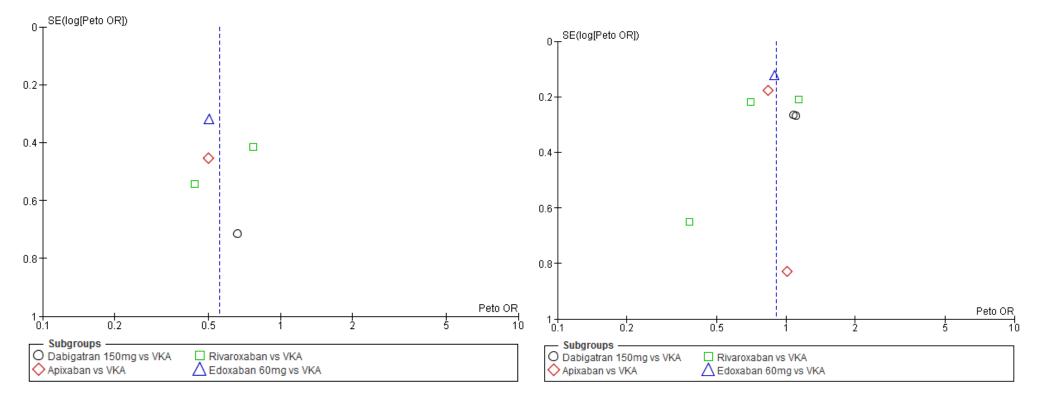


Figure S20. Funnel Plots for risk of Recurrent Venous Thromboembolism in VTE in Elderly (left) and Total population (right).

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