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

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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 ≥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.

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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

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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 ≥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 ≥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 ≥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

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

Study	Indication	Standard Dose	Phase	Duration, mo
Dabigatran				
Bibr 1048, 2005[24]	AF	110 mg BD or 150 mg BD	II	3
Petro, 2007[30]	AF	150 mg BD extracted	II	3
Re-ly, 2009[27]	AF	110 mg or 150 mg BD	III	24*
Recover I, 2010[28]	VTE	150 mg BD	III	6
Recover II, 2013[29]	VTE	150 mg BD	III	6
Apixaban				
Aristotle, 2011[26]	AF	5 mg BD	III	21.6*
Aristotle-J, 2011[32]	AF	5 mg BD extracted	II	3
Botticelli-DVT, 2008[33]	VTE	5 mg BD	II	3
Amplify, 2013[31]	VTE	10 mg BD for 7 days then 5 mg BD	III	6
Rivaroxaban				
Rocket-AF, 2011[22]	AF	20 mg OD	III	23.2*
J-Rocket AF, 2011[21]	AF	15 mg OD	III	30
Einstein-DVT Dose Study, 2008[23]	VTE	20 mg OD extracted	II	3
Einstein-DVT, 2010[19]	VTE	15 mg BD for 21 days then 20 mg OD	III	3, 6, or 12
Einstein-PE, 2012[20]	VTE	15 mg BD for 21 days then 20 mg OD	III	3, 6, or 12
Edoxaban				
Edox-P2, 2010[36]	AF	30 mg or 60 mg OD extracted	II	3
Edox-P2A, 2010[25]	AF	30 mg OD or 60 mg OD	II	3
Edox-J, 2012[37]	AF	30 mg or 60 mg OD extracted	II	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	III	3–12

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 ≥75 years out of a total of 102 479 participants aged ≥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 $CHADS_2$ 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 $CHADS_2$ 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

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

	Total Participants		Participants ≥75		Mean Age (SD)		Men, %		$CHADS_2$ (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, 2009[27]	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, 2011[32]	74	74	45	23	70.0 (8.1)	71.7 (7.0)	82.4	81.1	2.1	1.9	NA	NA
Botticelli-DVT,2008[33]	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, 2010[19]	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, 2010[36]	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, 2012[37]	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, 2013[34]	4143	4149	560	544	55.7 (16.3)	55.9 (16.2)	57.3	57.2	NA	NA	784 (19.0)	736 (17.9)

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

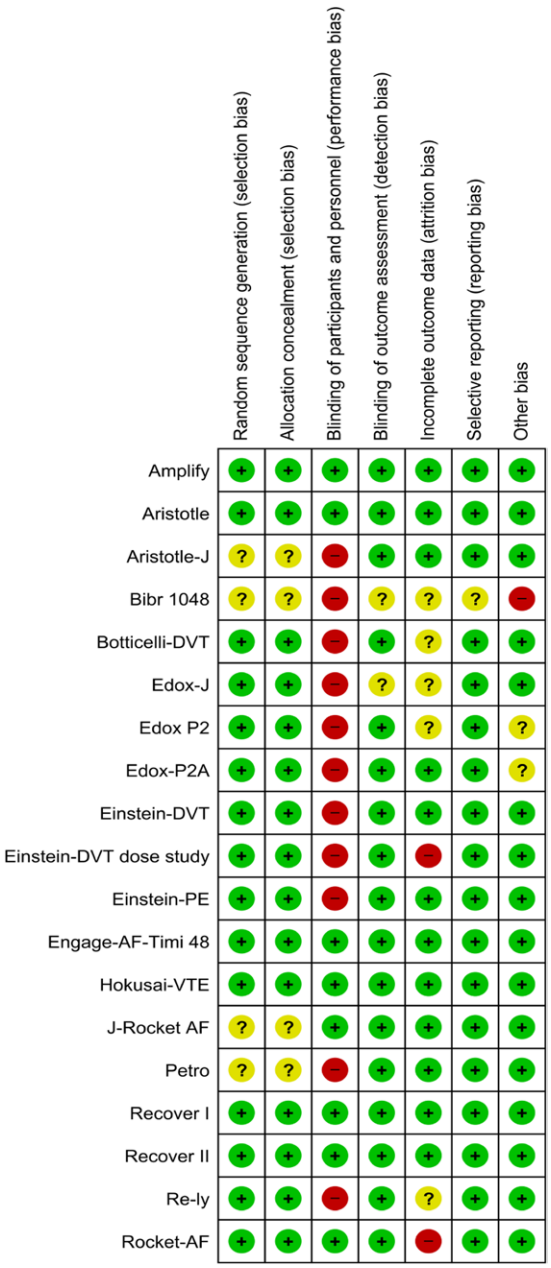

Figure 1. Summary of the risk of bias assessment. Green(+) indicates low-bias risk; red (–), high-bias risk; and yellow(?), unclear bias risk.

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.

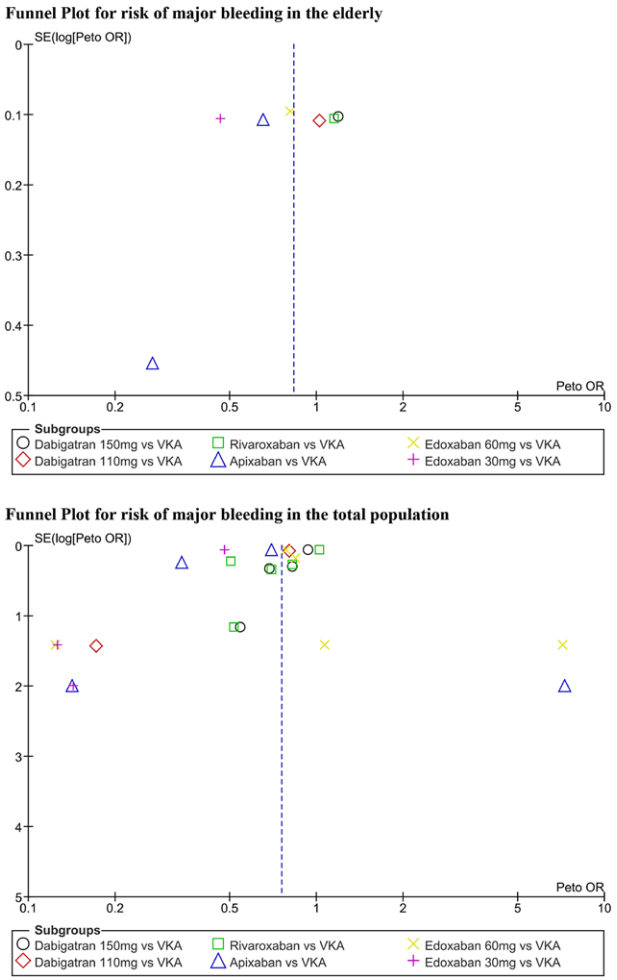

Figure 2. Funnel plot comparison for the risk of major bleeding in the elderly and the total population. OR indicates odds ratio; SE, standard error; and VKA, vitamin K antagonist.
*Note: *y* axis scales differ between plots above.

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).

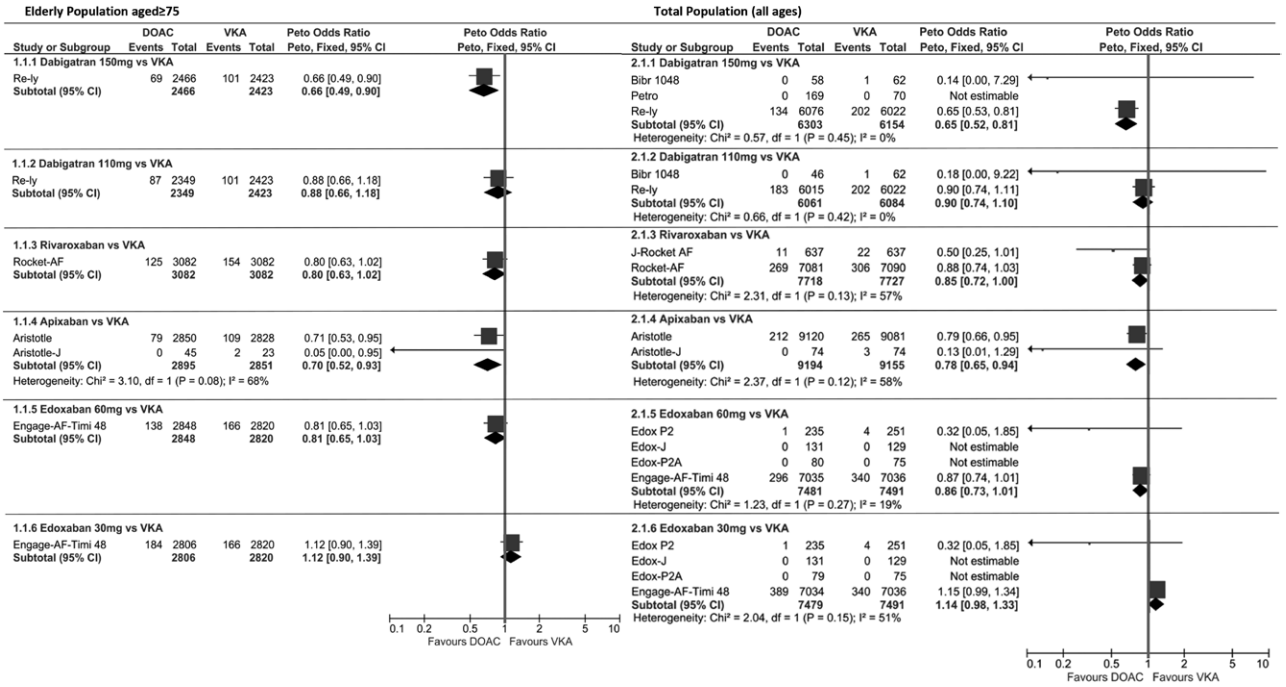

Figure 3. Risk of stroke or systemic embolism in atrial fibrillation studies in the elderly (**left**) and the total population (**right**). CI indicates confidence interval; DOAC, direct oral anticoagulants; and VKA, vitamin K antagonist. *Event numbers for Engage-AF-Timi 48 in the elderly have been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

Heterogeneity Assessment and Sensitivity Analysis

Significant heterogeneity (I^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 (I^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 (I^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

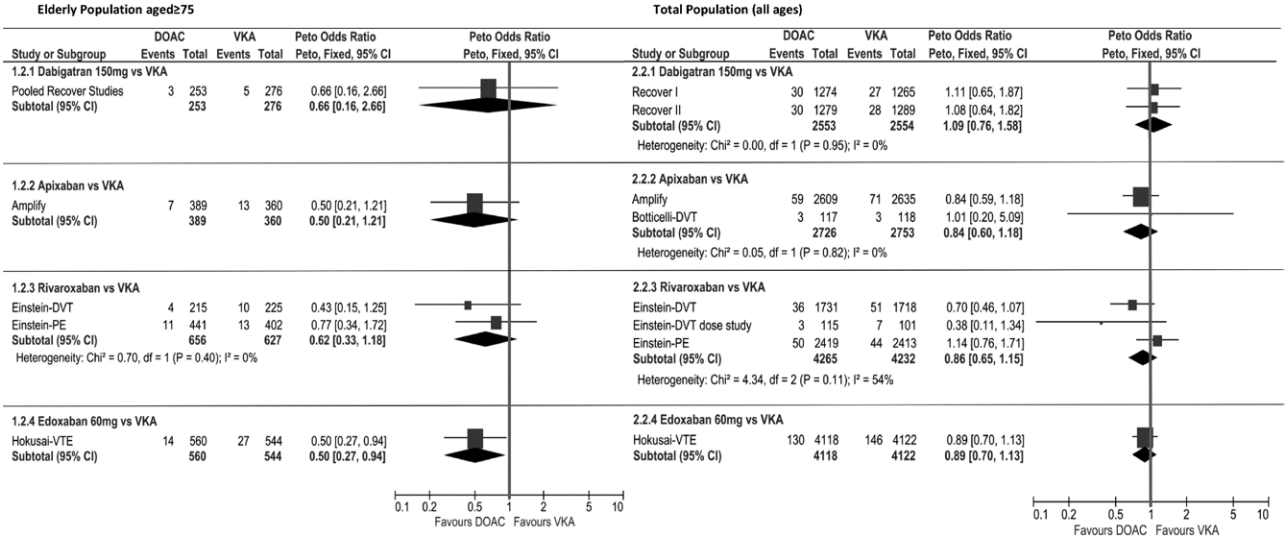

Figure 4. Risk of recurrent venous thromboembolism in venous thromboembolism studies in the elderly (**left**) and the total population (**right**). CI indicates confidence interval; DOAC, direct oral anticoagulants; and VKA, vitamin K antagonist.

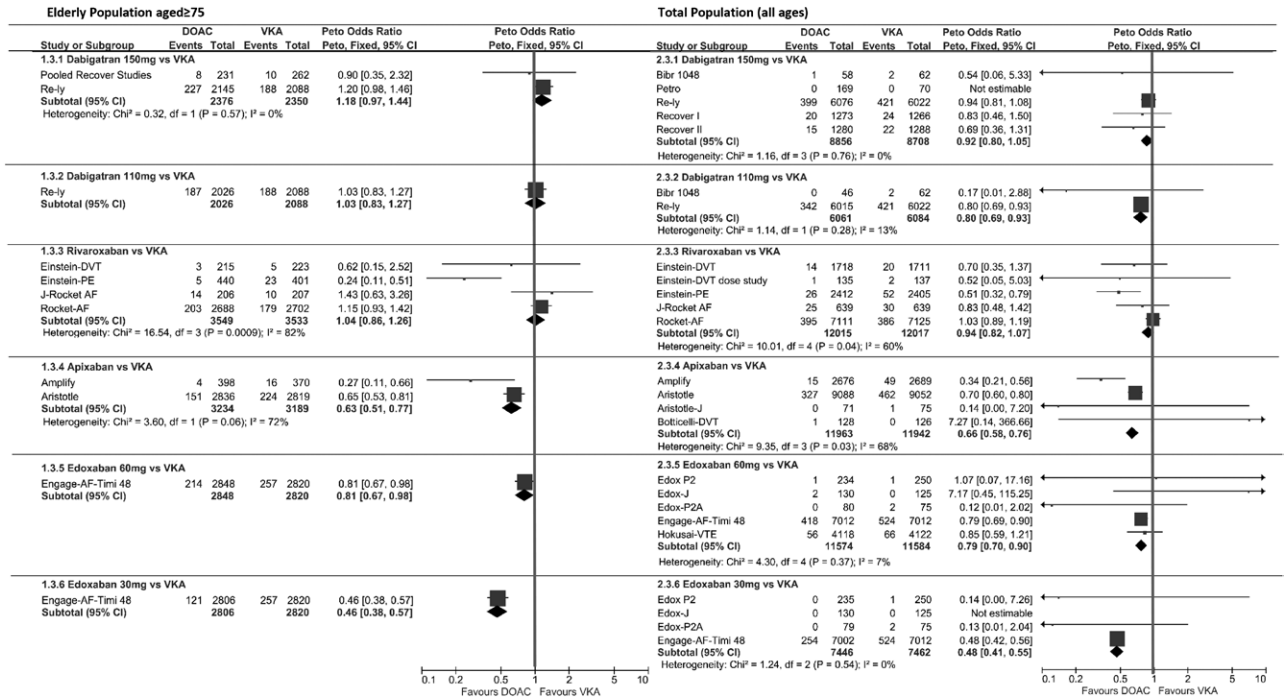

Figure 5. Risk of major bleeding in the elderly (**left**) and the total population (**right**). CI indicates confidence interval; DOAC, direct oral anticoagulants; and VKA, vitamin K antagonist. *Event numbers for Engage-AF-Timi-48 and J-Rocket AF in the elderly have been estimated from published confidence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

apixaban in the total population (I^2=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 ≥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 meta-analyses, with subjects aged ≥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.

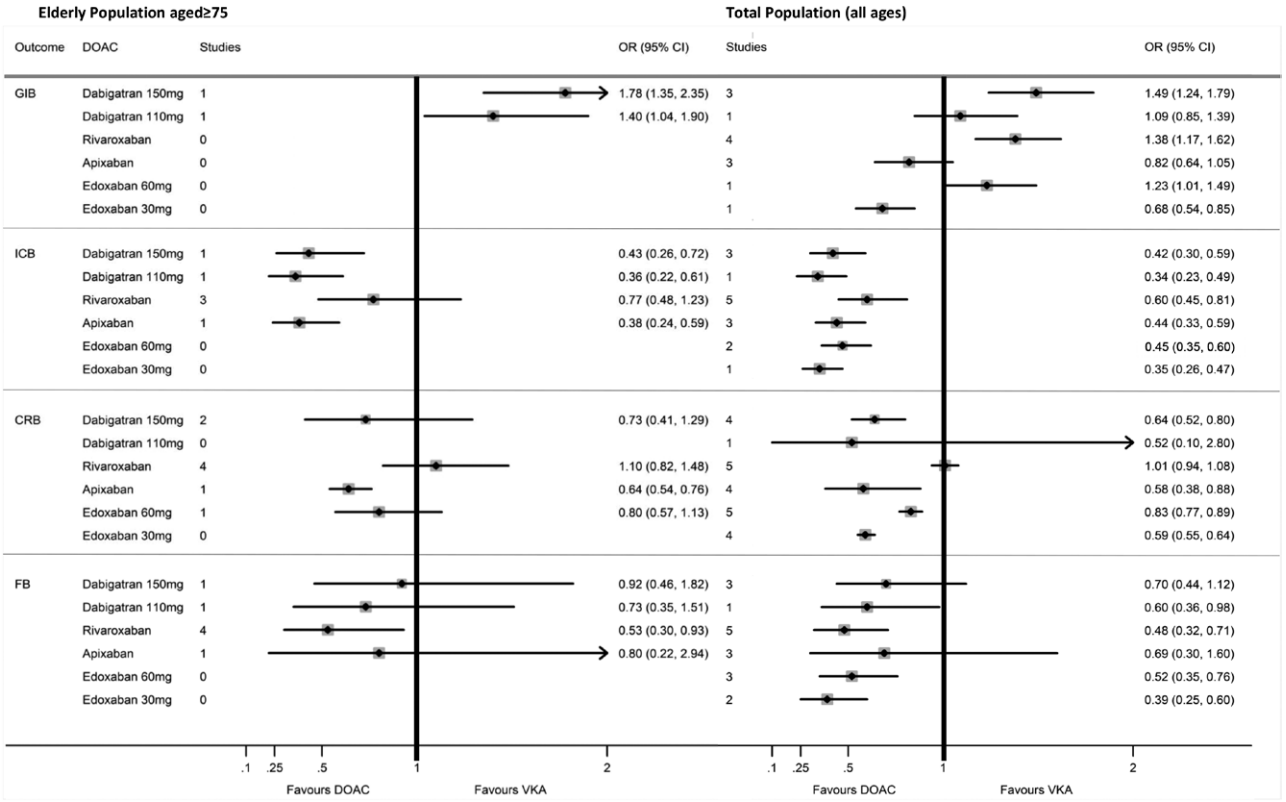

Figure 6. Risk of secondary outcomes in the elderly (**left**) and the total population (**right**). *CRB estimate was only estimate derived by using a random-effects model. **Note: Full Forest plots for each estimate above are available in the online-only Data Supplement. CI indicates confidence interval; 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 $CHADS_2$ 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 $CHADS_2$ 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.

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Disclosures

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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

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Supplemental Material

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:

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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)

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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:

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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)

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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

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

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

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 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	Y	Y	NR
Re-ly, 2009	Y	Y	Y	Y
Recover I, 2010	Y	Y	Y	NR
Recover II, 2013	Y	Y	Y	NR
APIXABAN				
Aristotle, 2011	Y	Y	Y	NR
Aristotle-J, 2011	Y	NR	NR	NR
Botticelli-DVT,2008	Y	NR	NR	NR
Amplify, 2013	Y	Y	Y	Y
RIVAROXABAN				
Rocket-AF, 2011	Y	NR	N	N
J-Rocket AF, 2011	Y	N	Y	NR
Einstein-DVT Dose Study, 2008	Y	Y	Y	Y
Einstein-DVT, 2010	Y	NR	NR	Y
Einstein-PE, 2012	Y	NR	NR	Y
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	N
Hokusai-VTE, 2013	Y	Y	NR	NR

Y=Yes
N=No
NR=Not Reported

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
DABIGATRAN						
Bibr 1048, 2005	110mg BD or 150mg BD	II	Aged≥20, NVAF and $CHADS_2$ of ≥1 or CAD	2-3	3	N
Petro, 2007	150mg BD extracted	II	Aged≥18, NVAF and $CHADS_2$ of ≥1 or CAD	2-3	3	N
Re-ly, 2009	110mg or 150mg BD	III	Aged≥18, NVAF and $CHADS_2$ 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	III	Aged≥18, NVAF and $CHADS_2$ of ≥1	2-3	21.6*	N
Aristotle-J, 2011	5mg BD extracted	II	Aged≥20, NVAF and $CHADS_2$ of ≥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	III	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*	N
J-Rocket AF, 2011	15mg OD	III	Japanese, Aged≥20, NVAF and $CHADS_2$ of ≥2	2-3 and 1.6–2.6 if aged≥70	30	N
Einstein-DVT Dose Study, 2008	20mg OD extracted	II	Aged≥18 and confirmed DVT	2-3	3	N
Einstein-DVT, 2010	15mg BD for 21 days then 20mg OD	III	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	III	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 $CHADS_2$ of ≥2	2-3	3	N
Edox-P2A, 2010	30mg OD and 60mg OD	II	Aged≥20, NVAF and $CHADS_2$ of ≥1	2-3	3	N

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	III	Aged≥21, NVAF and $CHADS_2$ of ≥2	2-3	33.6*	N
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-valvular atrial fibrillation
VTE=Venous Thromboembolism
DVT=Deep-vein thrombosis
PE= Pulmonary Embolism
CAD= Coronary Artery Disease

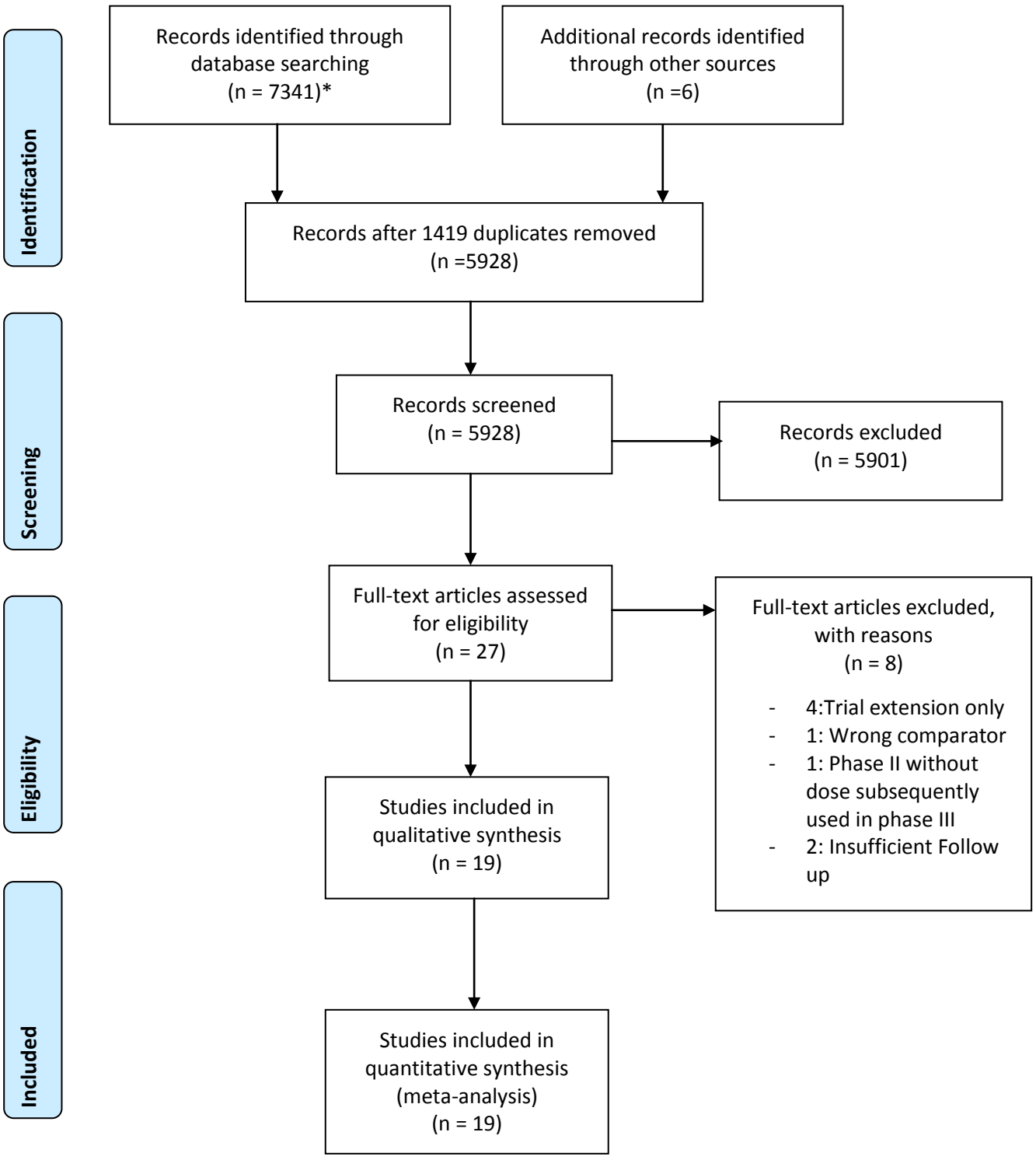


Figure S1. PRISMA Flow Diagram – Study Identification, Selection and Exclusions.

*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.

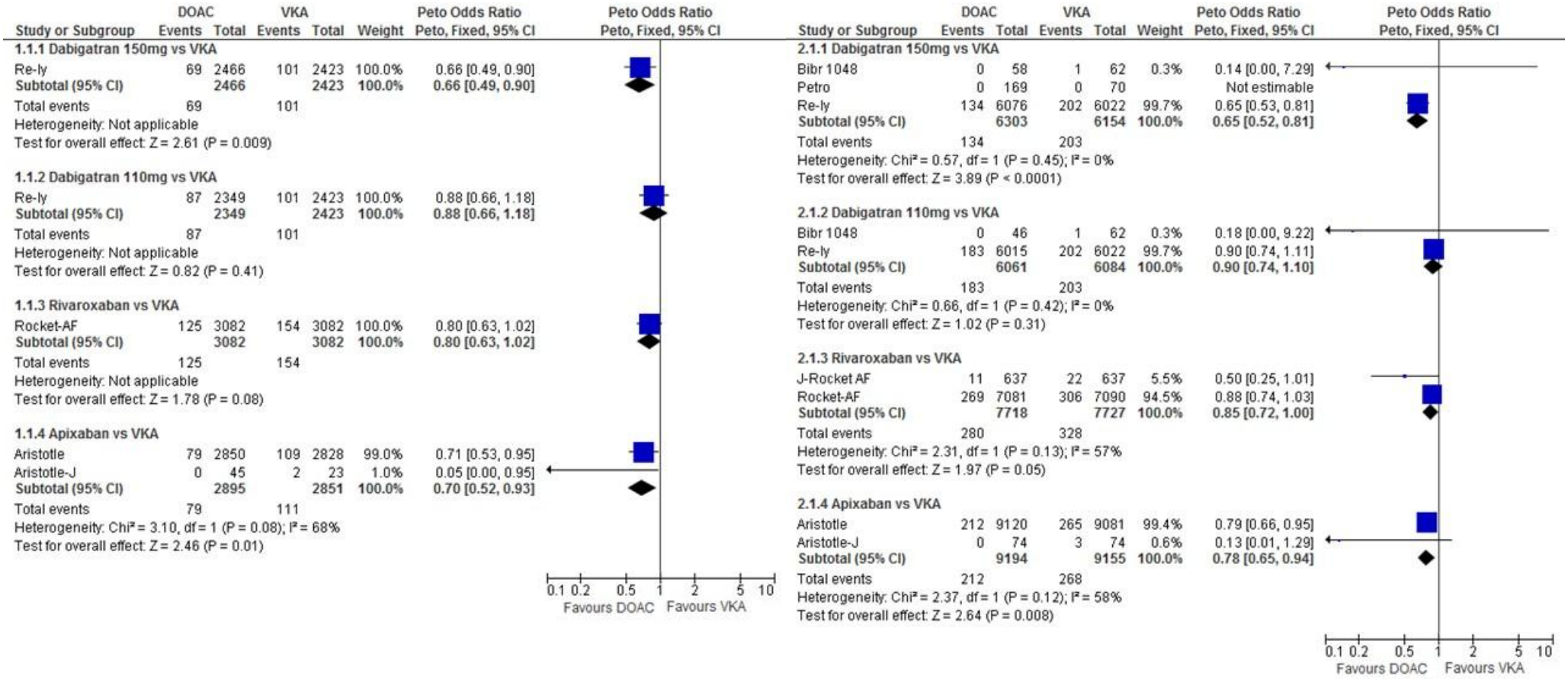


Figure S2. Forest Plots for risk of Stroke or Systemic Embolism in AF in Elderly (left) and Total Population (right).
*Event numbers for Engage-AF-Timi 48 in elderly have been estimated from published confidence intervals.

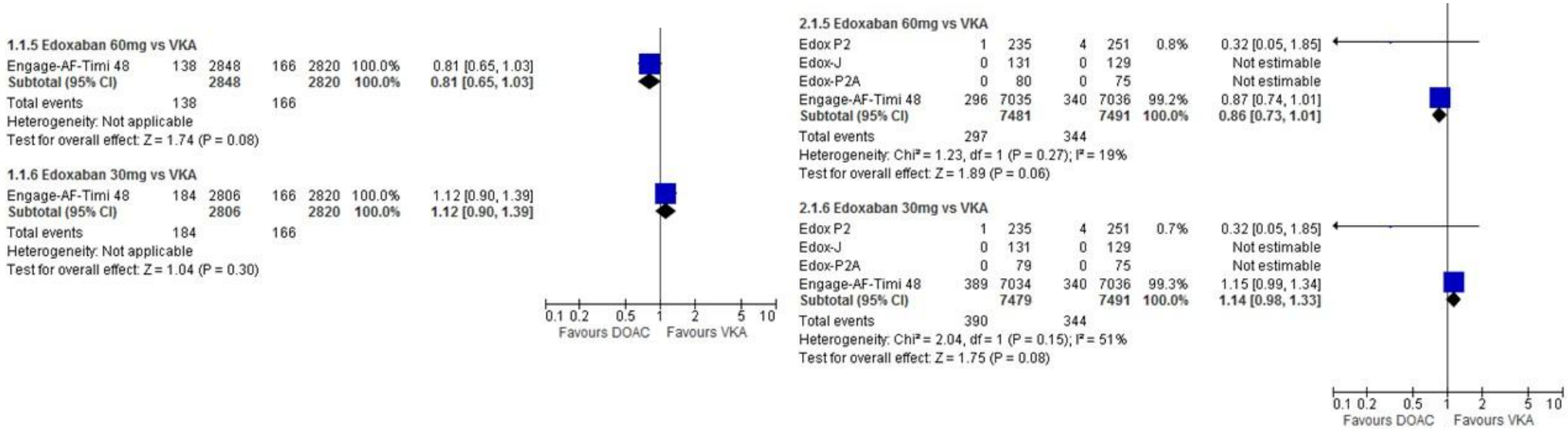


Figure S2. (contd) Forest Plots for risk of Stroke or Systemic Embolism in AF in Elderly (left) and Total Population (right).
*Event numbers for Engage-AF-Timi 48 in elderly have been estimated from published confidence intervals.

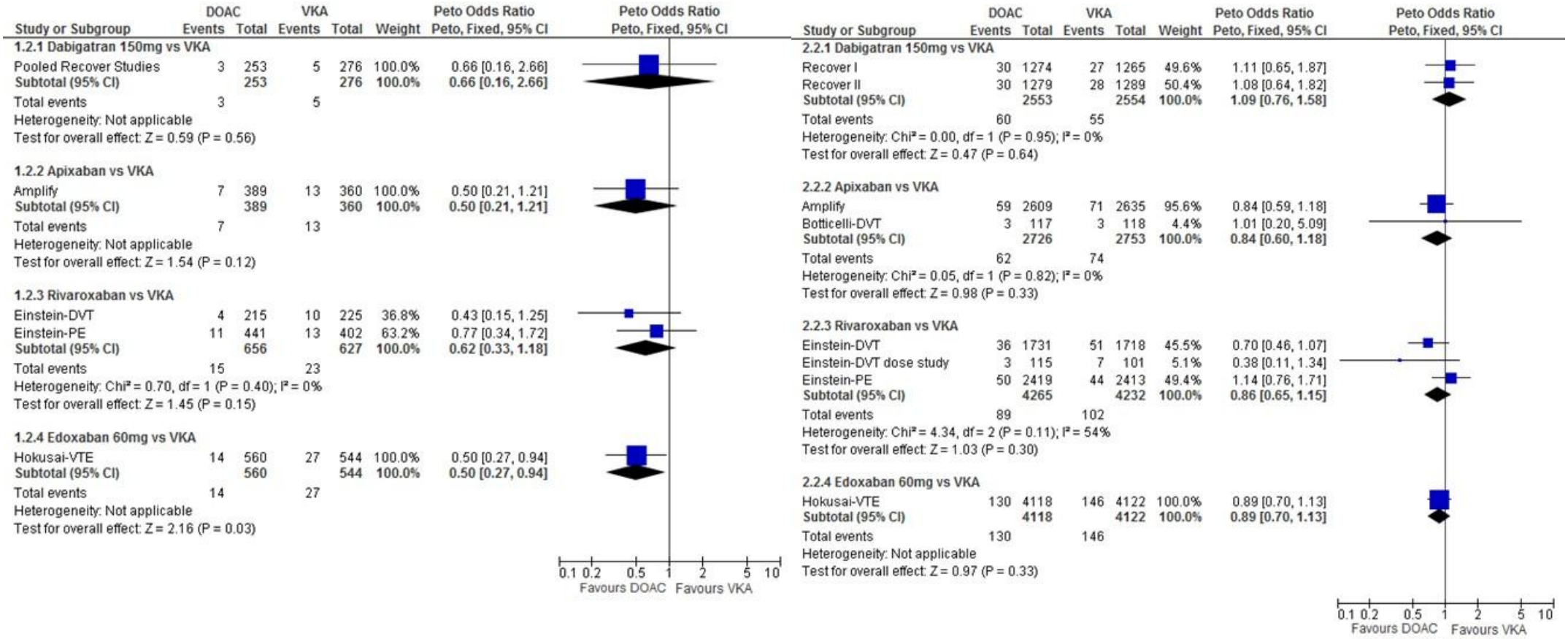


Figure S3. Forest Plots for risk of Recurrent Venous Thromboembolism in VTE in Elderly (left) and Total Population (right).

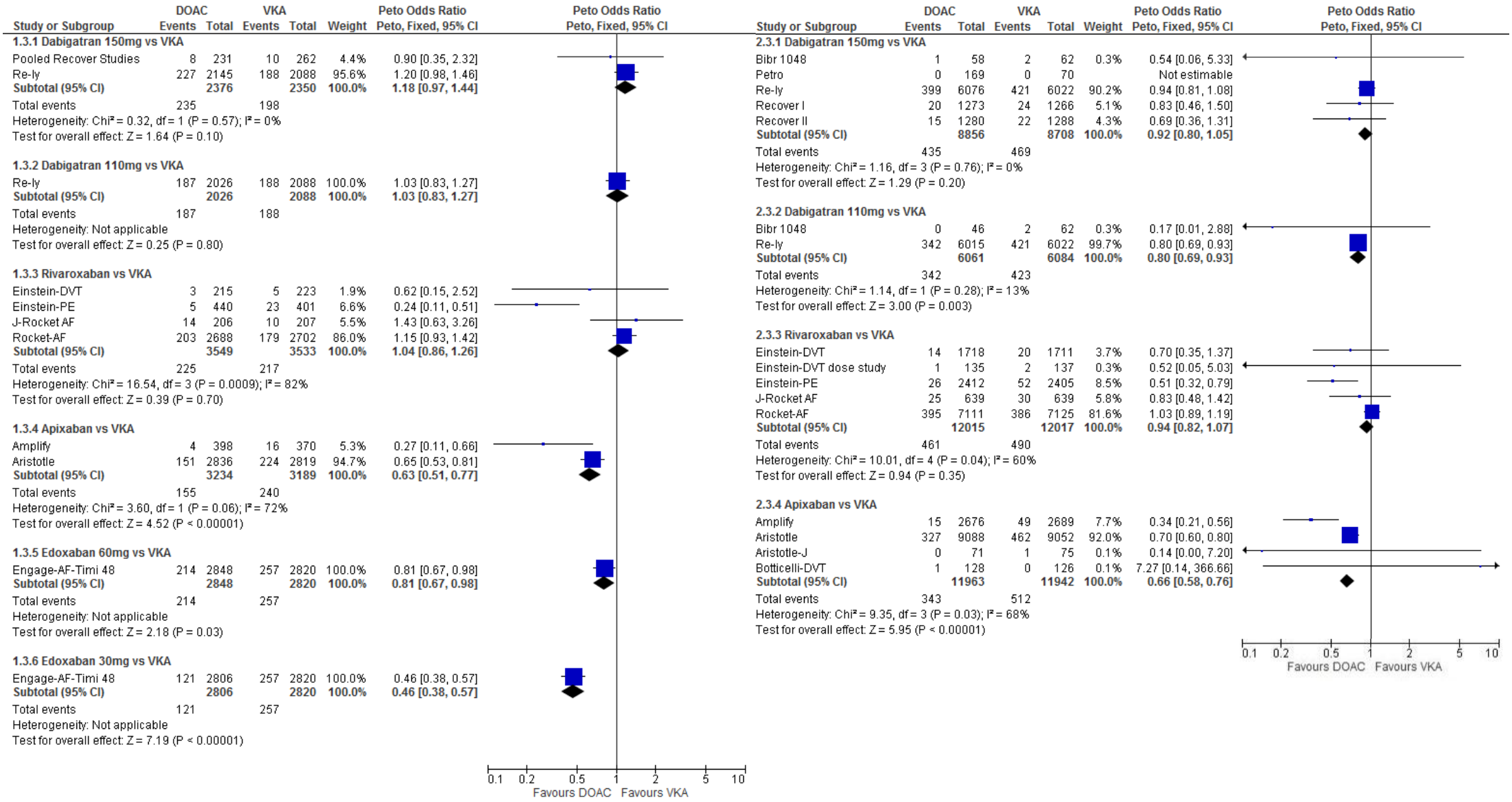


Figure S4. Forest Plots for risk of Major Bleeding in Elderly (left) and Total Population (right).

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

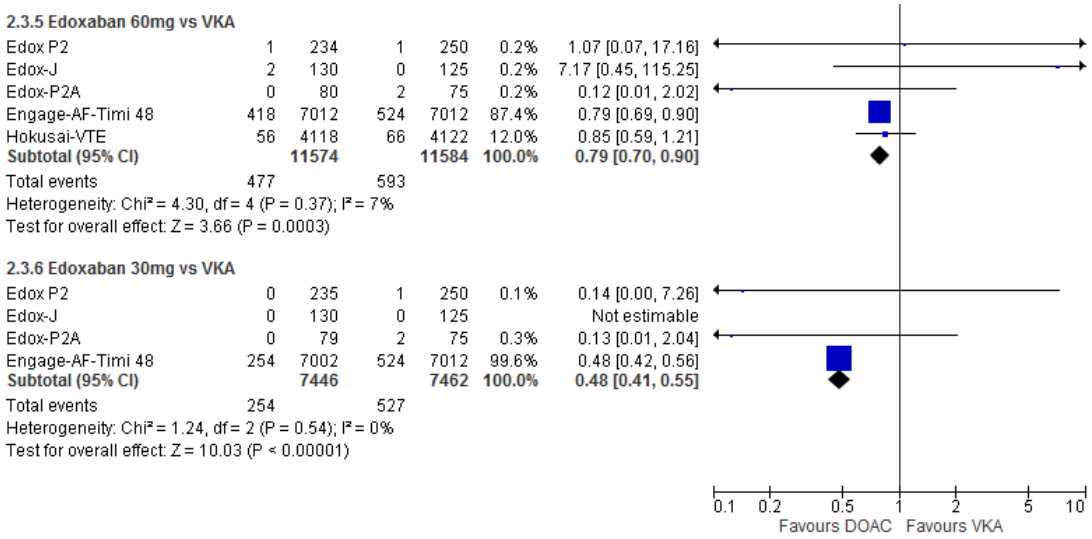


Figure S4. (contd) Forest Plots for risk of Major Bleeding in Total Population (right).

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

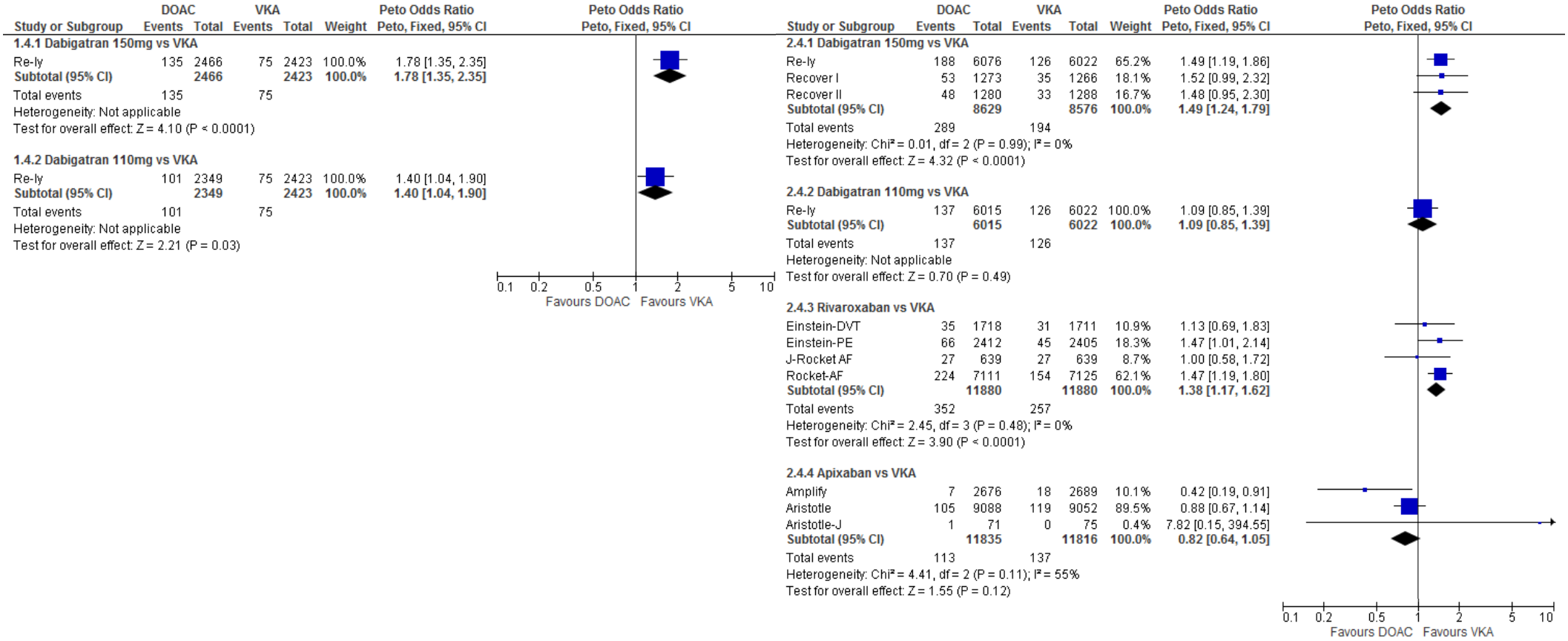


Figure S5. Forest Plots for risk of Gastrointestinal Bleeding in Elderly (left) and Total Population (right).

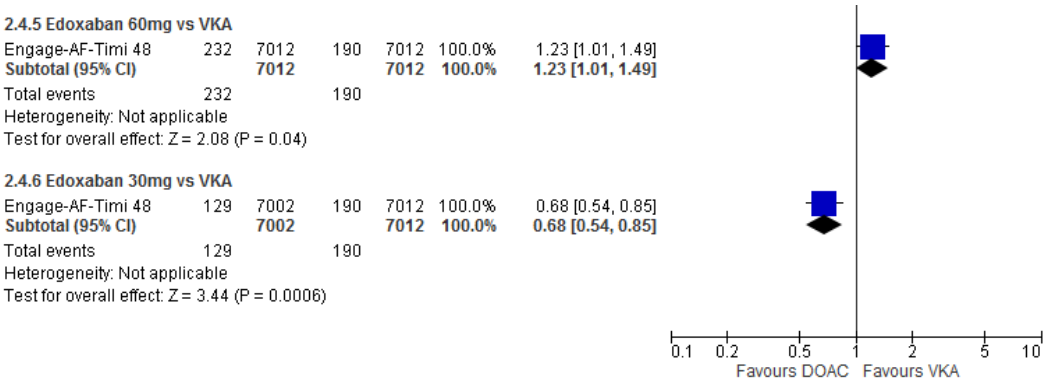


Figure S5. (contd) Forest Plots for risk of Gastrointestinal Bleeding in Total Population (right).

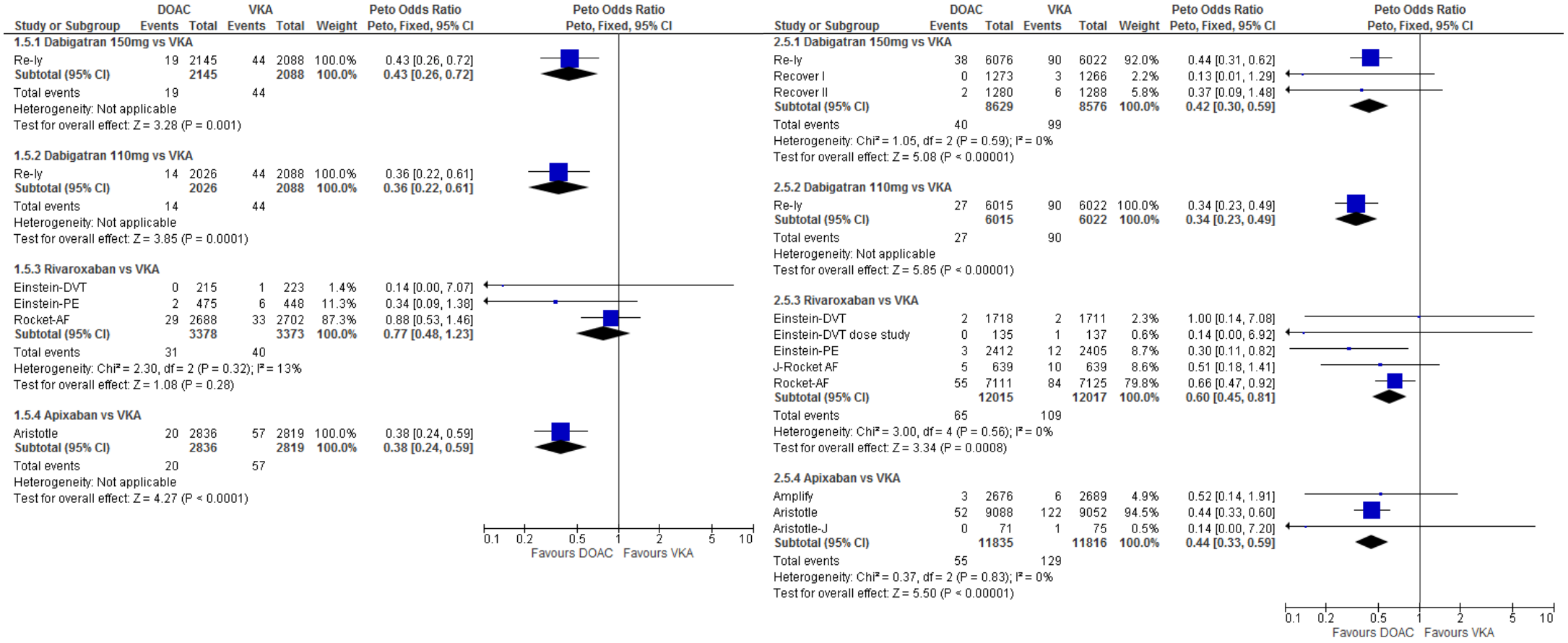


Figure S6. Forest Plots for risk of Intracranial Bleeding in in Elderly (left) and Total Population (right).

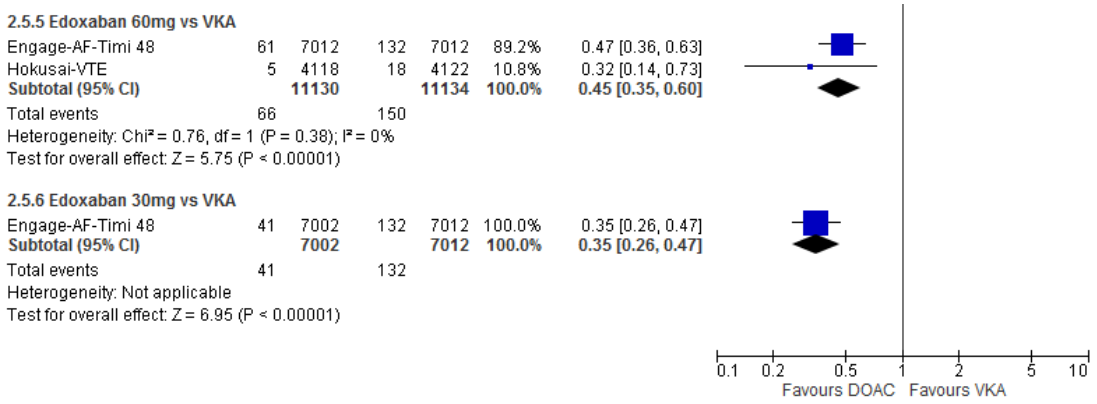


Figure S6. (contd) Forest Plots for risk of Intracranial Bleeding in Total Population (right).

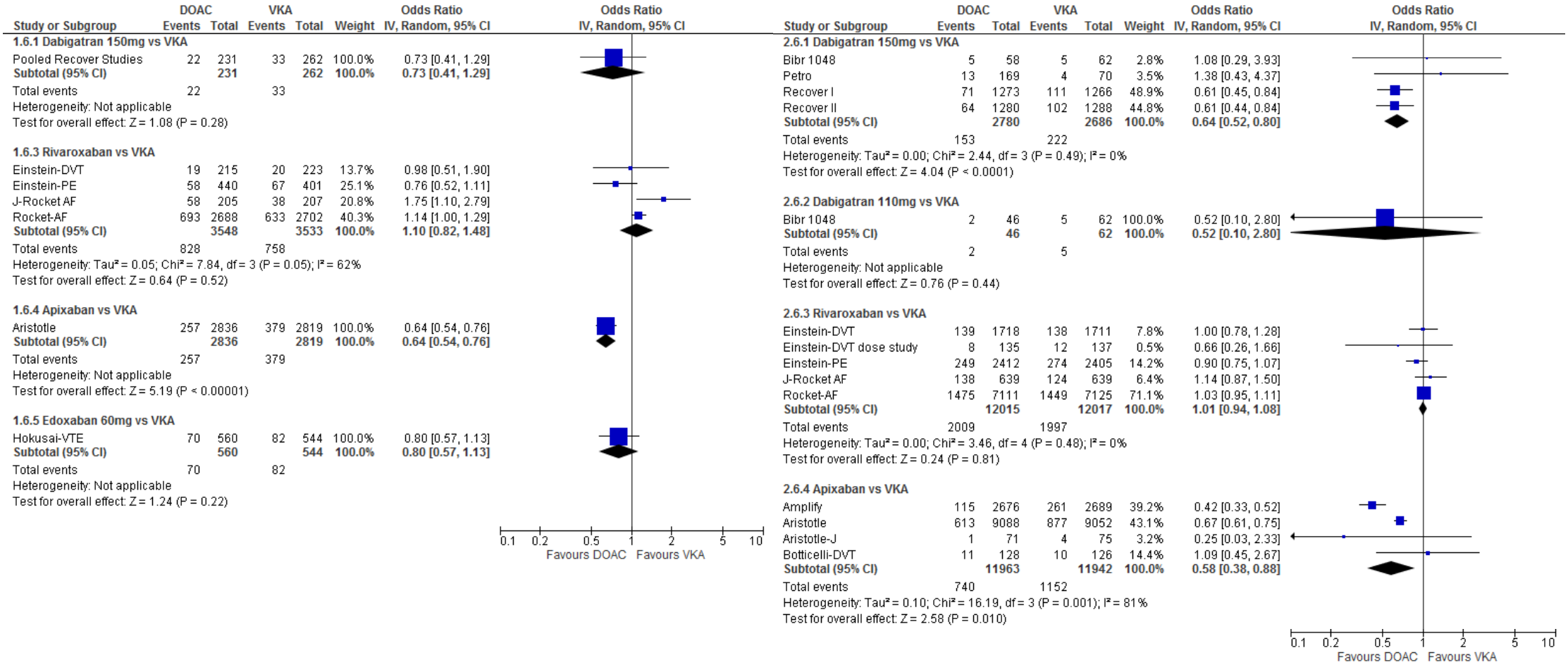


Figure S7. Forest Plots for risk of Clinically Relevant Bleeding in Elderly (left) and Total Population (right) - Random Effects Model

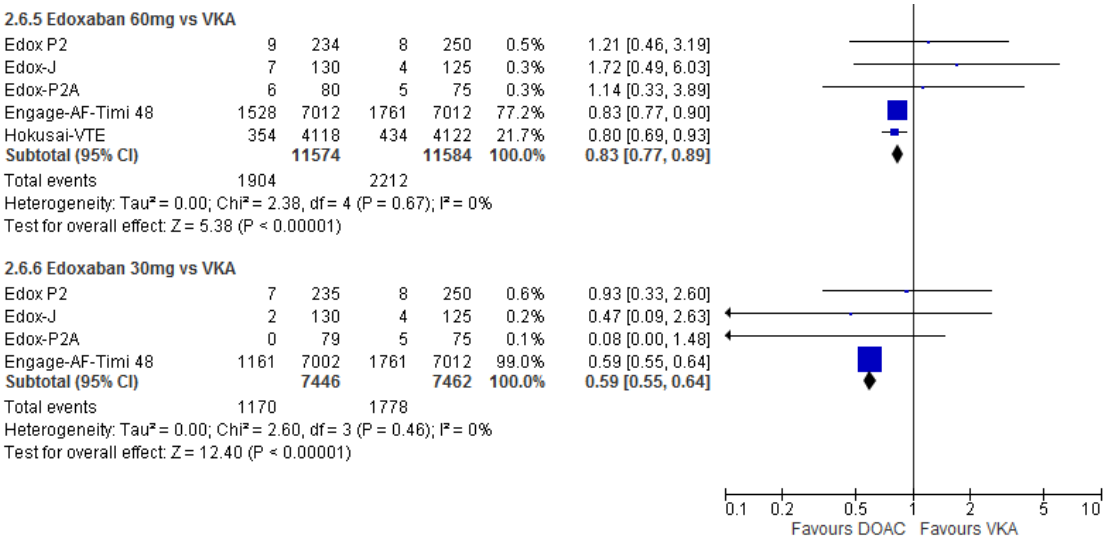
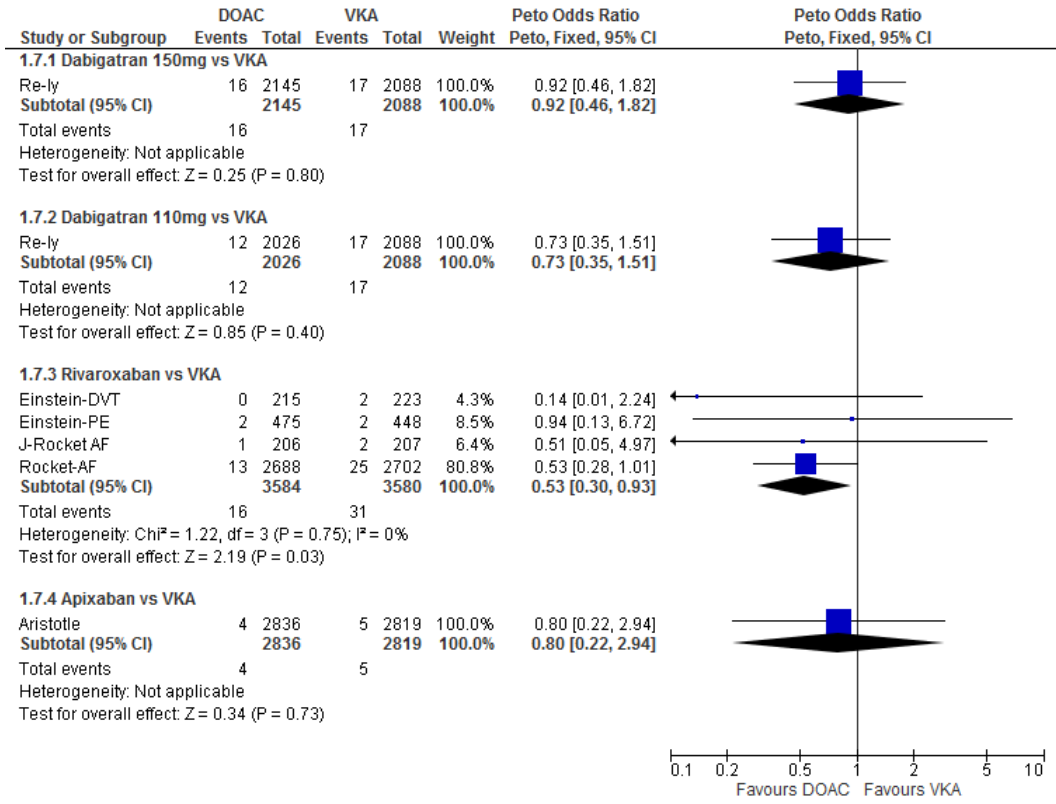


Figure S7. (contd) Forest Plots for risk of Clinically Relevant Bleeding in Total Population (right)- Random Effects Model



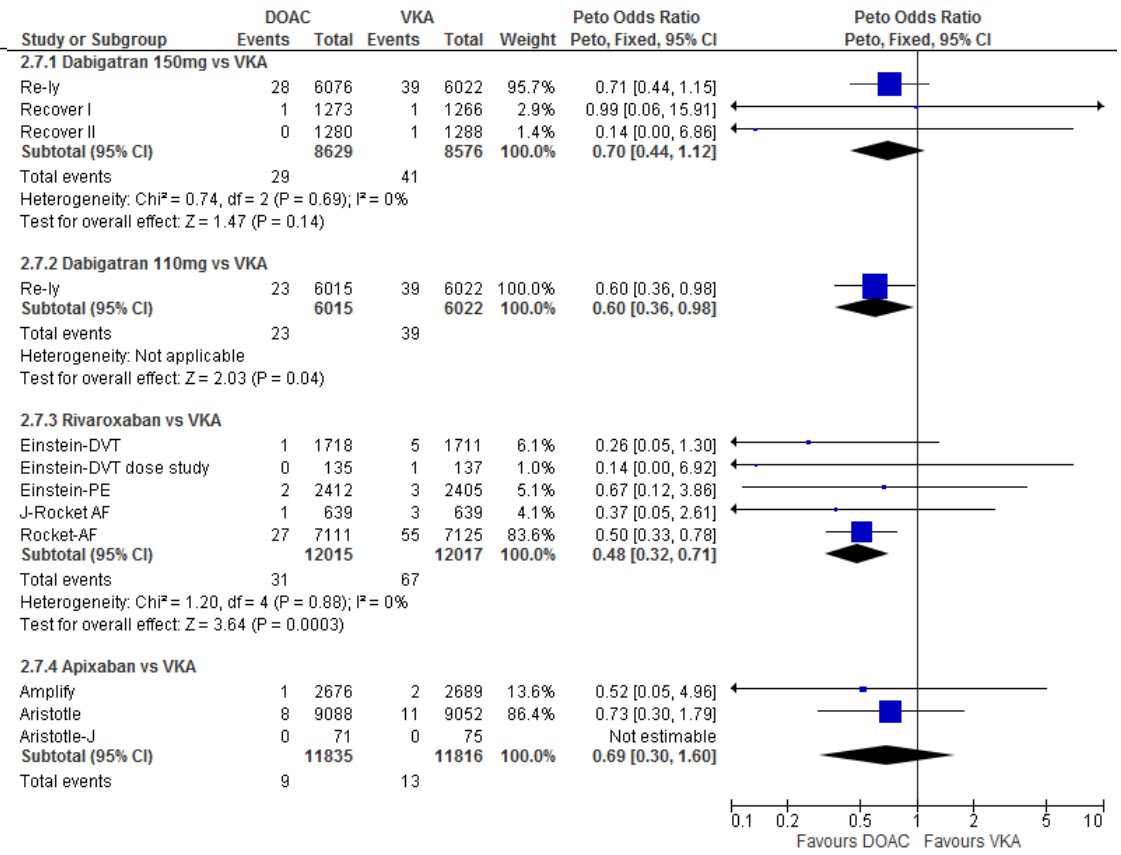


Figure S8. Forest Plots for risk of Fatal Bleeding in Elderly (left) and Total Population (right).

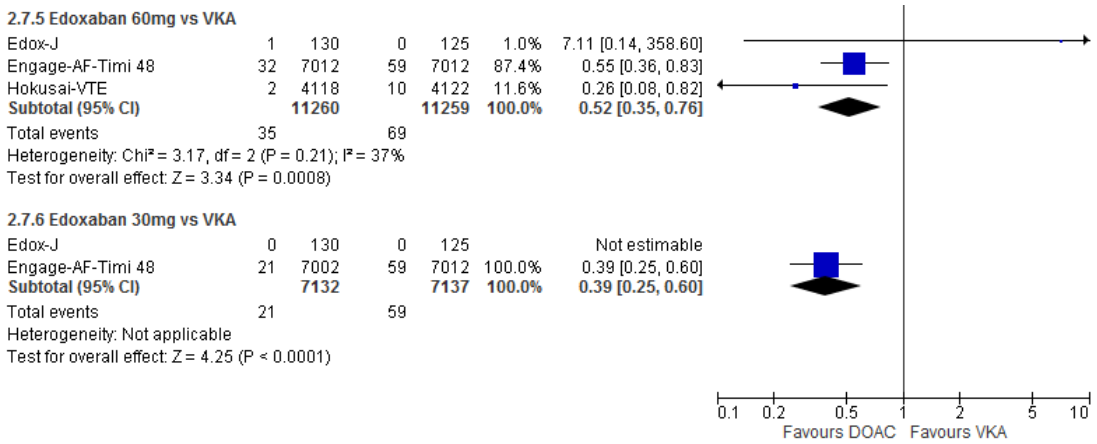


Figure S8. (contd) Forest Plots for risk of Fatal Bleeding in Elderly (left) and Total Population (right).

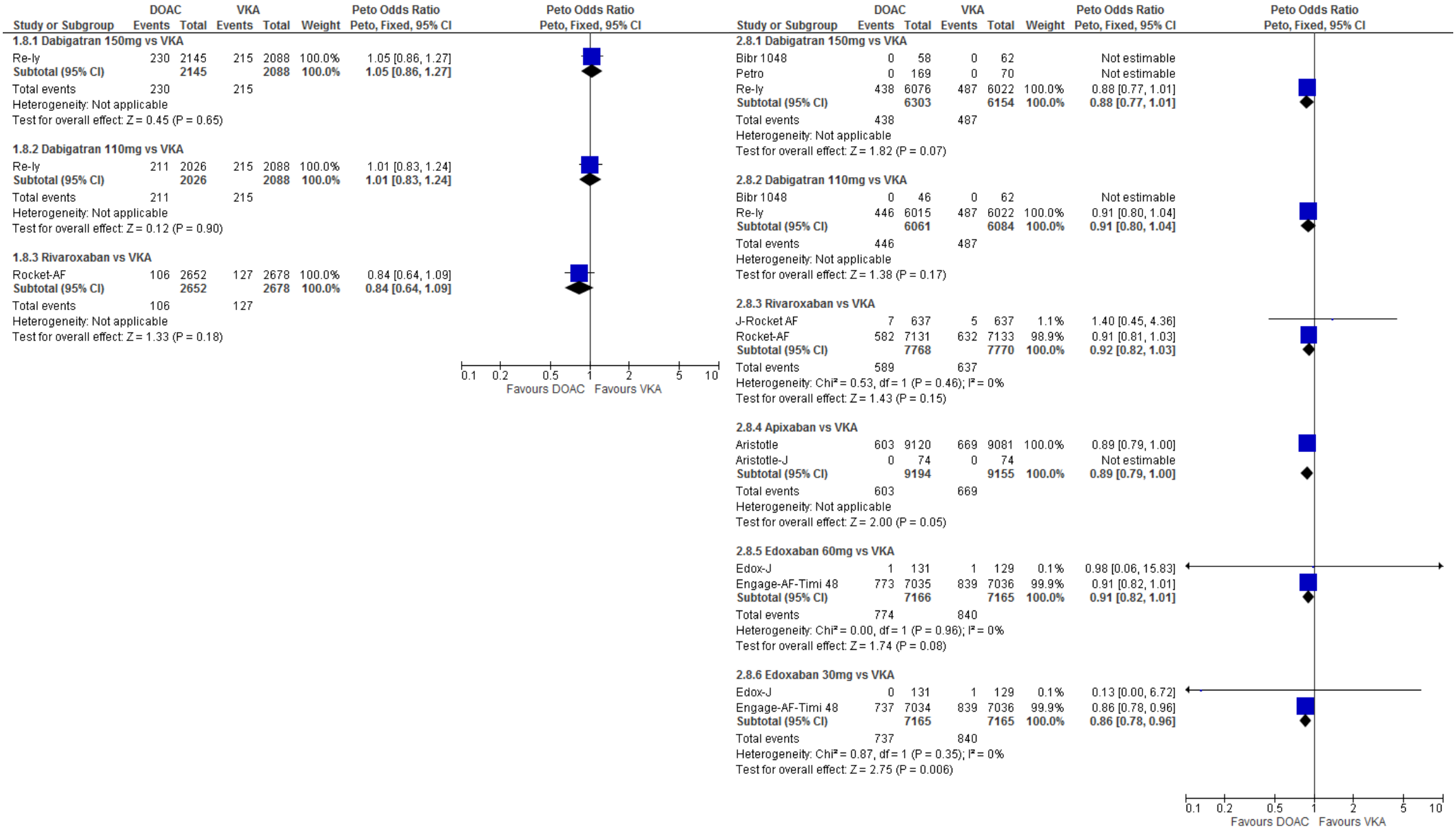


Figure S9. Forest Plots for risk of All Cause Death in Atrial Fibrillation in Elderly (left) and Total Population (right).

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

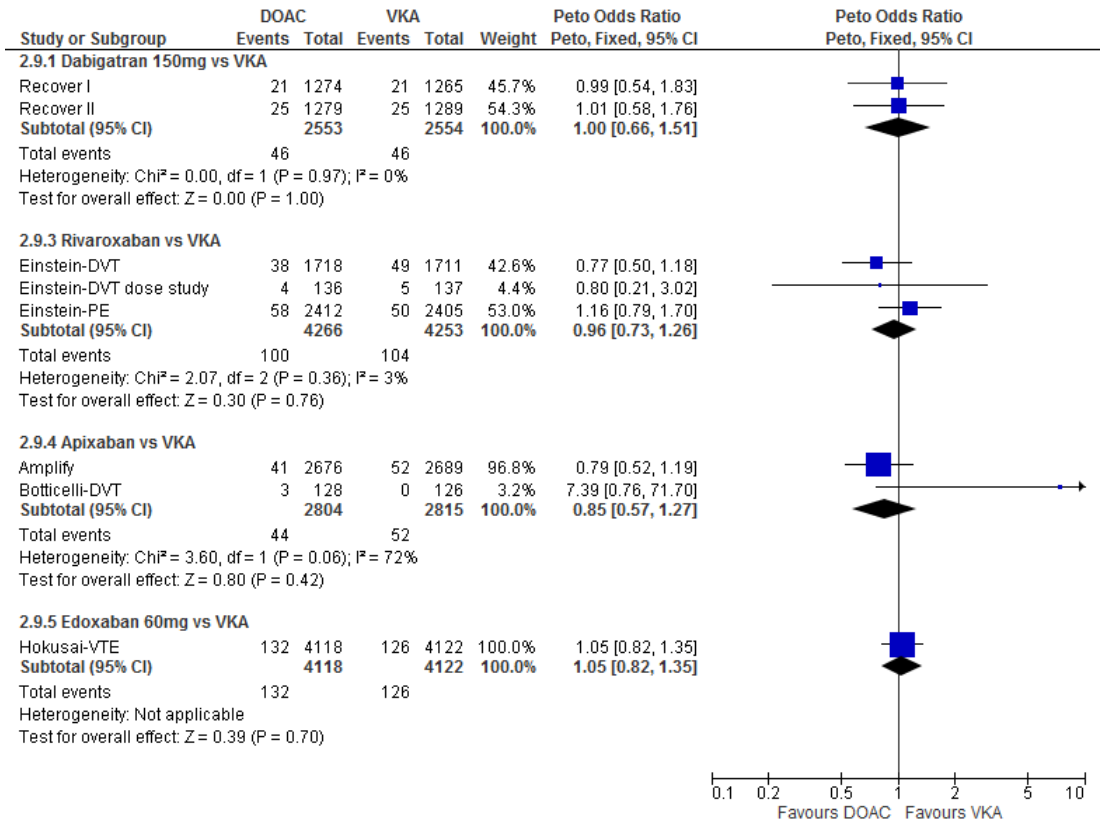


Figure S10. Forest Plots for risk of All Cause Death in Venous thromboembolism in Total Population (right).
*No results available for the elderly for this outcome

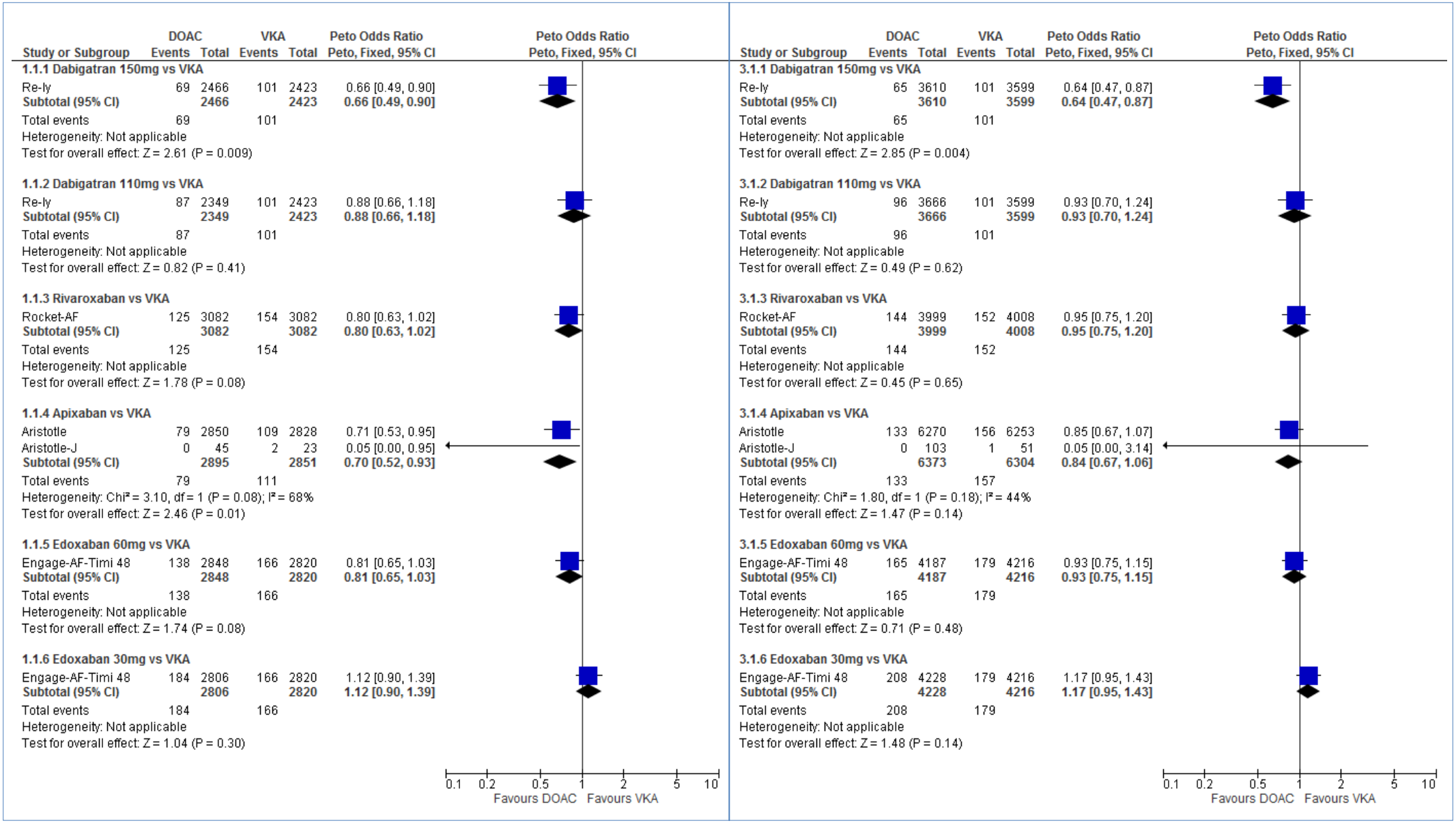


Figure S11. Forest Plots for risk of Stroke or Systemic Embolism in AF in Elderly (left) and <75 Population (right).

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

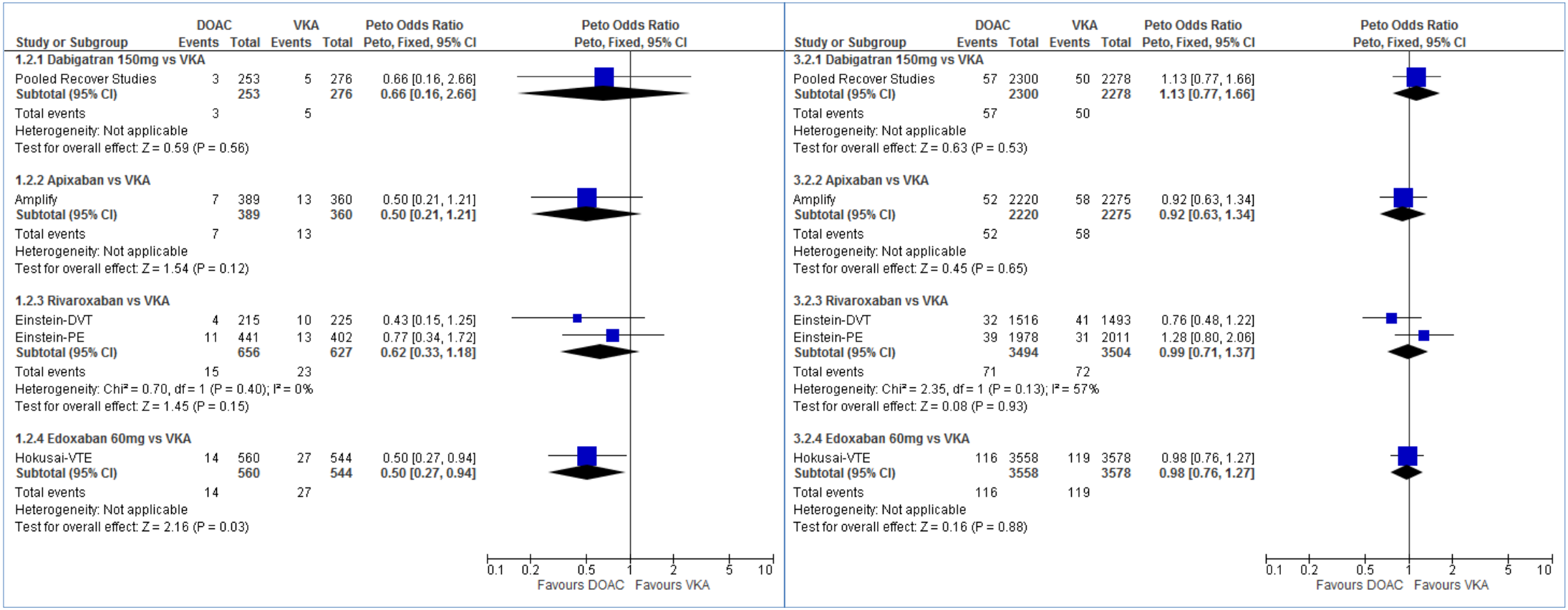


Figure S12. Forest Plots for risk of Venous Thromboembolism in VTE in Elderly (left) and <75 Population (right).

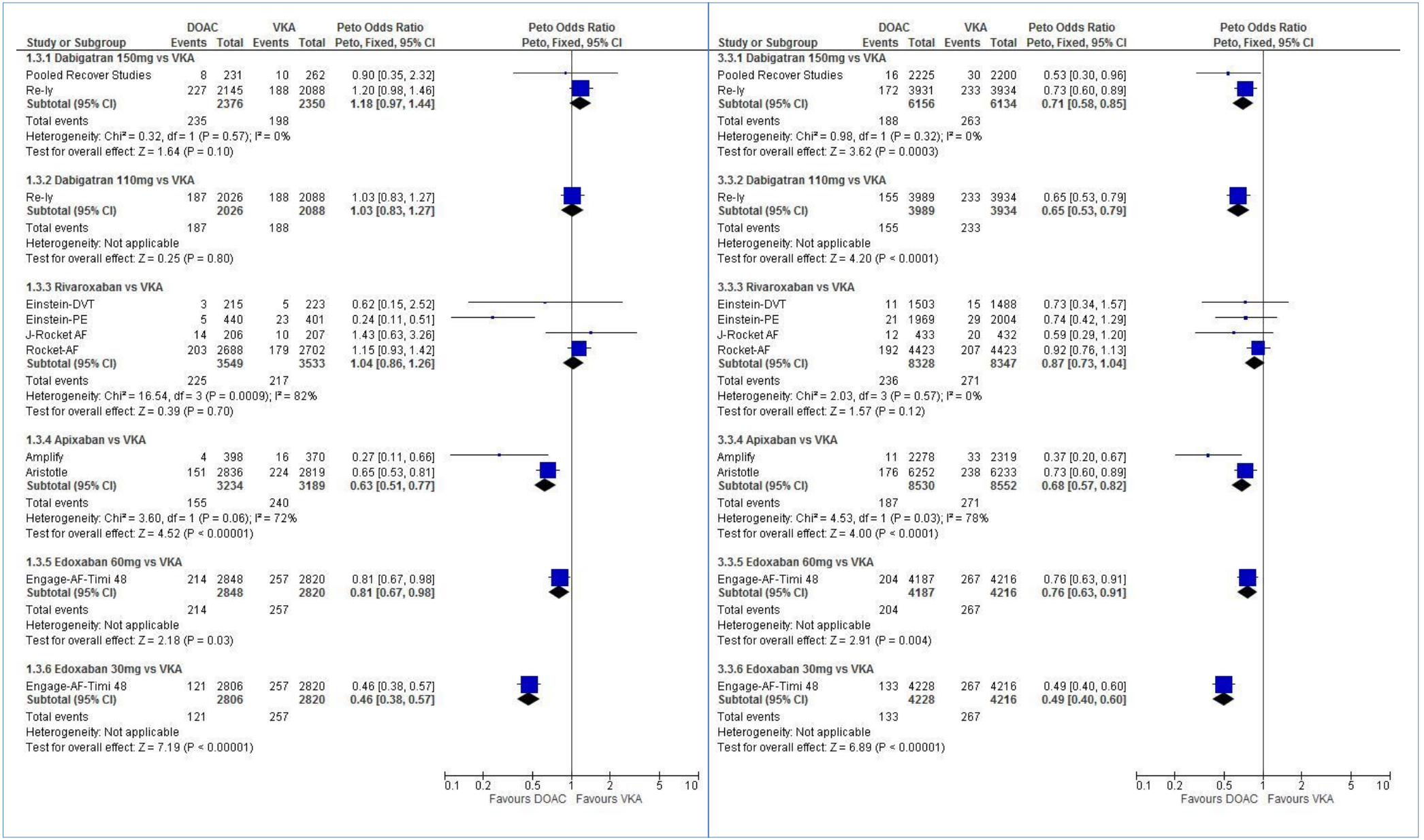


Figure S13. Forest Plots for risk of Major Bleeding in Elderly (left) and <75 Population (right).

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

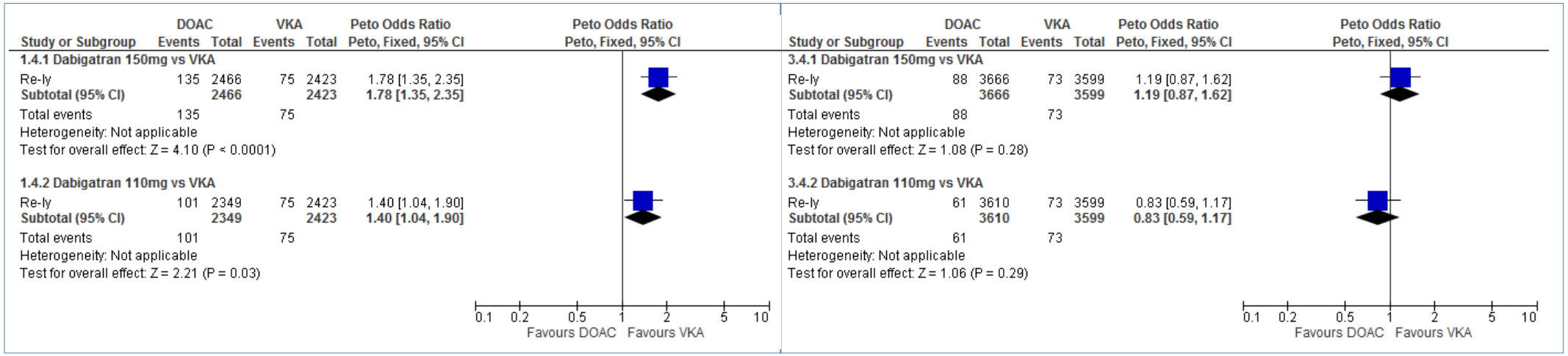


Figure S14. Forest Plots for risk of Gastrointestinal Bleeding in Elderly (left) and <75 Population (right).

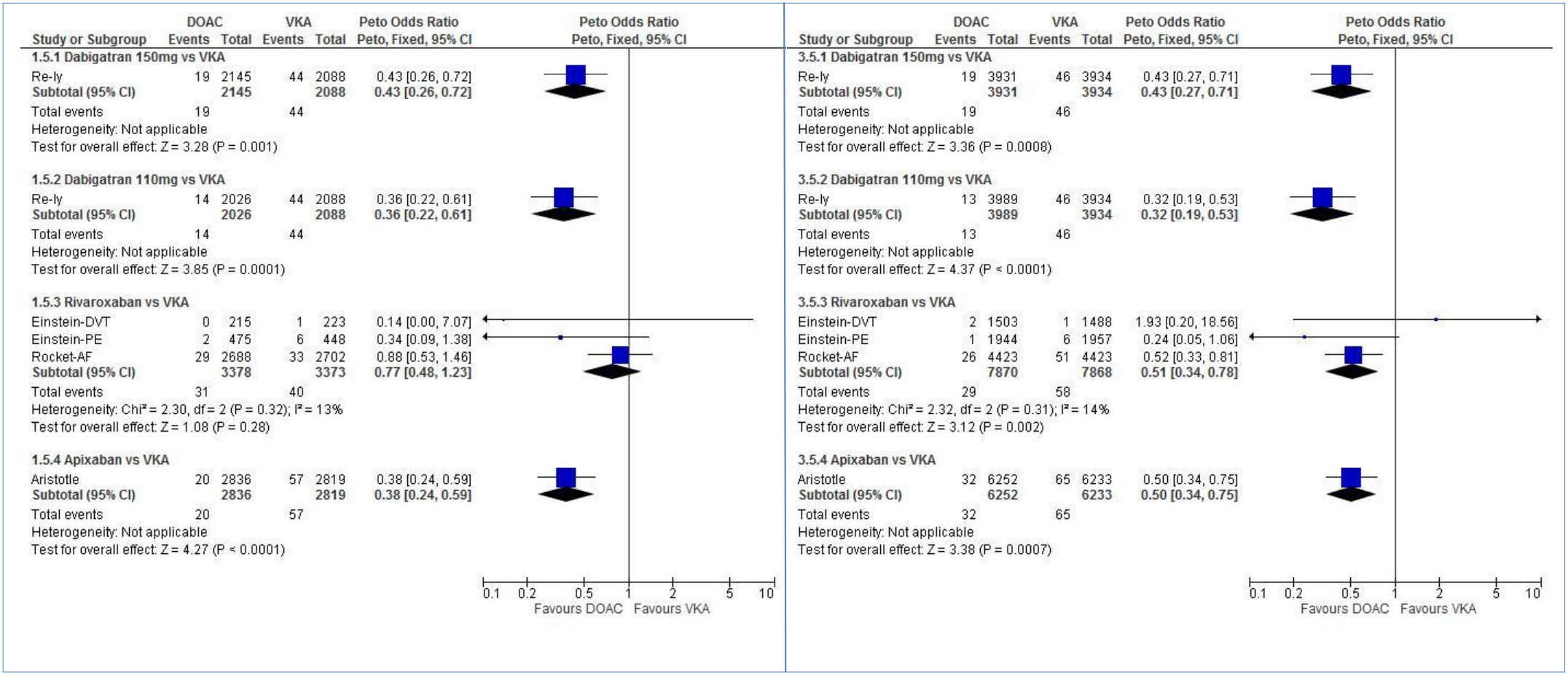


Figure S15. Forest Plots for risk of Intracranial Bleeding in Elderly (left) and <75 Population (right).

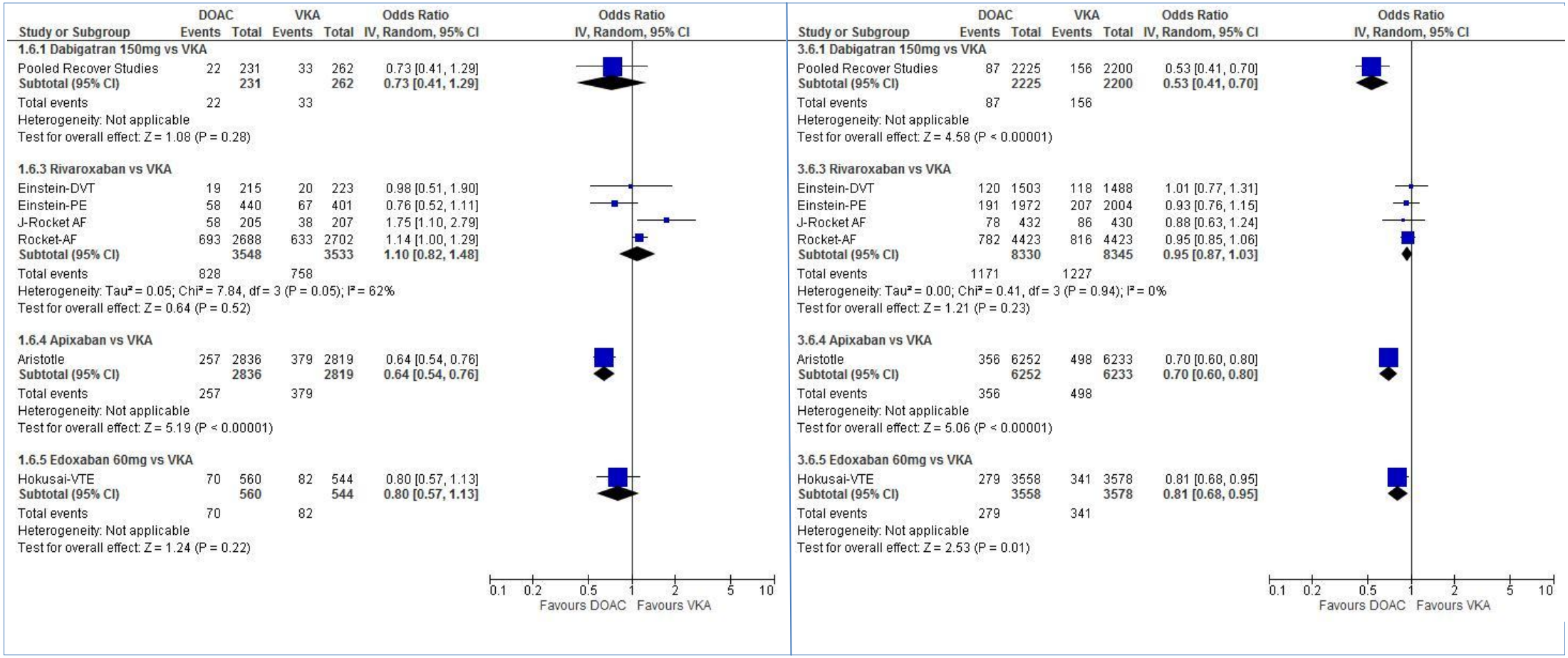


Figure S16. Forest Plots for risk of Clinically Relevant Bleeding in Elderly (left) and <75 Population (right) - Random Effects Model.

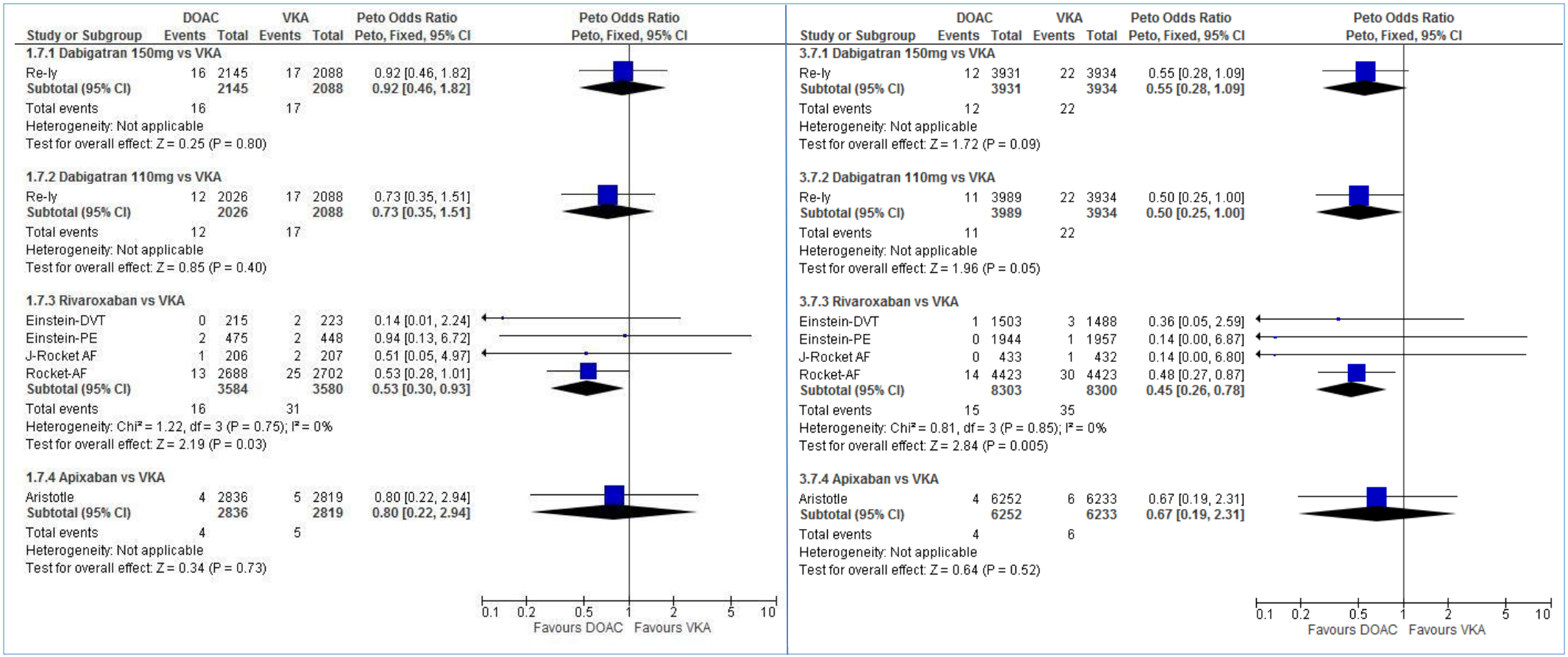


Figure S17. Forest Plots for risk of Fatal Bleeding in Elderly (left) and <75 Population (right).

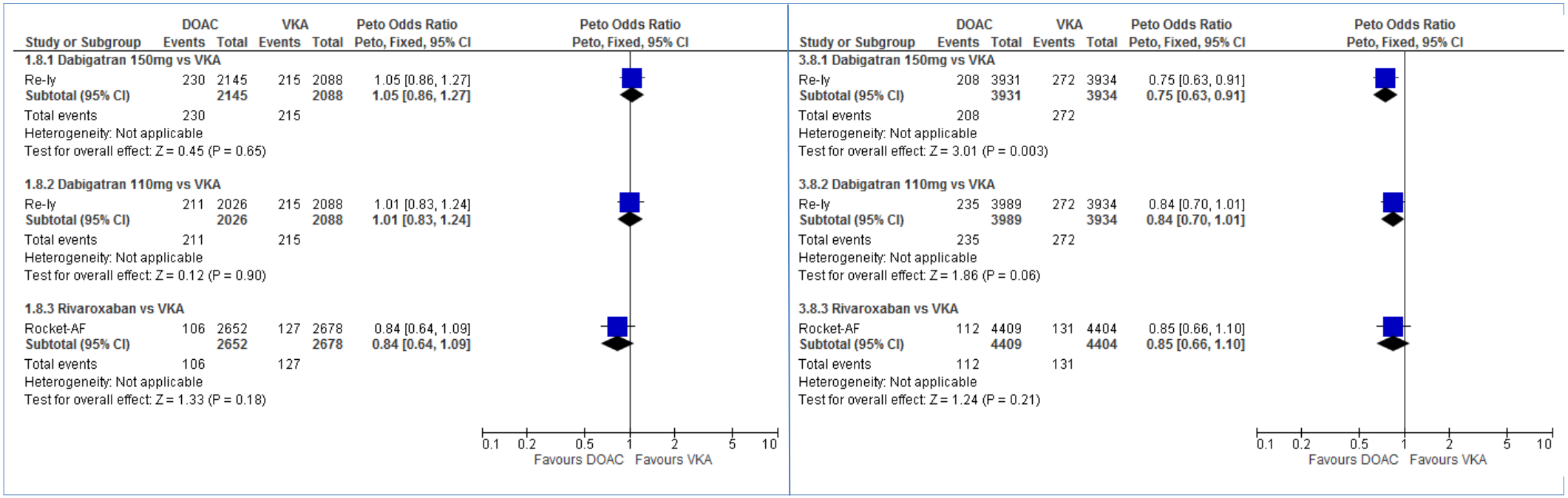


Figure S18. Forest Plots for risk of All Cause Death in AF in Elderly (left) and <75 Population (right).
*Event numbers for Rocket-AF in elderly have been estimated from published confidence intervals.

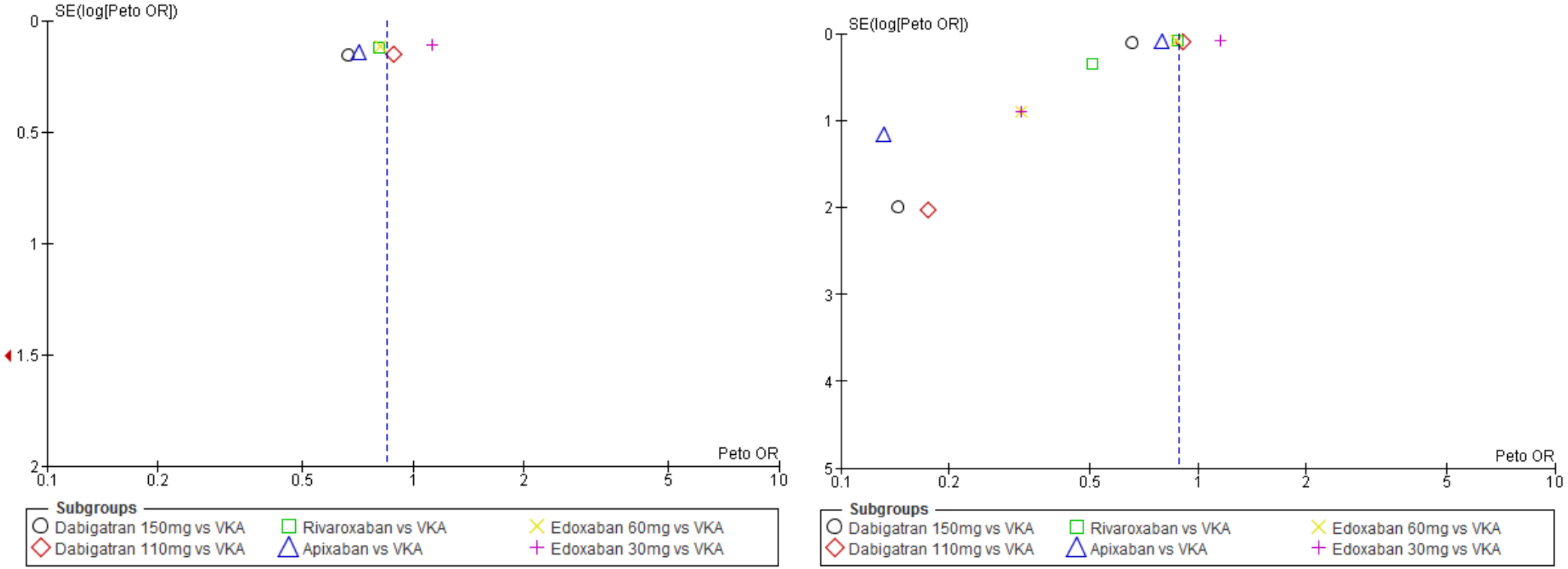


Figure S19. Funnel Plots for Stroke or Systemic Embolism in AF in Elderly (left) and Total population (right).

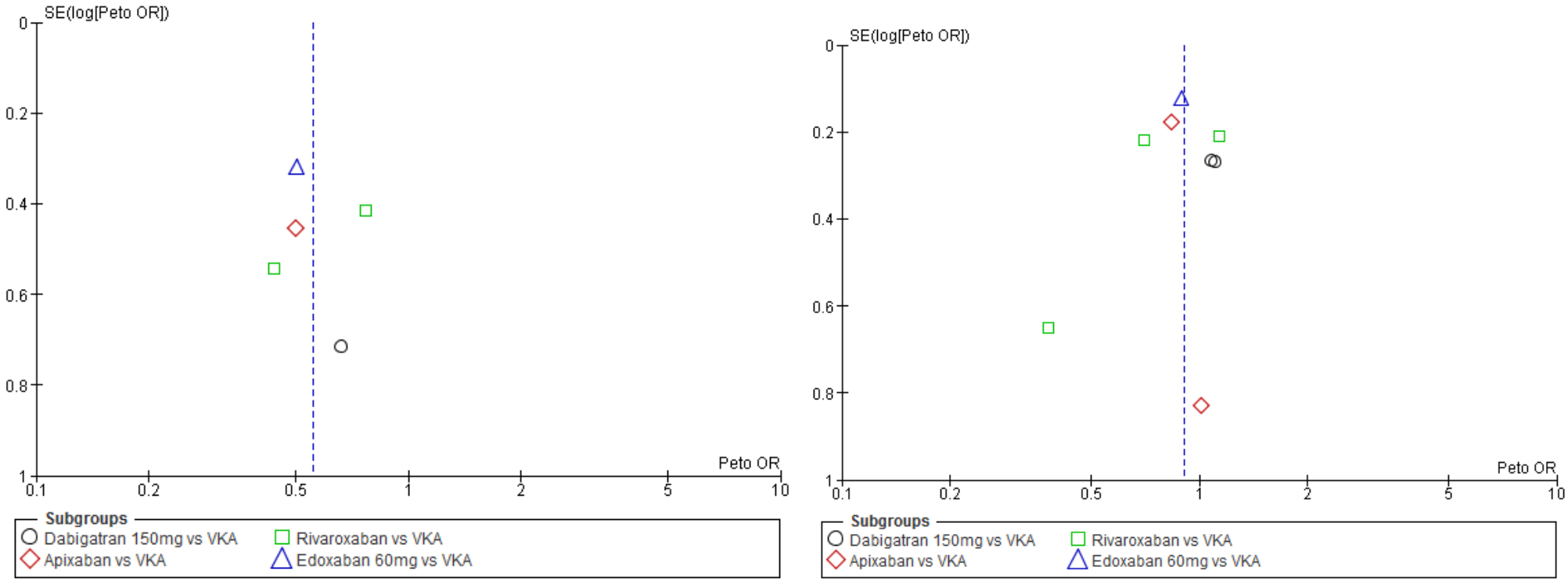


Figure S20. Funnel Plots for risk of Recurrent Venous Thromboembolism in VTE in Elderly (left) and Total population (right).

Supplemental References

1. Connolly SJ, Wallentin L, Ezekowitz MD, Eikelboom J, Oldgren J, Reilly PA, Brueckmann M, Pogue J, Alings M, Amerena JV, Avezum A, Baumgartner I, Budaj AJ, Chen JH, Dans AL, Darius H, Di Pasquale G, Ferreira J, Flaker GC, Flather MD, Franzosi MG, Golitsyn SP, Halon DA, Heidbuchel H, Hohnloser SH, Huber K, Jansky P, Kamensky G, Keltai M, Kim SS, Lau CP, Le Heuzey JY, Lewis BS, Liu L, Nanas J, Omar R, Pais P, Pedersen KE, Piegas LS, Raev D, Smith PJ, Talajic M, Tan RS, Tanomsup S, Toivonen L, Vinereanu D, Xavier D, Zhu J, Wang SQ, Duffy CO, Themeles E, Yusuf S. The Long-Term Multicenter Observational Study of Dabigatran Treatment in Patients With Atrial Fibrillation (RELY-ABLE) Study. *Circulation*. 2013;128:237-43.
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4. Agnelli G, Gallus A, Goldhaber SZ, Haas S, Huisman MV, Hull RD, Kakkar AK, Misselwitz F, Schellong S. Treatment of proximal deep-vein thrombosis with the oral direct factor Xa inhibitor rivaroxaban (BAY 59-7939): the ODIXa-DVT (Oral Direct Factor Xa Inhibitor BAY 59-7939 in Patients With Acute Symptomatic Deep-Vein Thrombosis) study. *Circulation*. 2007;116:180-7.
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6. [Bayer]. BAY59-7939 Japanese in Atrial Fibrillation NCT00973323. http://www.clinicaltrials.gov/ct2/show/NCT00973323. Accessed June 4, 2014.
7. Diener HC, Eikelboom J, Connolly SJ, Joyner CD, Hart RG, Lip GY, O'Donnell M, Hohnloser SH, Hankey GJ, Shestakovska O, Yusuf S. Apixaban versus aspirin in patients with atrial fibrillation and previous stroke or transient ischaemic attack: a predefined subgroup analysis from AVERROES, a randomised trial. *Lancet Neurol*. 2012;11:225-31.
8. Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, Porcari A, Raskob GE, Weitz JI. Apixaban for Extended Treatment of Venous Thromboembolism. *N Eng J Med*. 2013;368:699-708.

Supplemental Material

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:

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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)

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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:

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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)

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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

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

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

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 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	Y	Y	NR
Re-ly, 2009	Y	Y	Y	Y
Recover I, 2010	Y	Y	Y	NR
Recover II, 2013	Y	Y	Y	NR
APIXABAN				
Aristotle, 2011	Y	Y	Y	NR
Aristotle-J, 2011	Y	NR	NR	NR
Botticelli-DVT,2008	Y	NR	NR	NR
Amplify, 2013	Y	Y	Y	Y
RIVAROXABAN				
Rocket-AF, 2011	Y	NR	N	N
J-Rocket AF, 2011	Y	N	Y	NR
Einstein-DVT Dose Study, 2008	Y	Y	Y	Y
Einstein-DVT, 2010	Y	NR	NR	Y
Einstein-PE, 2012	Y	NR	NR	Y
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	N
Hokusai-VTE, 2013	Y	Y	NR	NR

Y=Yes
N=No
NR=Not Reported

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
DABIGATRAN						
Bibr 1048, 2005	110mg BD or 150mg BD	II	Aged≥20, NVAF and $CHADS_2$ of ≥1 or CAD	2-3	3	N
Petro, 2007	150mg BD extracted	II	Aged≥18, NVAF and $CHADS_2$ of ≥1 or CAD	2-3	3	N
Re-ly, 2009	110mg or 150mg BD	III	Aged≥18, NVAF and $CHADS_2$ 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	III	Aged≥18, NVAF and $CHADS_2$ of ≥1	2-3	21.6*	N
Aristotle-J, 2011	5mg BD extracted	II	Aged≥20, NVAF and $CHADS_2$ of ≥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	III	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*	N
J-Rocket AF, 2011	15mg OD	III	Japanese, Aged≥20, NVAF and $CHADS_2$ of ≥2	2-3 and 1.6–2.6 if aged≥70	30	N
Einstein-DVT Dose Study, 2008	20mg OD extracted	II	Aged≥18 and confirmed DVT	2-3	3	N
Einstein-DVT, 2010	15mg BD for 21 days then 20mg OD	III	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	III	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 $CHADS_2$ of ≥2	2-3	3	N
Edox-P2A, 2010	30mg OD and 60mg OD	II	Aged≥20, NVAF and $CHADS_2$ of ≥1	2-3	3	N

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	III	Aged≥21, NVAF and $CHADS_2$ of ≥2	2-3	33.6*	N
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-valvular atrial fibrillation
VTE=Venous Thromboembolism
DVT=Deep-vein thrombosis
PE= Pulmonary Embolism
CAD= Coronary Artery Disease

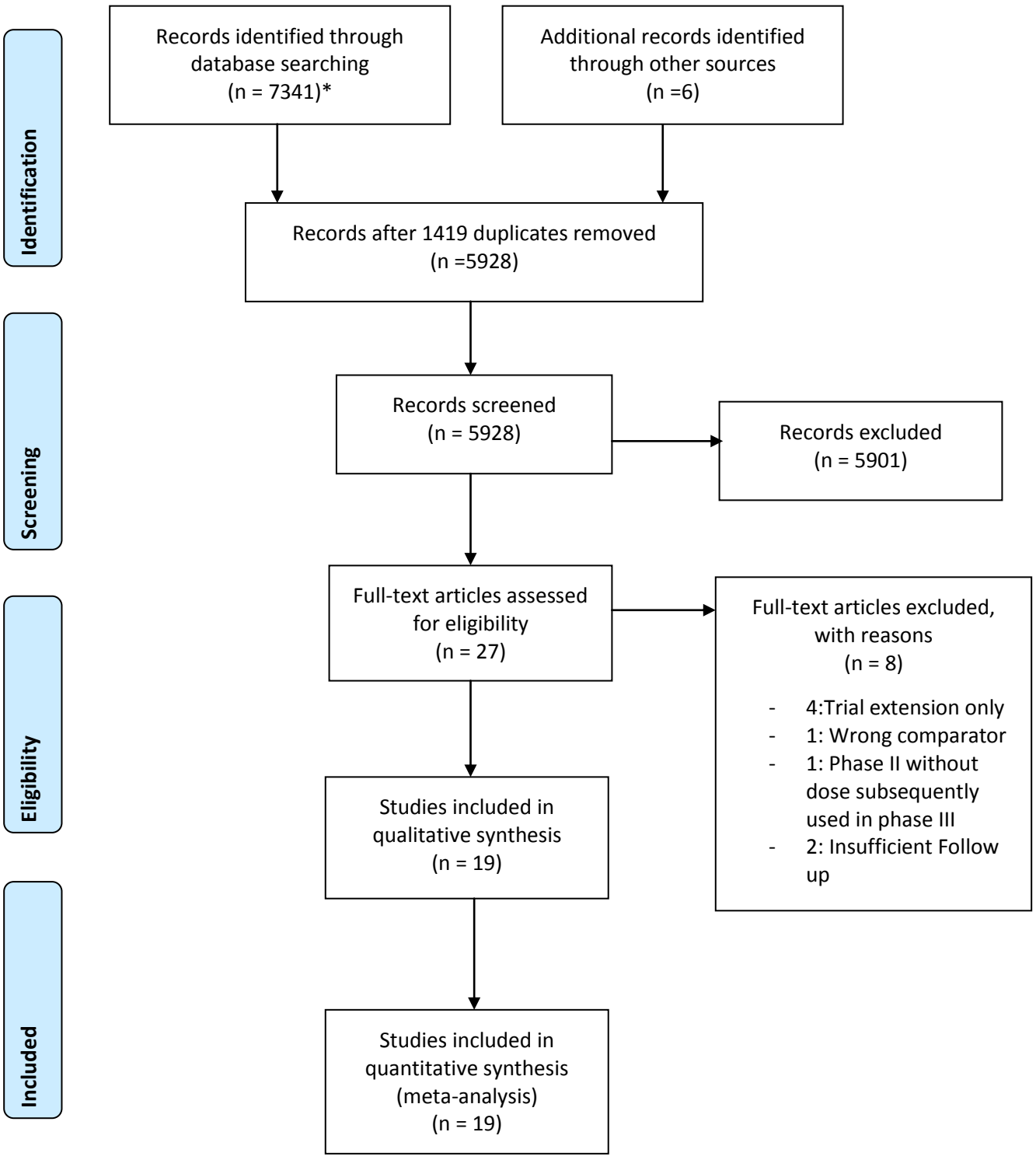


Figure S1. PRISMA Flow Diagram – Study Identification, Selection and Exclusions.

*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.

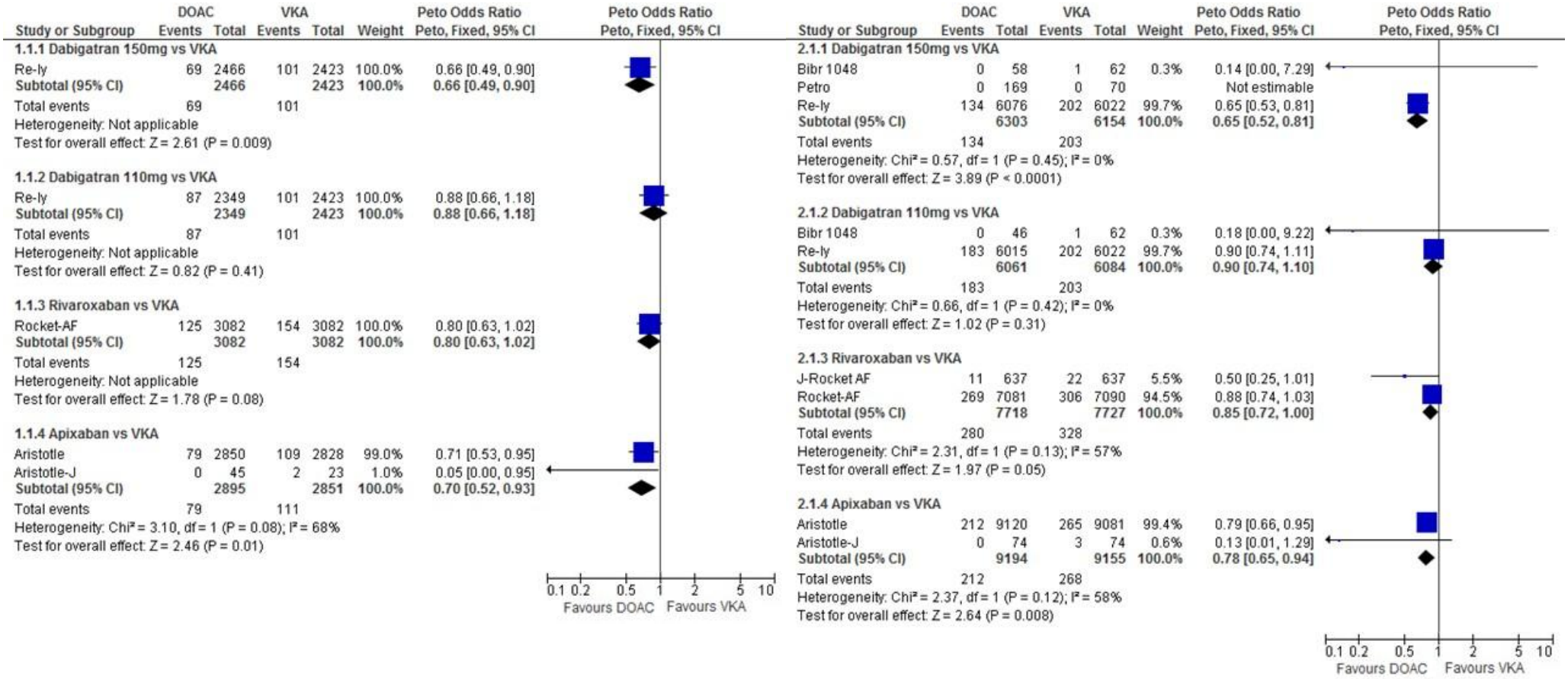


Figure S2. Forest Plots for risk of Stroke or Systemic Embolism in AF in Elderly (left) and Total Population (right).
*Event numbers for Engage-AF-Timi 48 in elderly have been estimated from published confidence intervals.

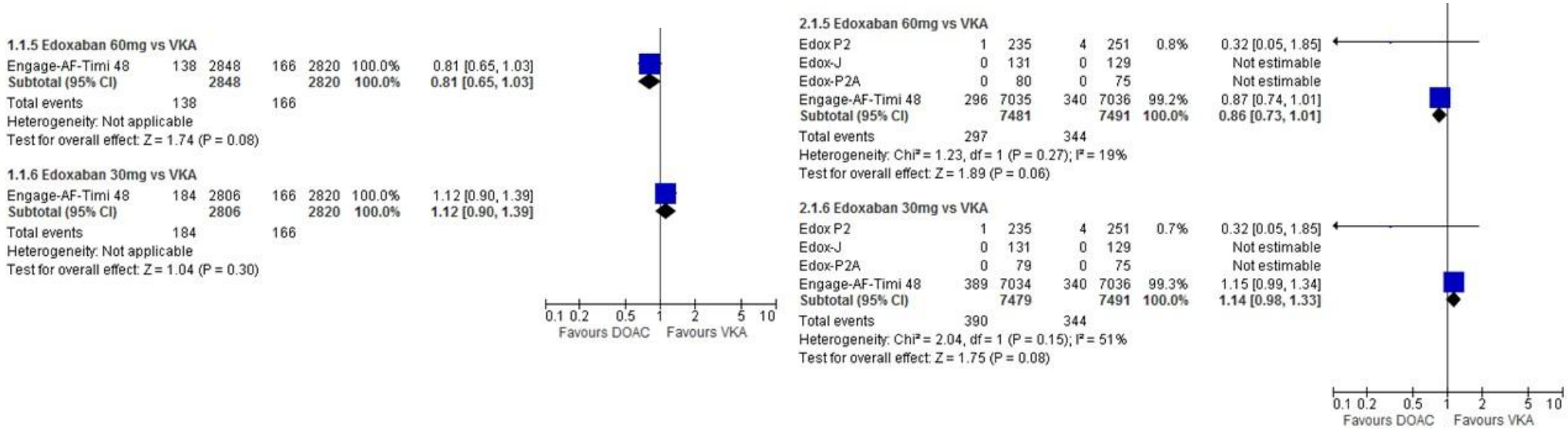


Figure S2. (contd) Forest Plots for risk of Stroke or Systemic Embolism in AF in Elderly (left) and Total Population (right).
*Event numbers for Engage-AF-Timi 48 in elderly have been estimated from published confidence intervals.

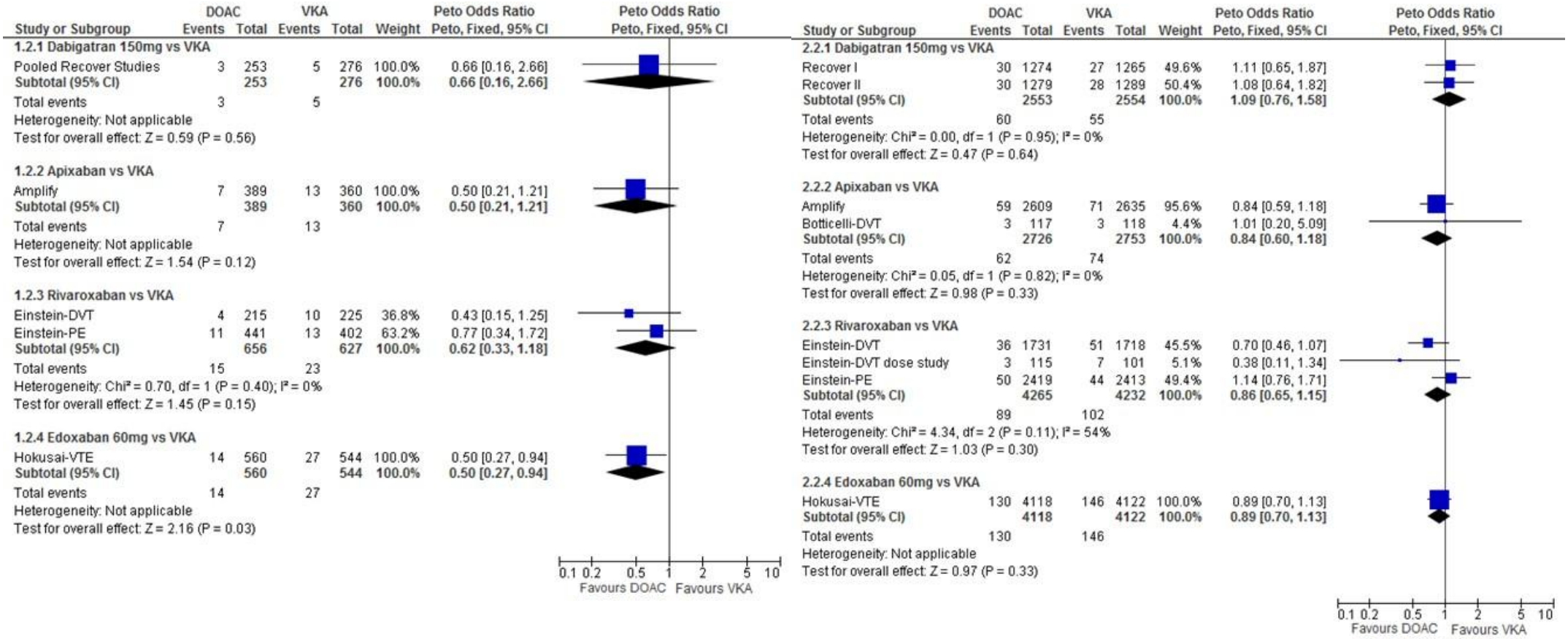


Figure S3. Forest Plots for risk of Recurrent Venous Thromboembolism in VTE in Elderly (left) and Total Population (right).

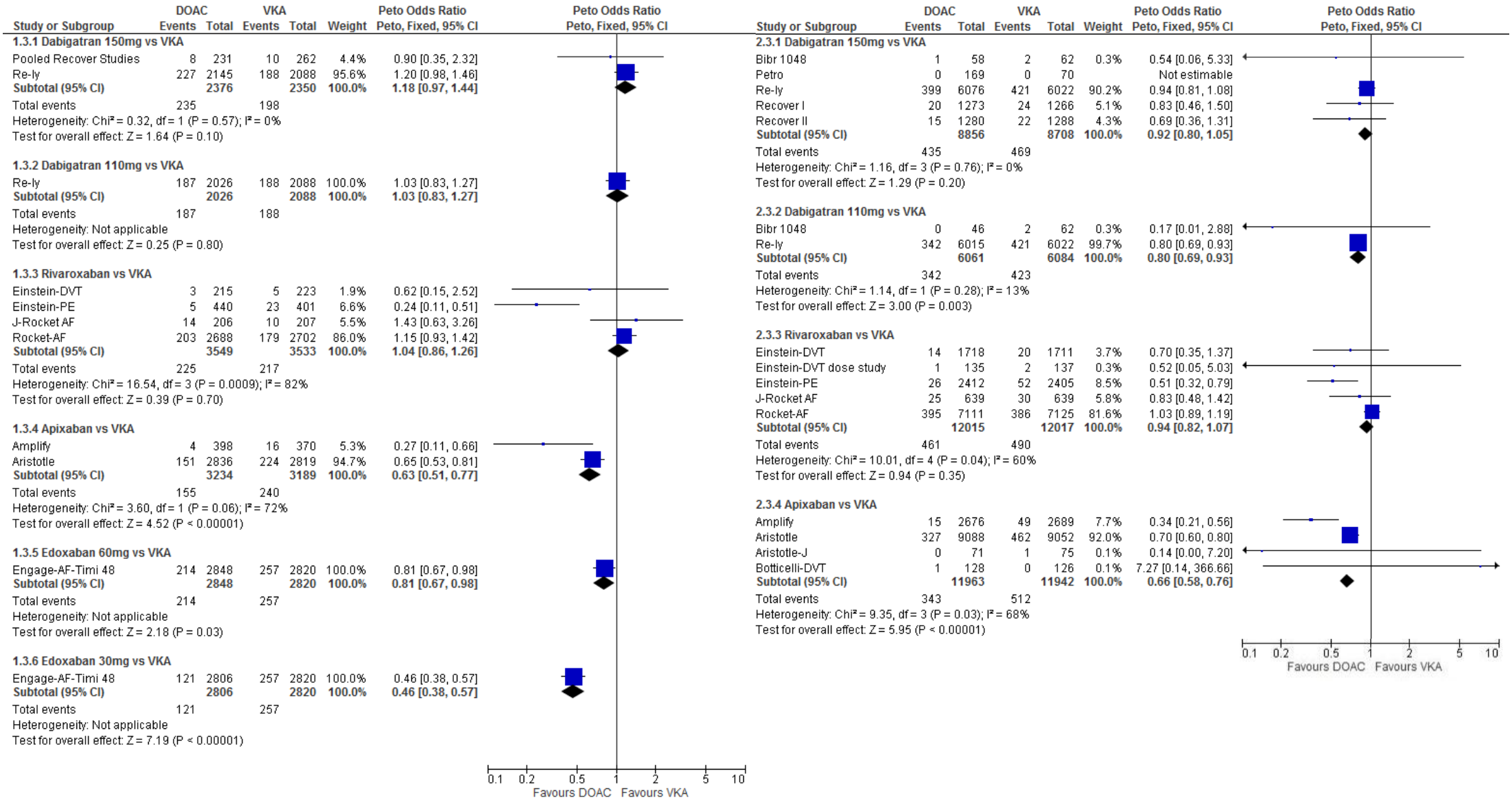


Figure S4. Forest Plots for risk of Major Bleeding in Elderly (left) and Total Population (right).

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

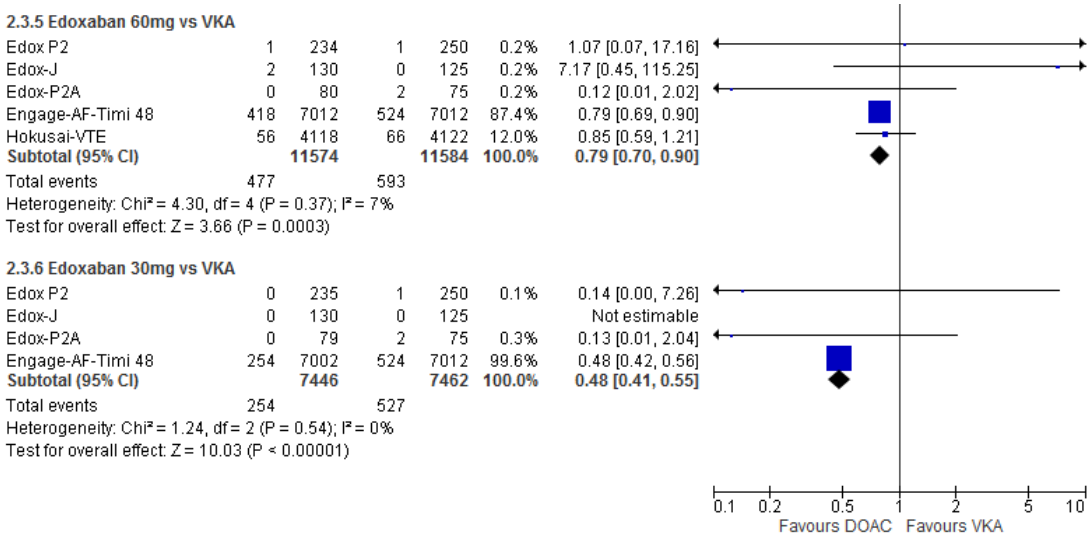


Figure S4. (contd) Forest Plots for risk of Major Bleeding in Total Population (right).

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

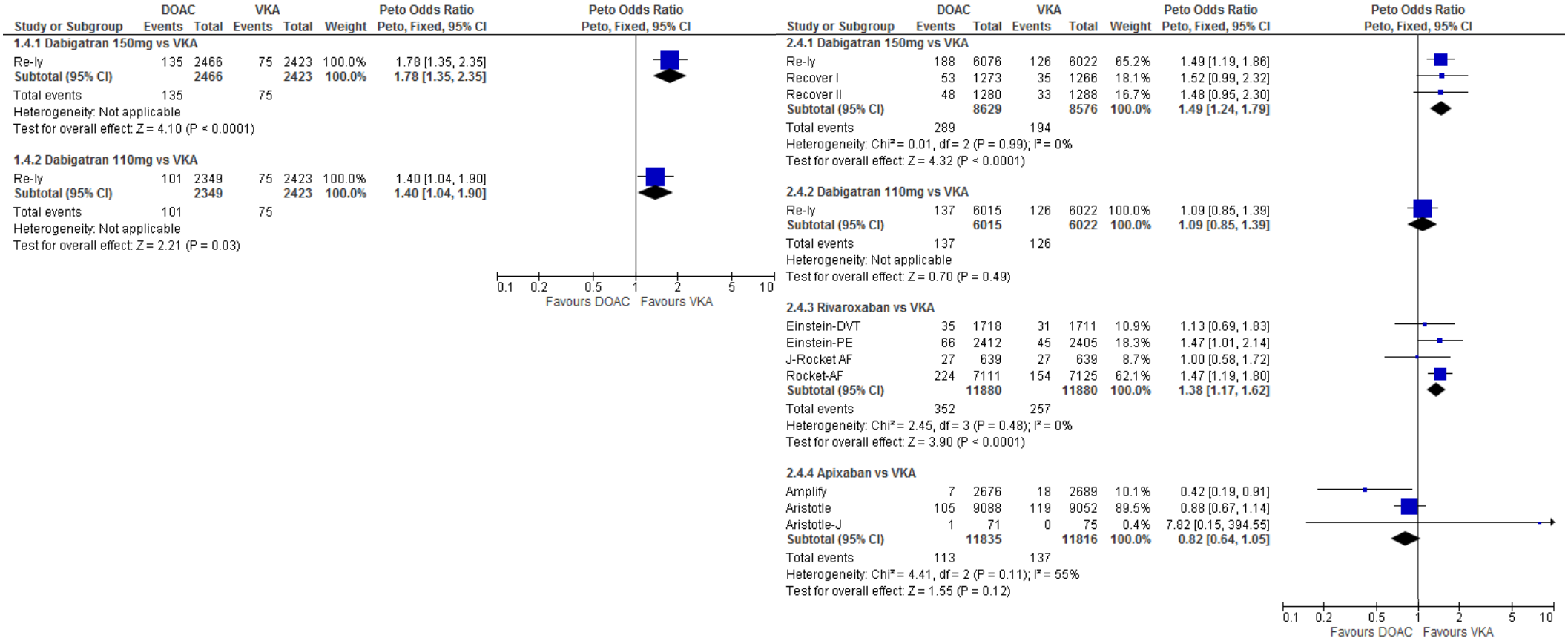


Figure S5. Forest Plots for risk of Gastrointestinal Bleeding in Elderly (left) and Total Population (right).

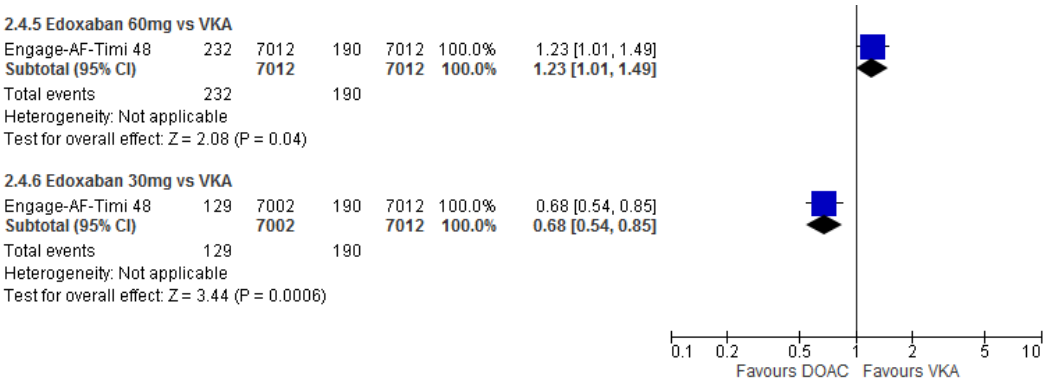


Figure S5. (contd) Forest Plots for risk of Gastrointestinal Bleeding in Total Population (right).

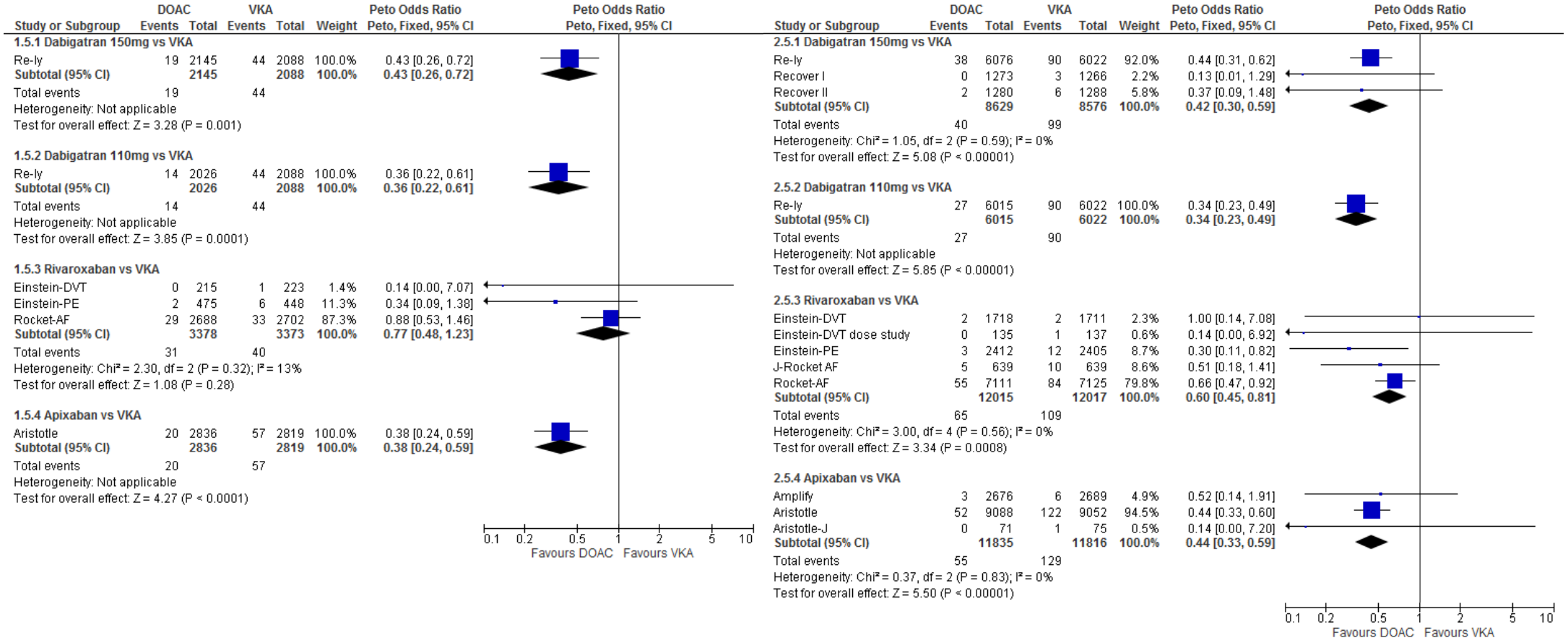


Figure S6. Forest Plots for risk of Intracranial Bleeding in in Elderly (left) and Total Population (right).

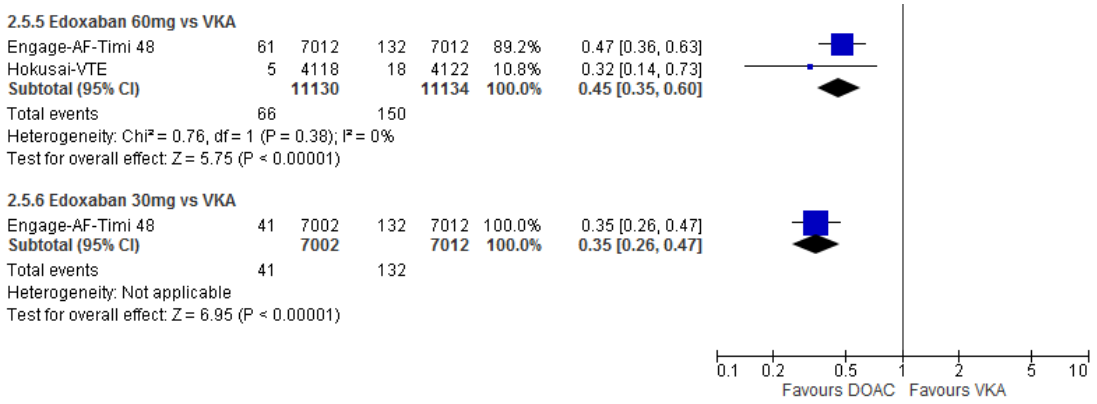


Figure S6. (contd) Forest Plots for risk of Intracranial Bleeding in Total Population (right).

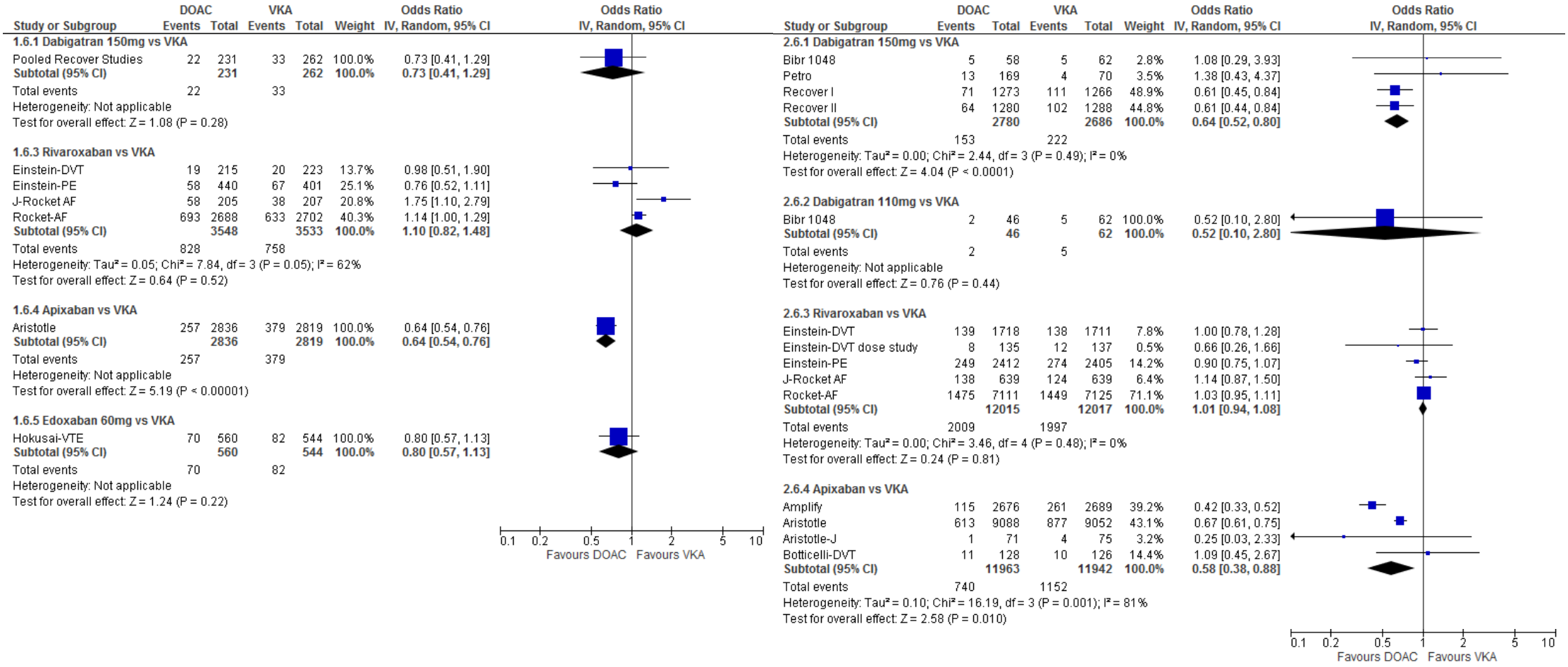


Figure S7. Forest Plots for risk of Clinically Relevant Bleeding in Elderly (left) and Total Population (right) - Random Effects Model

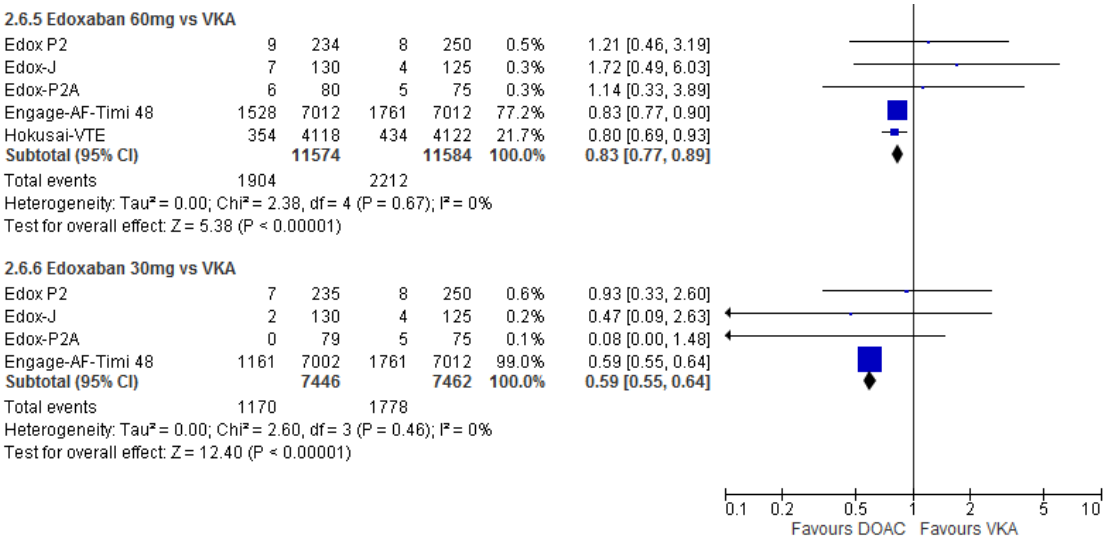
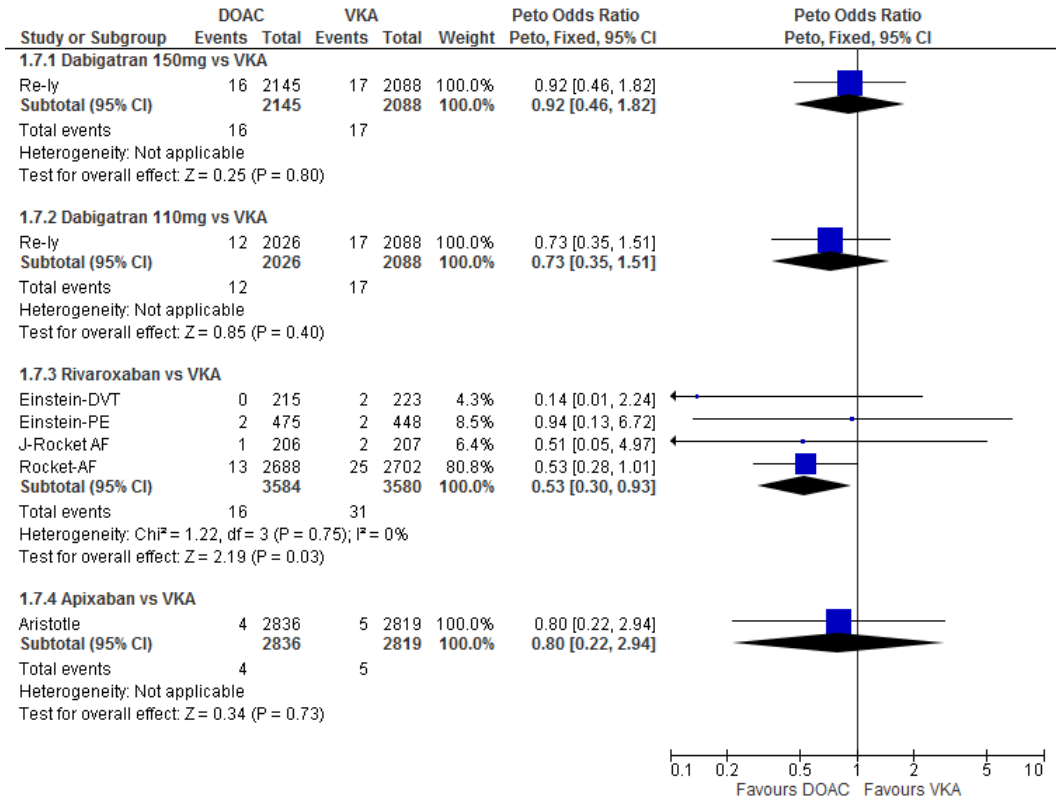


Figure S7. (contd) Forest Plots for risk of Clinically Relevant Bleeding in Total Population (right)- Random Effects Model



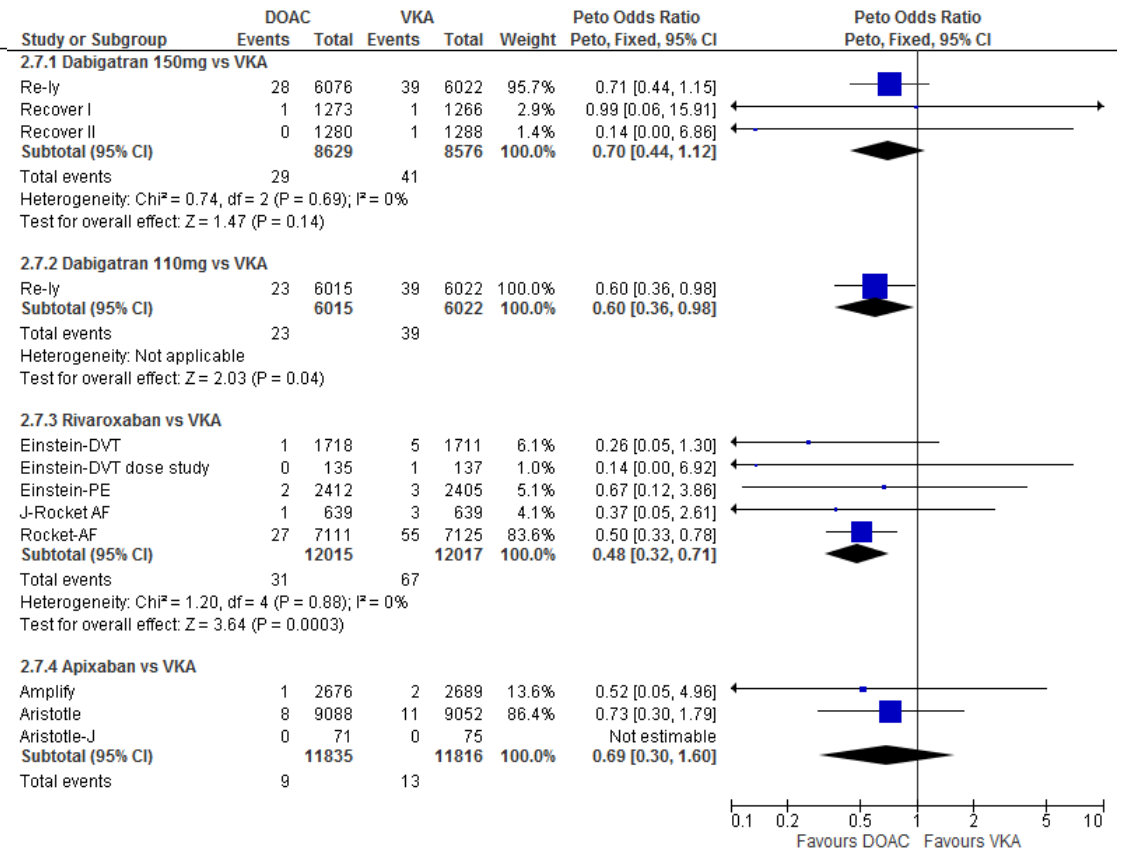


Figure S8. Forest Plots for risk of Fatal Bleeding in Elderly (left) and Total Population (right).

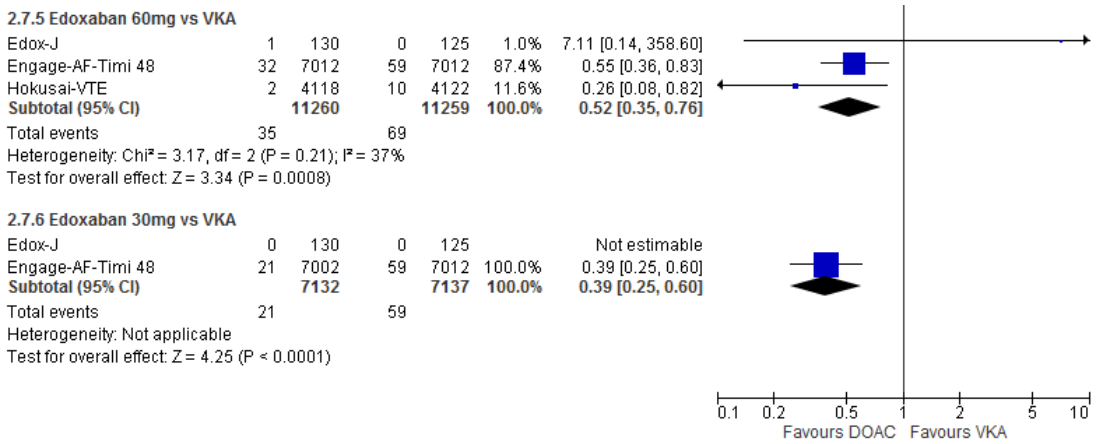


Figure S8. (contd) Forest Plots for risk of Fatal Bleeding in Elderly (left) and Total Population (right).

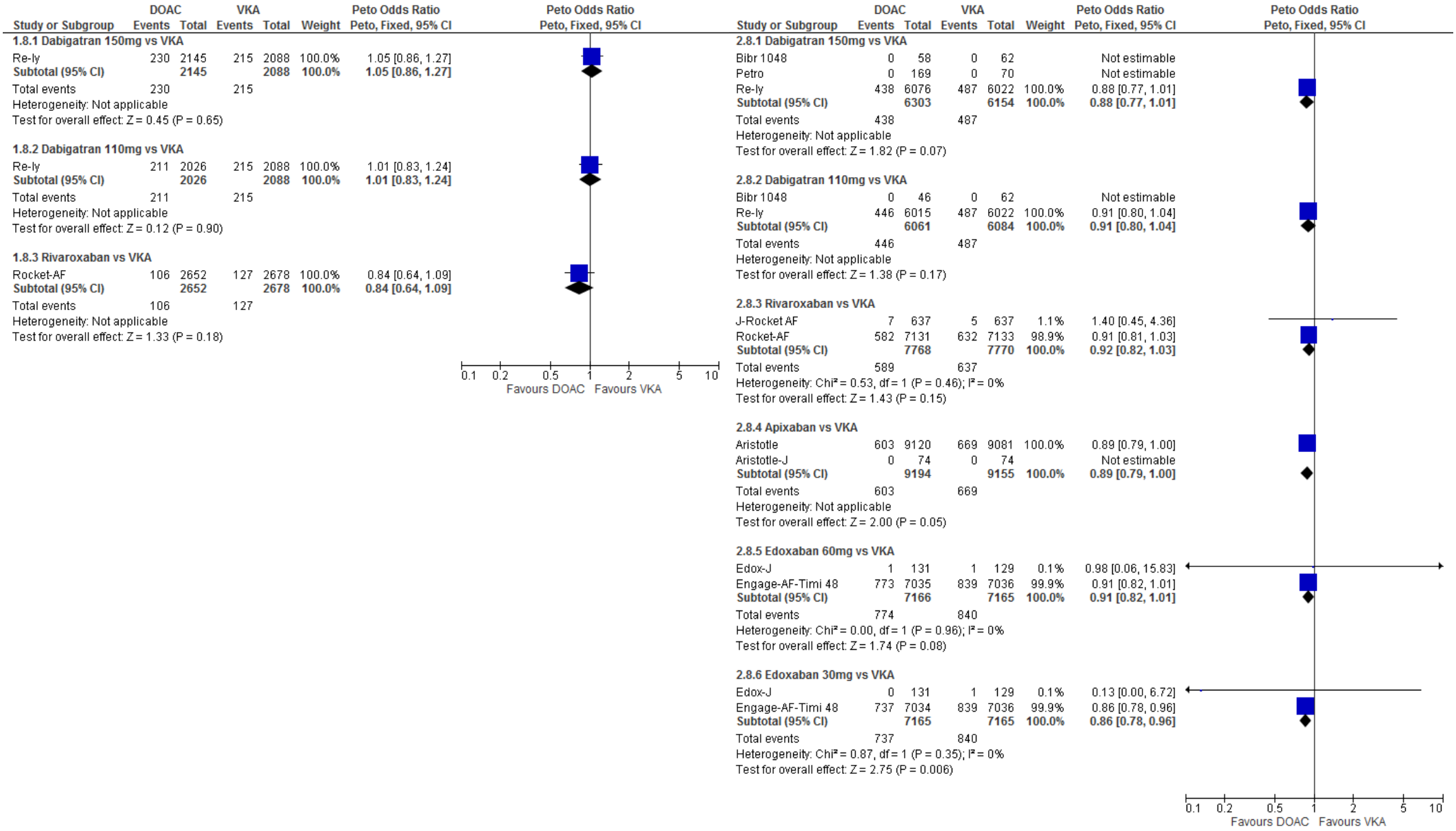


Figure S9. Forest Plots for risk of All Cause Death in Atrial Fibrillation in Elderly (left) and Total Population (right).

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

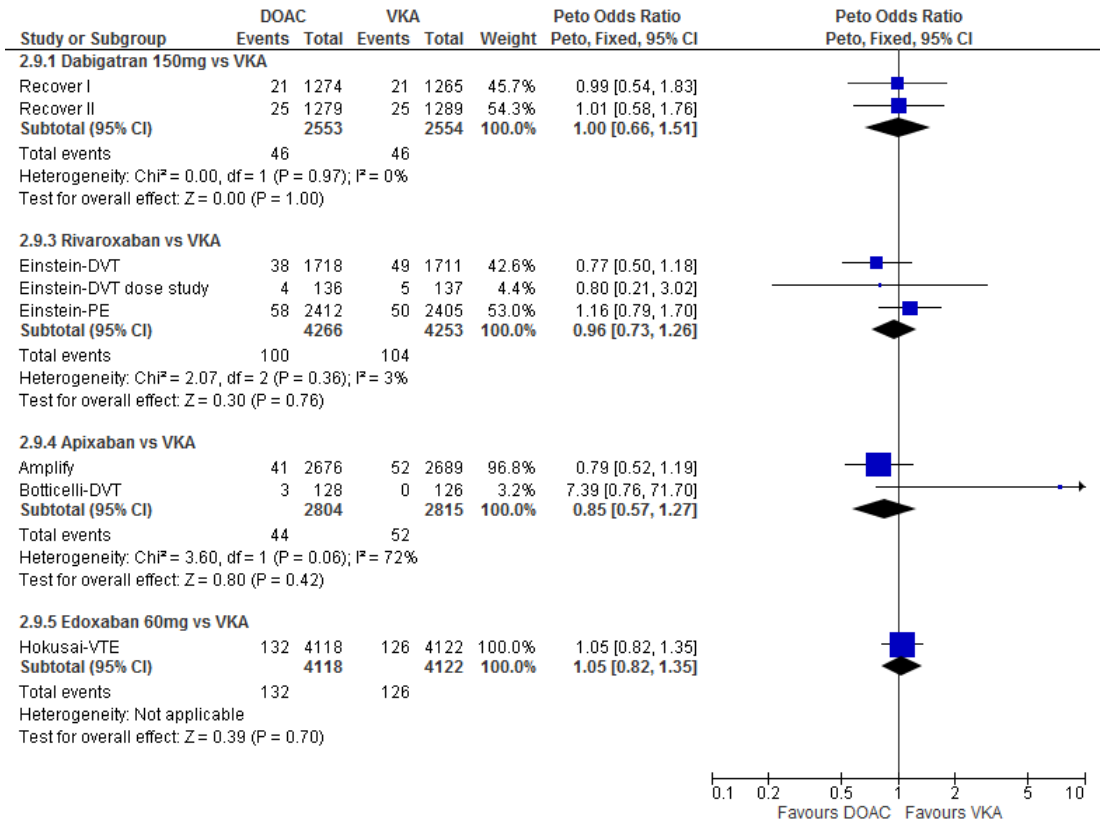


Figure S10. Forest Plots for risk of All Cause Death in Venous thromboembolism in Total Population (right).
*No results available for the elderly for this outcome

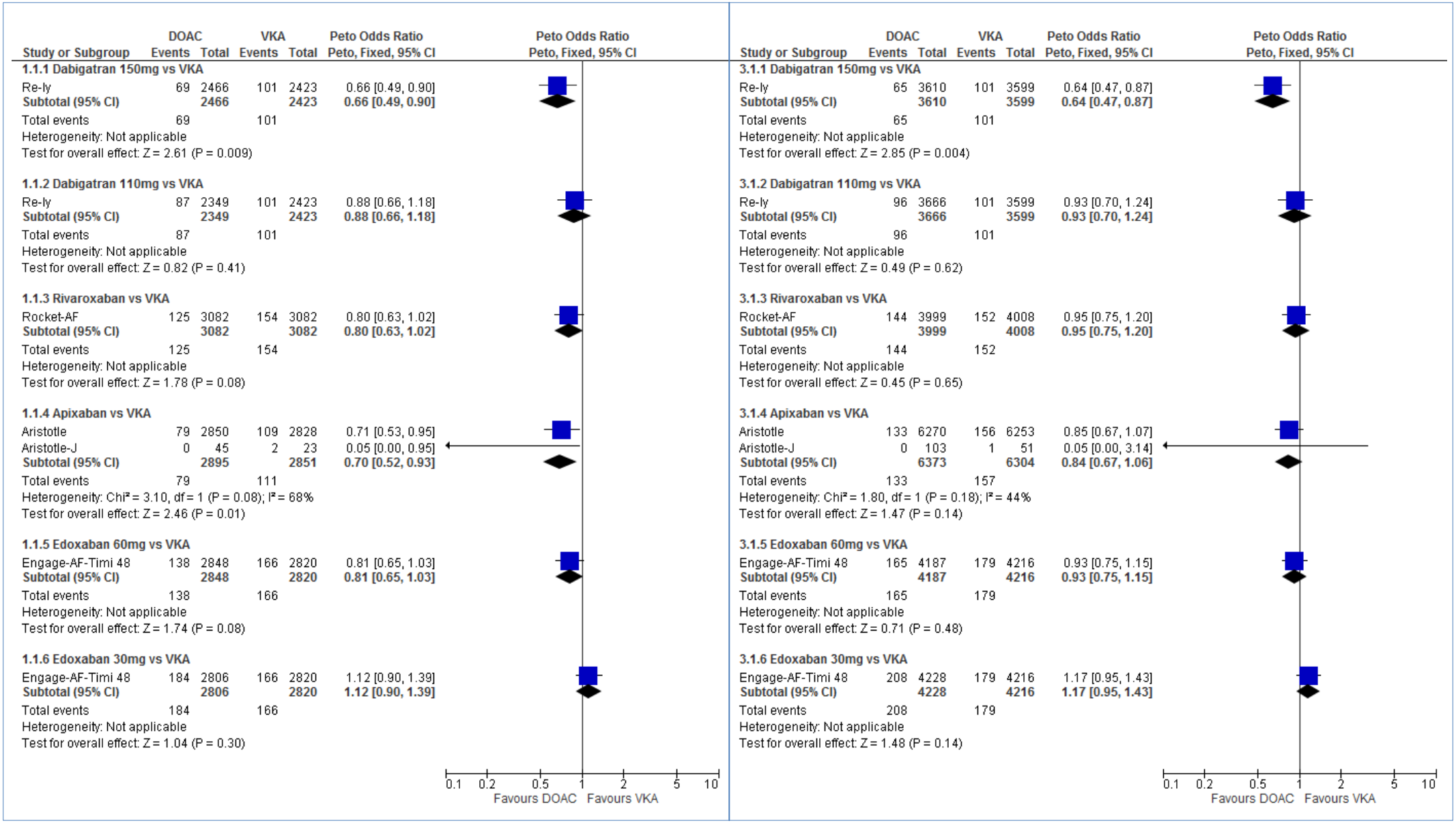


Figure S11. Forest Plots for risk of Stroke or Systemic Embolism in AF in Elderly (left) and <75 Population (right).

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

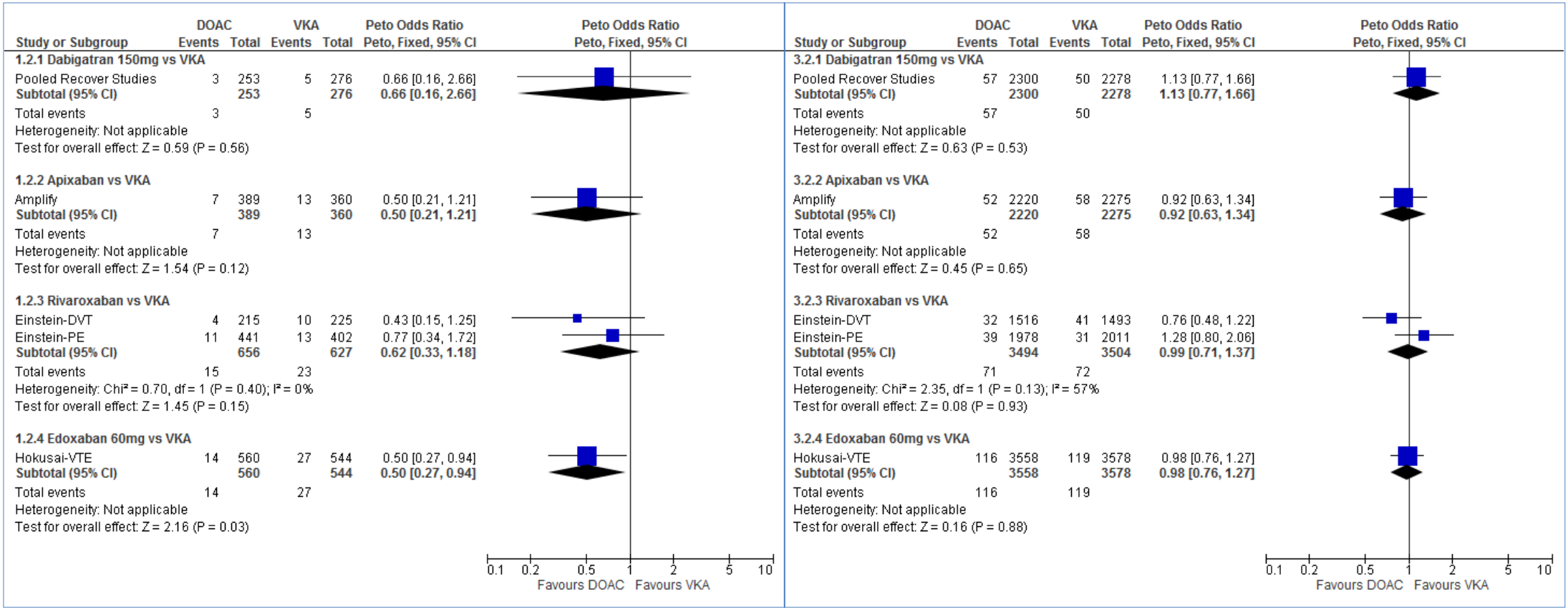


Figure S12. Forest Plots for risk of Venous Thromboembolism in VTE in Elderly (left) and <75 Population (right).

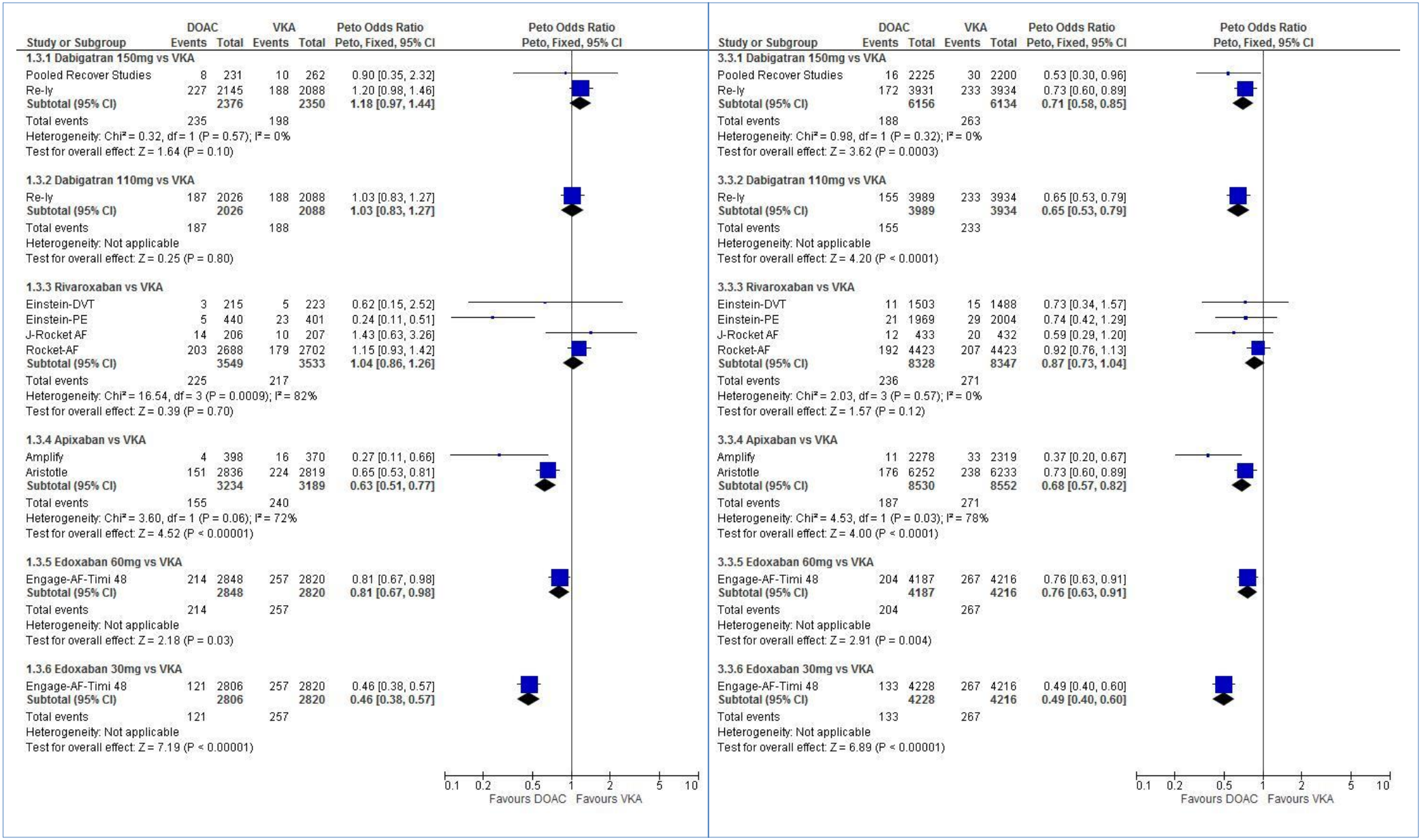


Figure S13. Forest Plots for risk of Major Bleeding in Elderly (left) and <75 Population (right).

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

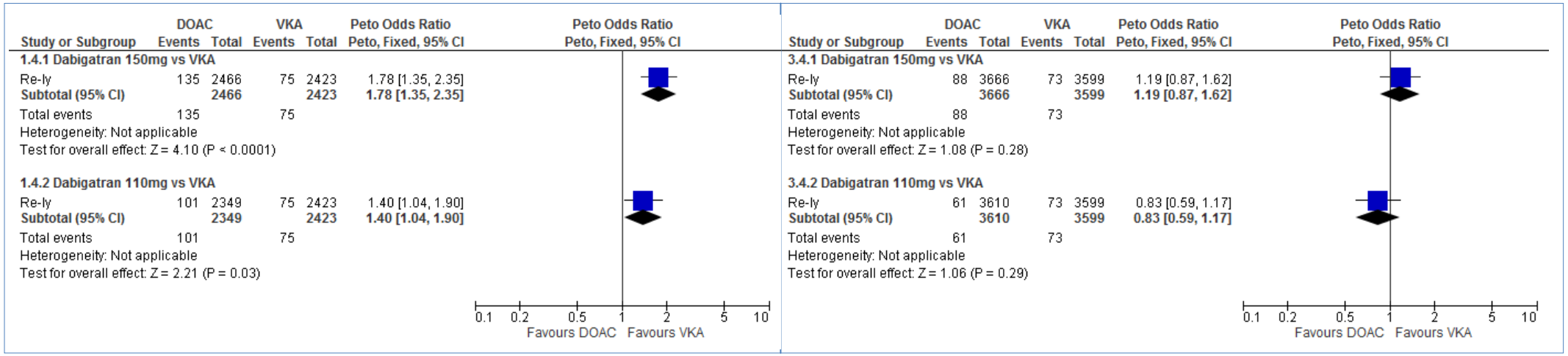


Figure S14. Forest Plots for risk of Gastrointestinal Bleeding in Elderly (left) and <75 Population (right).

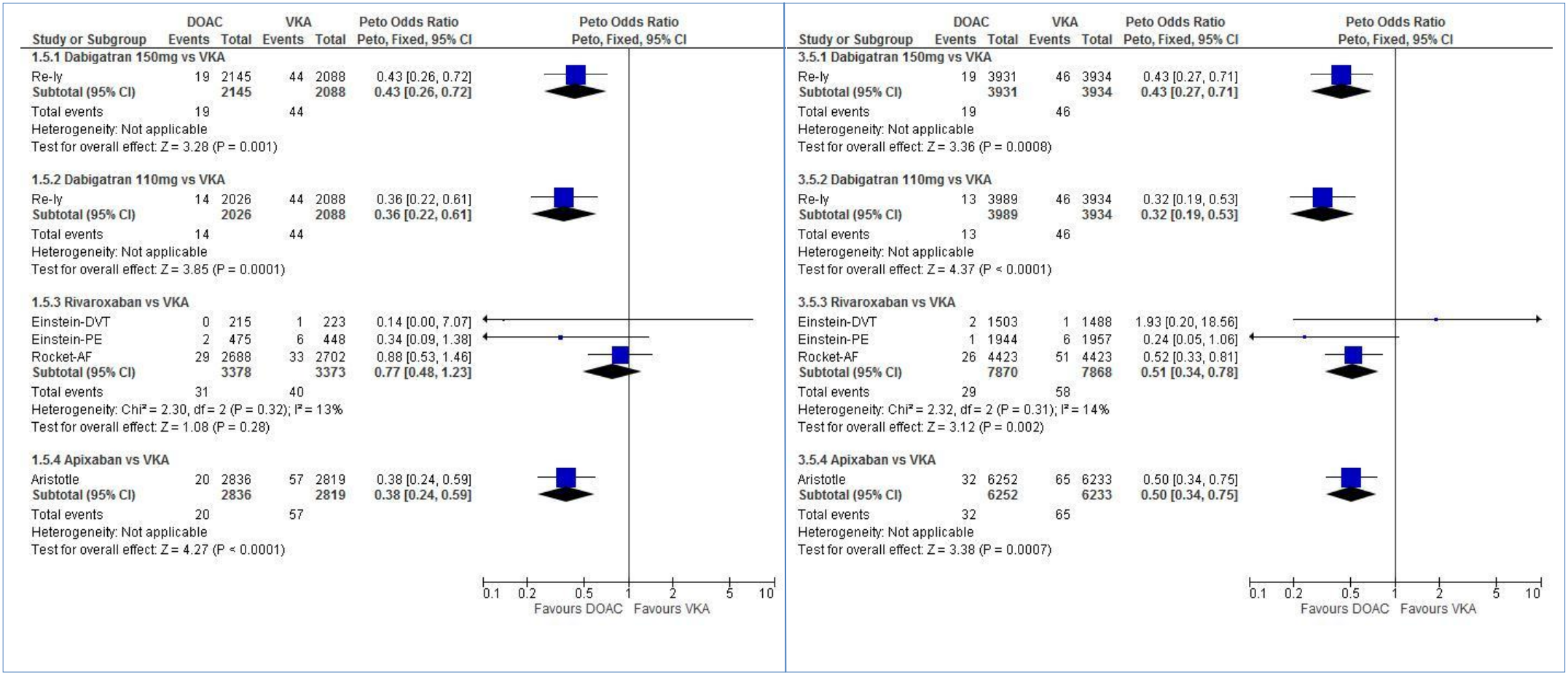


Figure S15. Forest Plots for risk of Intracranial Bleeding in Elderly (left) and <75 Population (right).

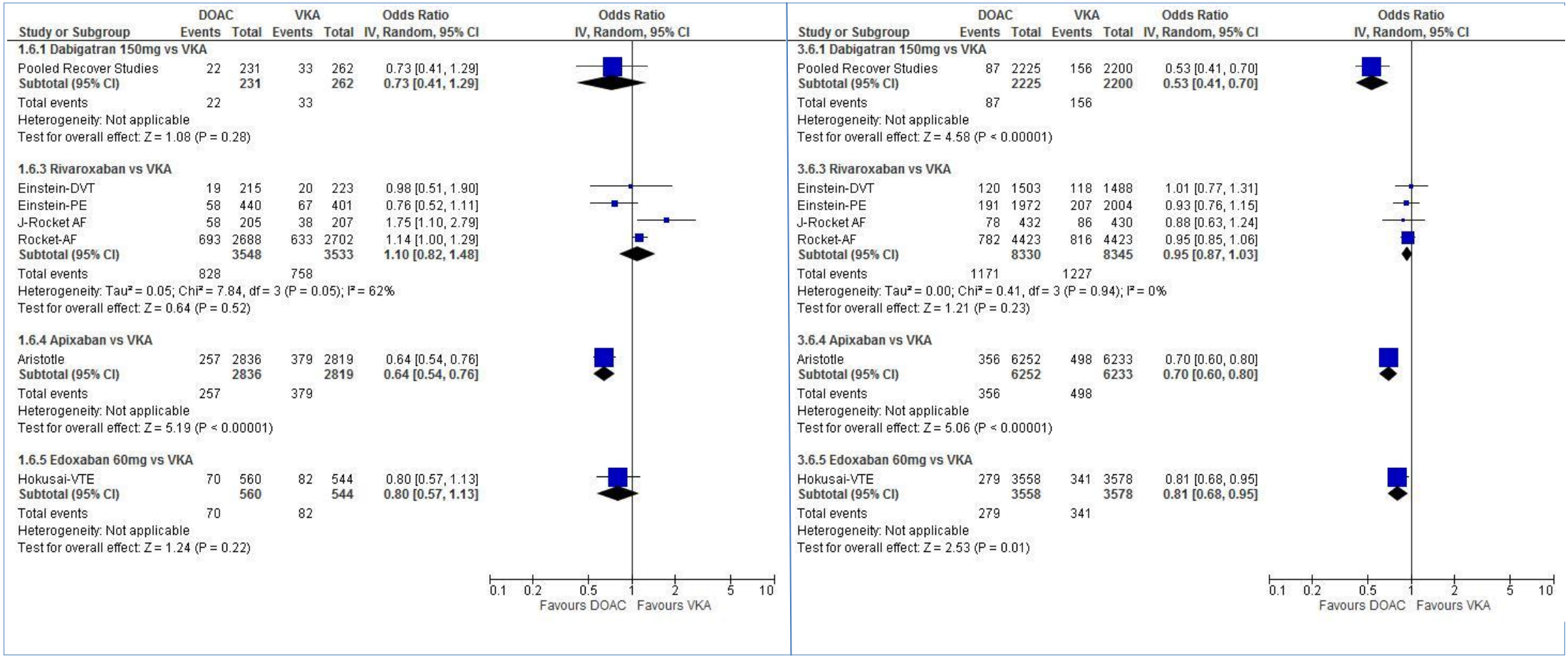


Figure S16. Forest Plots for risk of Clinically Relevant Bleeding in Elderly (left) and <75 Population (right) - Random Effects Model.

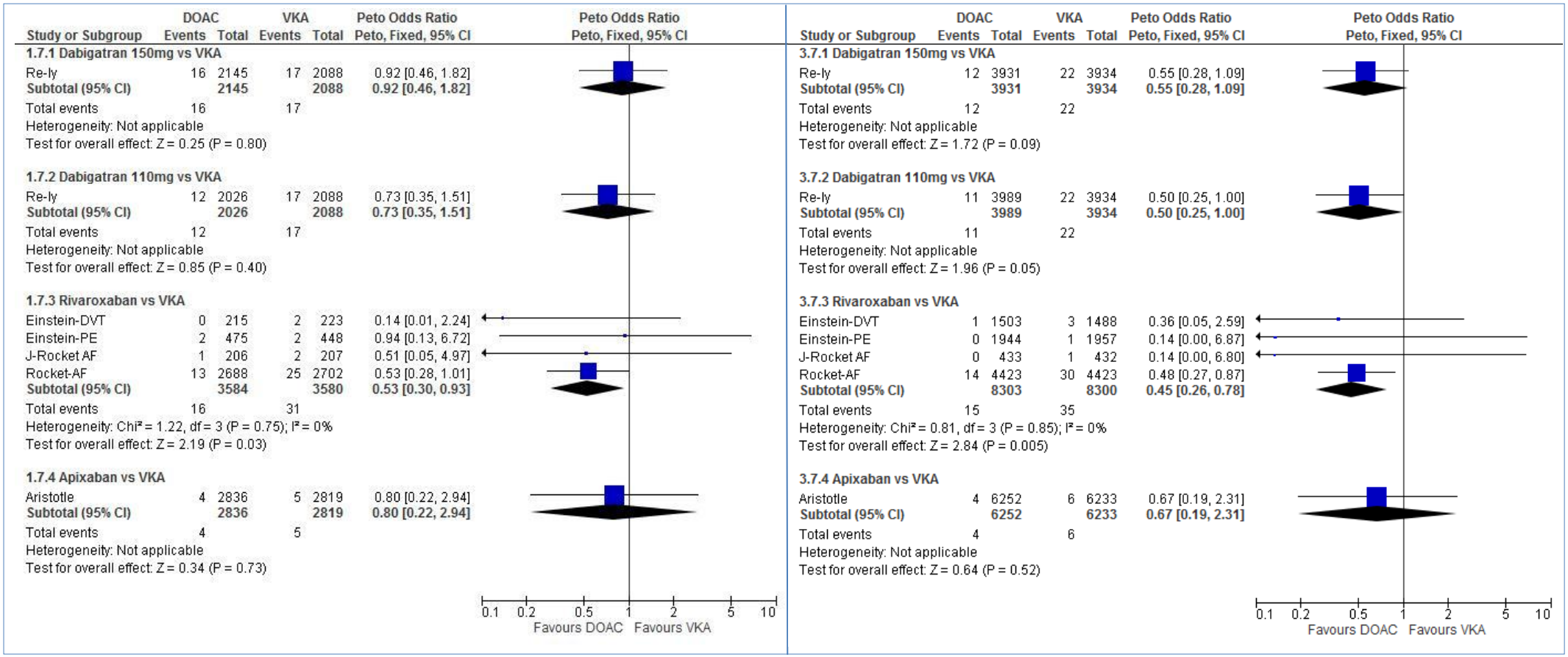


Figure S17. Forest Plots for risk of Fatal Bleeding in Elderly (left) and <75 Population (right).

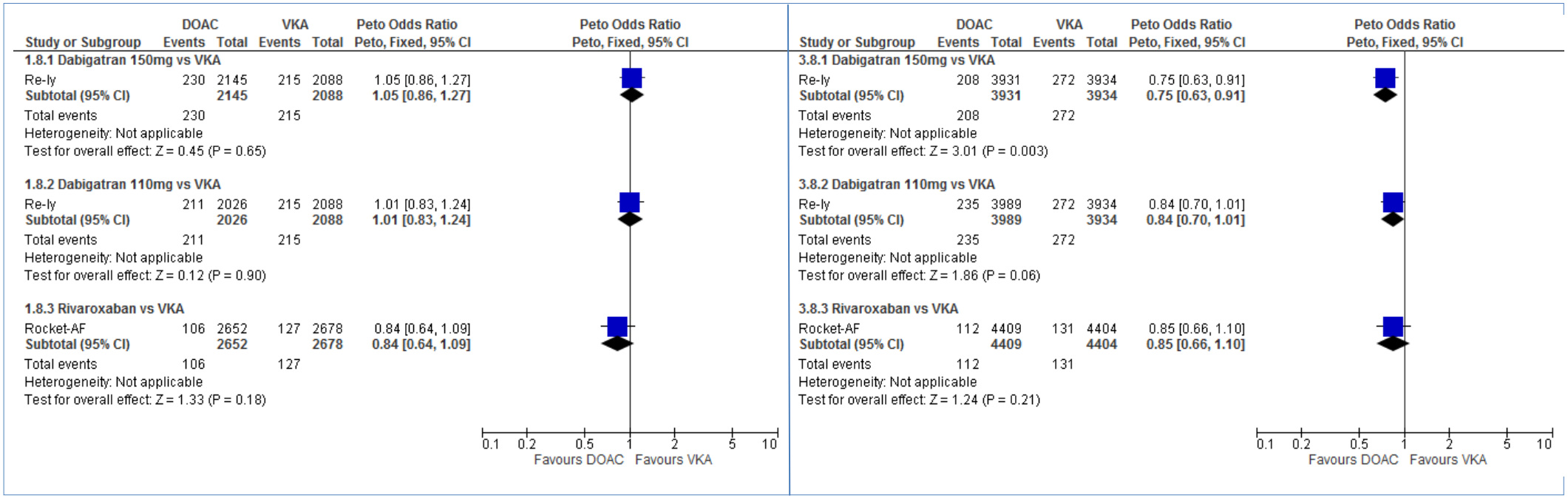


Figure S18. Forest Plots for risk of All Cause Death in AF in Elderly (left) and <75 Population (right).
*Event numbers for Rocket-AF in elderly have been estimated from published confidence intervals.

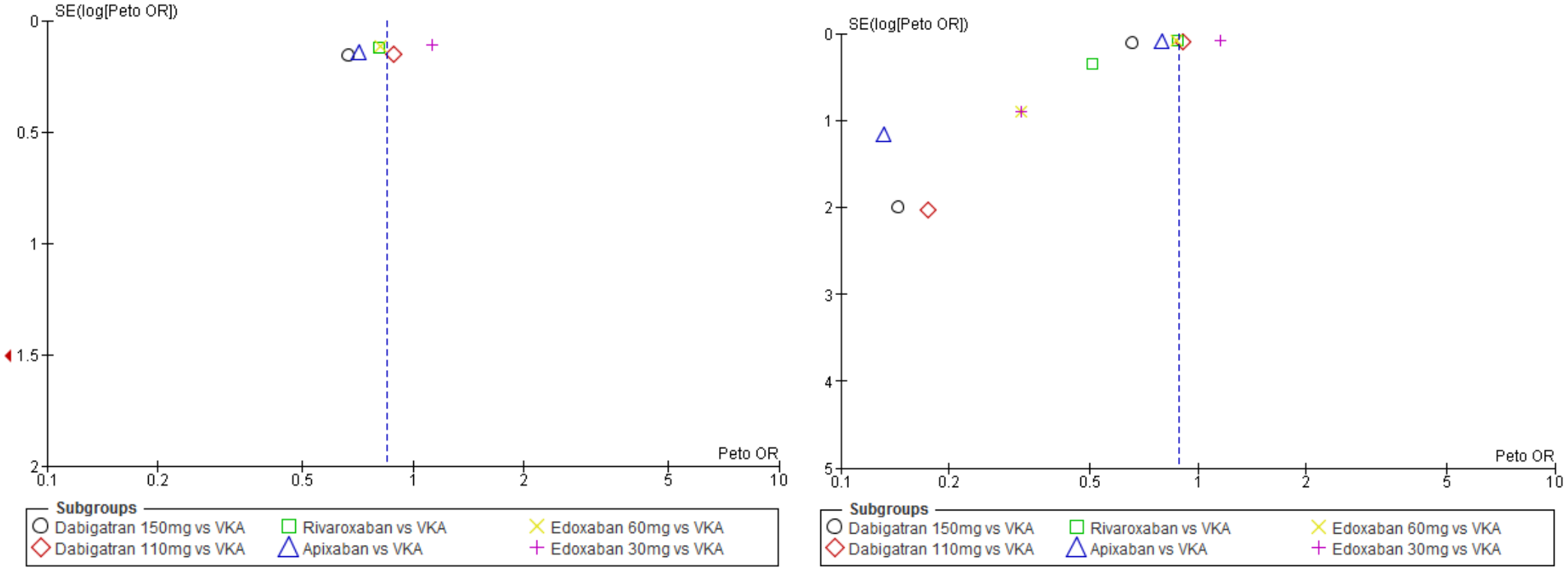


Figure S19. Funnel Plots for Stroke or Systemic Embolism in AF in Elderly (left) and Total population (right).

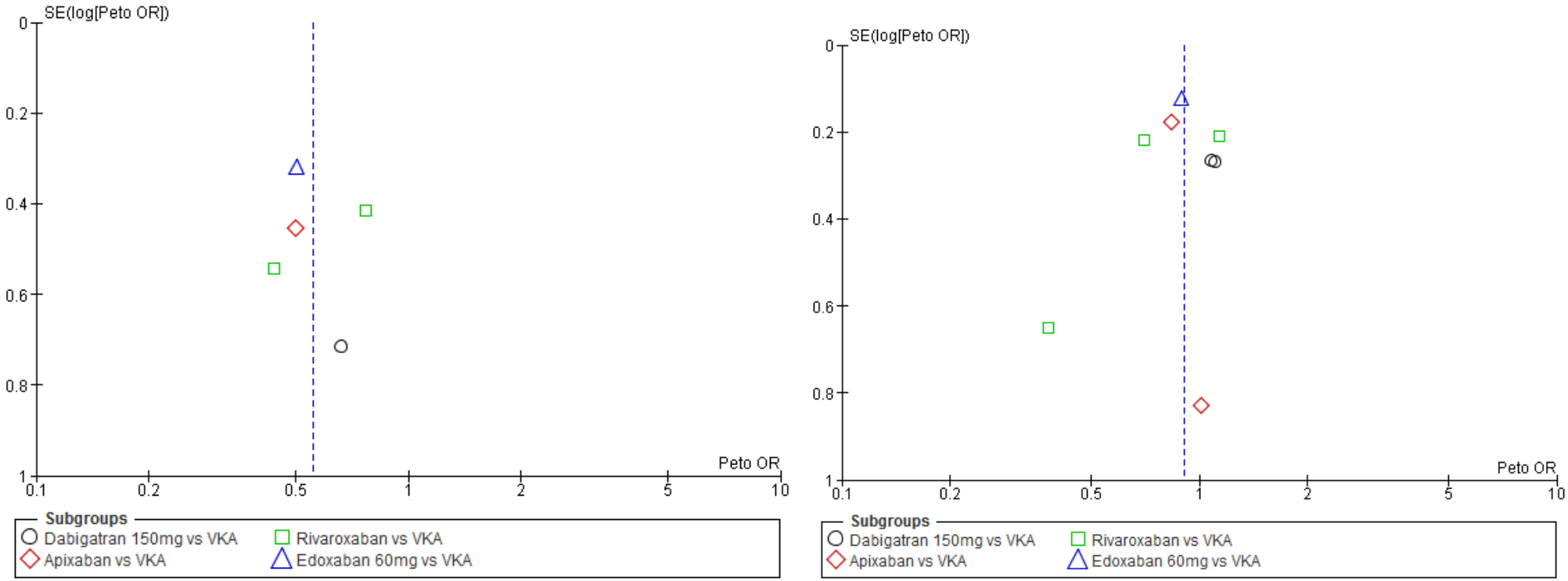


Figure S20. Funnel Plots for risk of Recurrent Venous Thromboembolism in VTE in Elderly (left) and Total population (right).

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8. Agnelli G, Buller HR, Cohen A, Curto M, Gallus AS, Johnson M, Porcari A, Raskob GE, Weitz JI. Apixaban for Extended Treatment of Venous Thromboembolism. *N Eng J Med*. 2013;368:699-708.