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

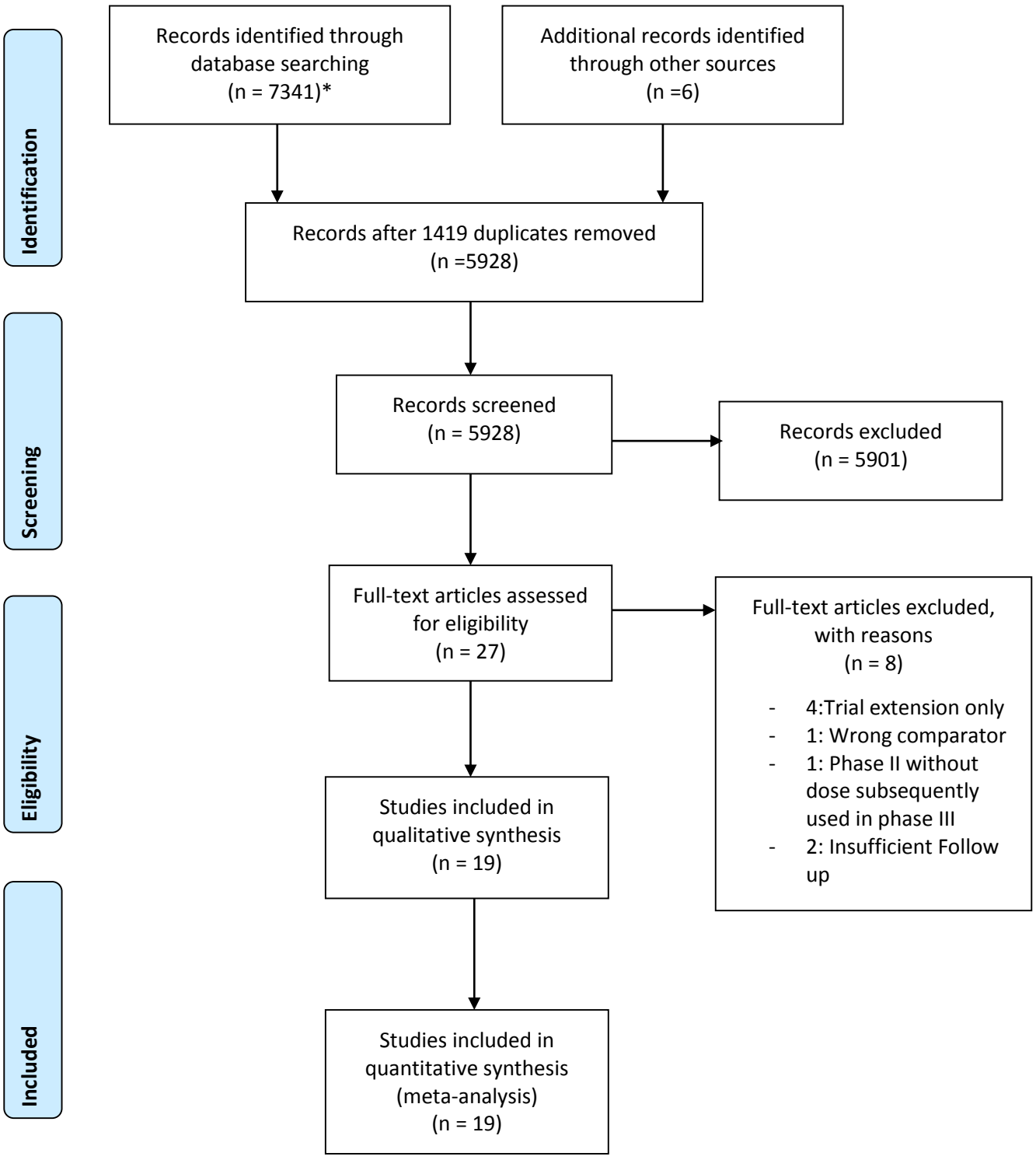


Figure S1. PRISMA Flow Diagram – Study Identification, Selection and Exclusions.

*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.

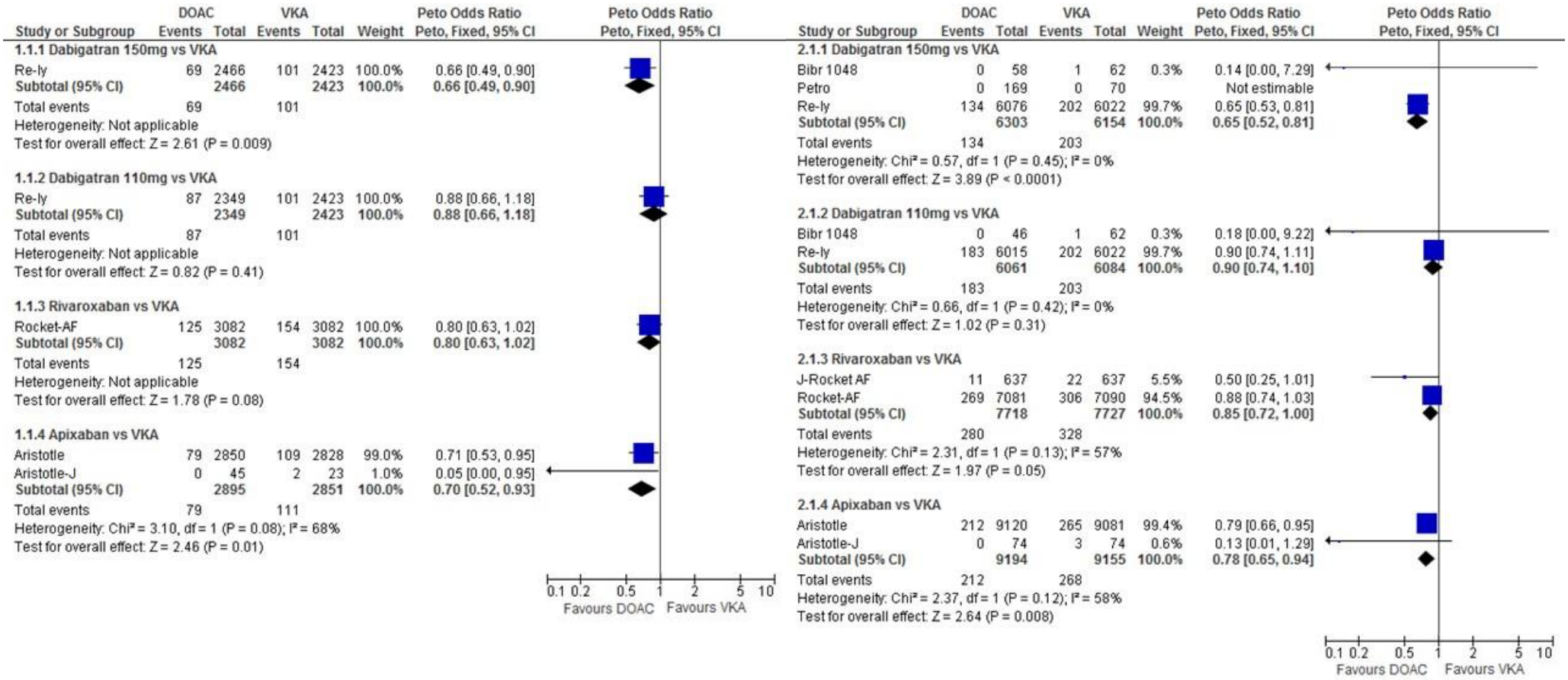


Figure S2. Forest Plots for risk of Stroke or Systemic Embolism in AF in Elderly (left) and Total Population (right).
*Event numbers for Engage-AF-Timi 48 in elderly have been estimated from published confidence intervals.

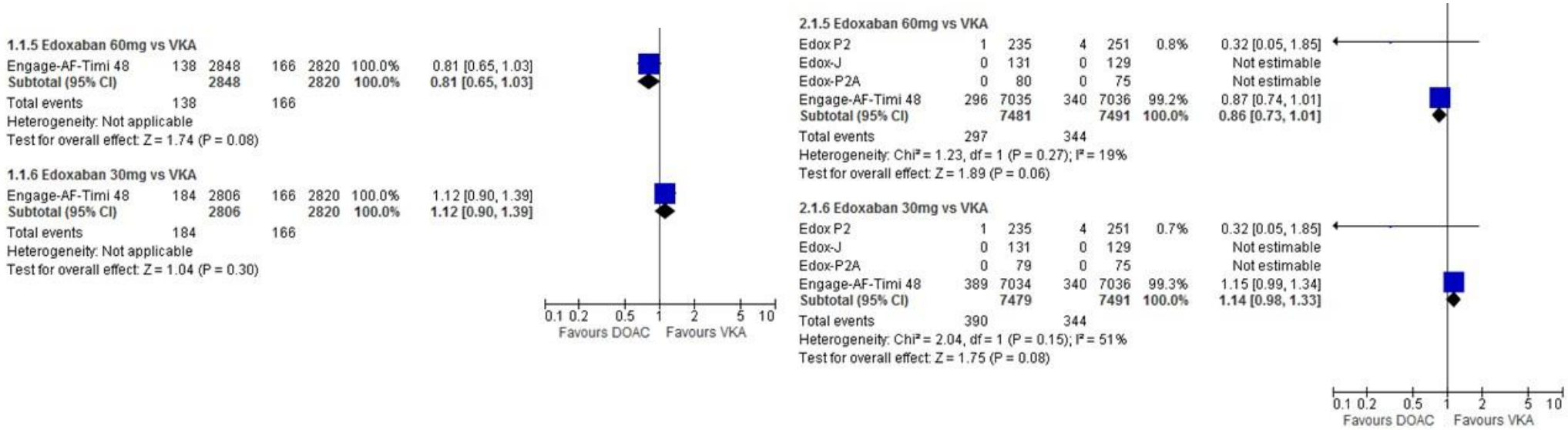


Figure S2. (contd) Forest Plots for risk of Stroke or Systemic Embolism in AF in Elderly (left) and Total Population (right).
*Event numbers for Engage-AF-Timi 48 in elderly have been estimated from published confidence intervals.

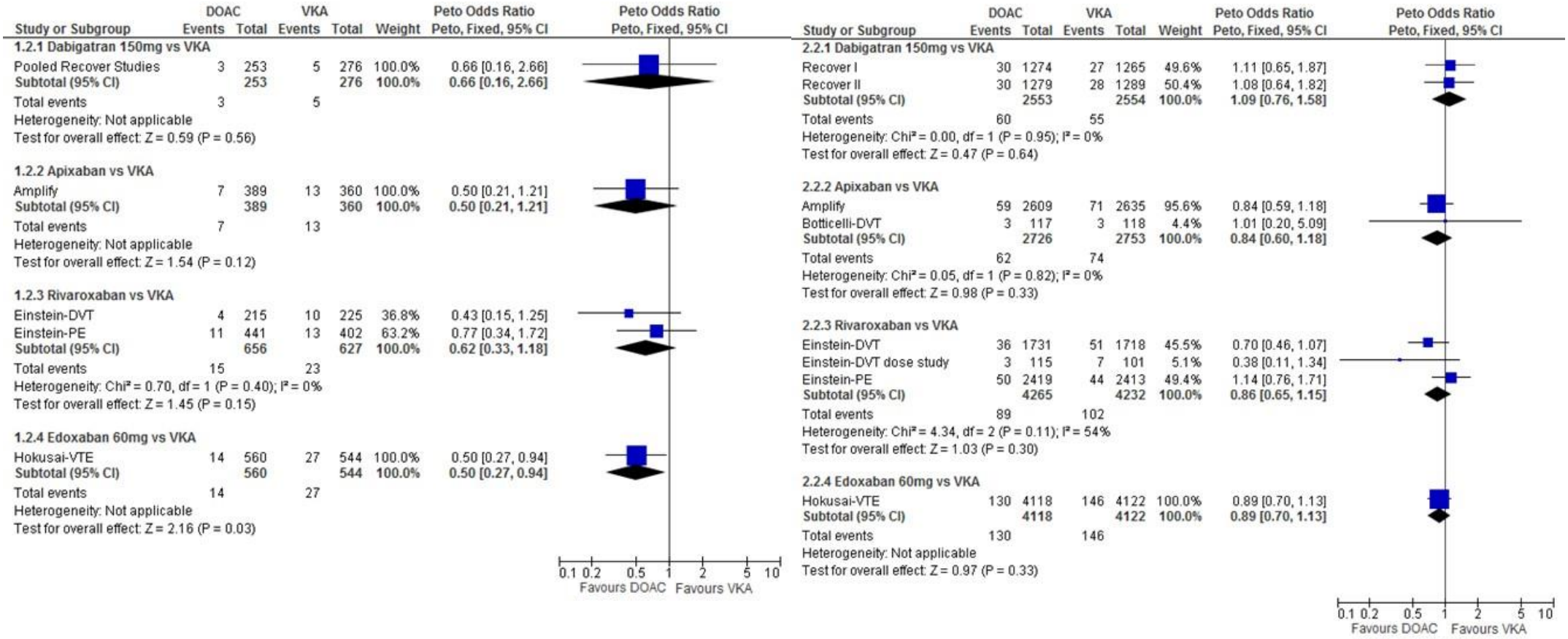


Figure S3. Forest Plots for risk of Recurrent Venous Thromboembolism in VTE in Elderly (left) and Total Population (right).

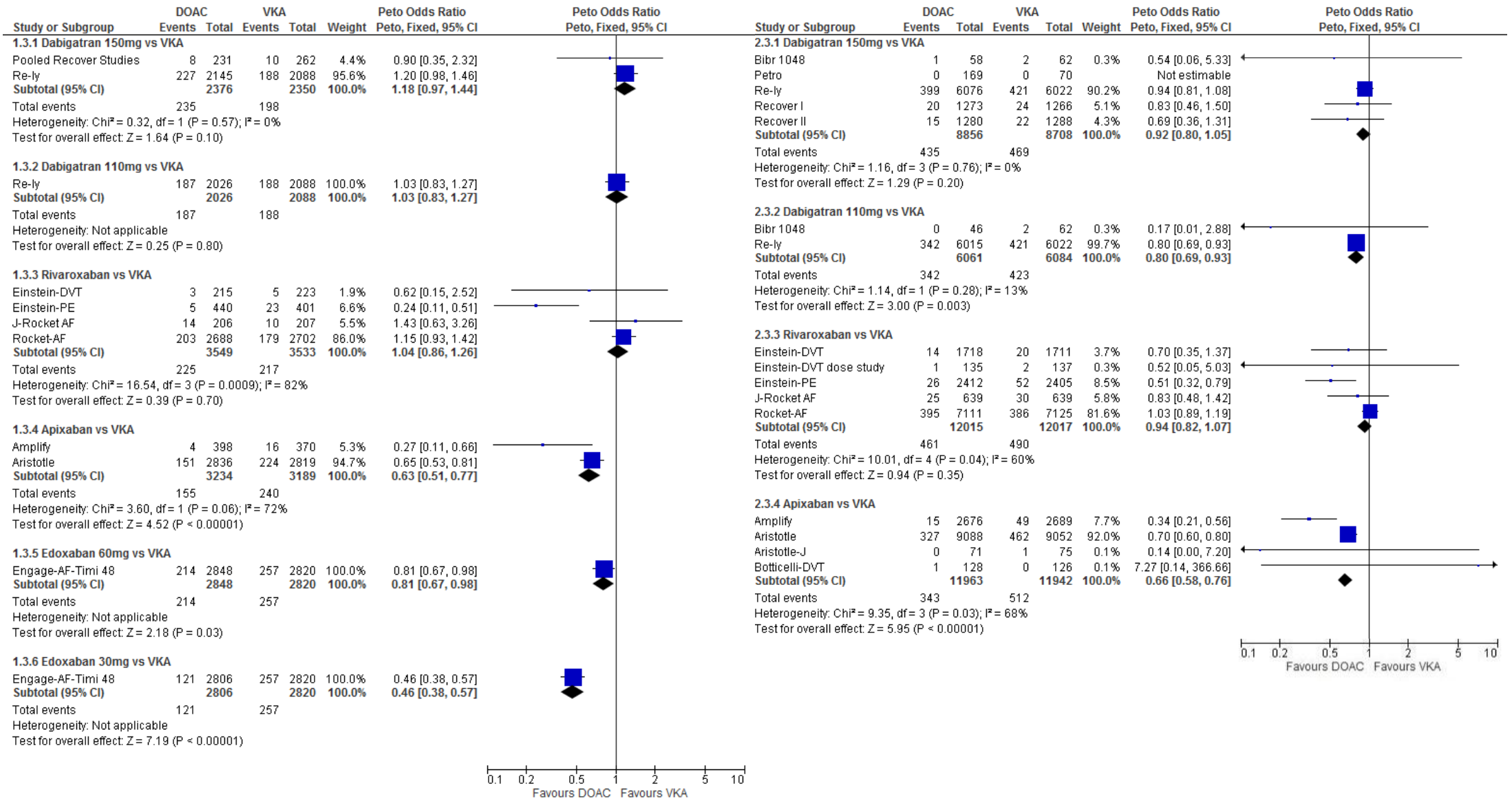


Figure S4. Forest Plots for risk of Major Bleeding in Elderly (left) and Total Population (right).

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

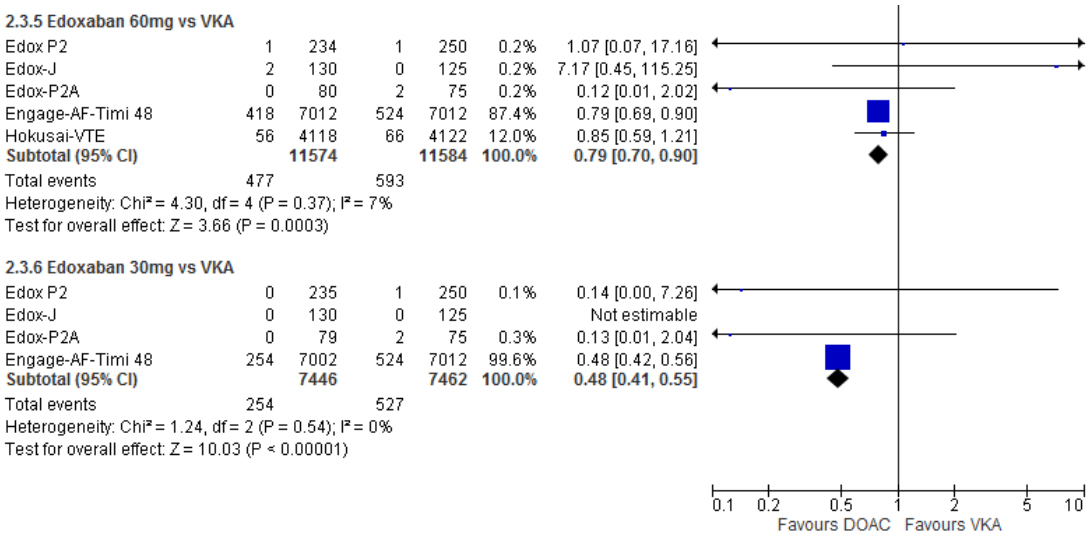
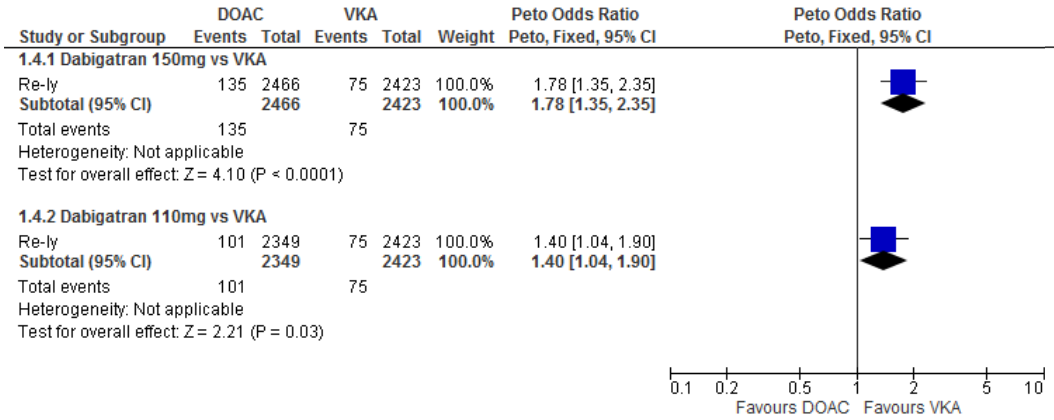


Figure S4. (contd) Forest Plots for risk of Major Bleeding in Total Population (right).

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



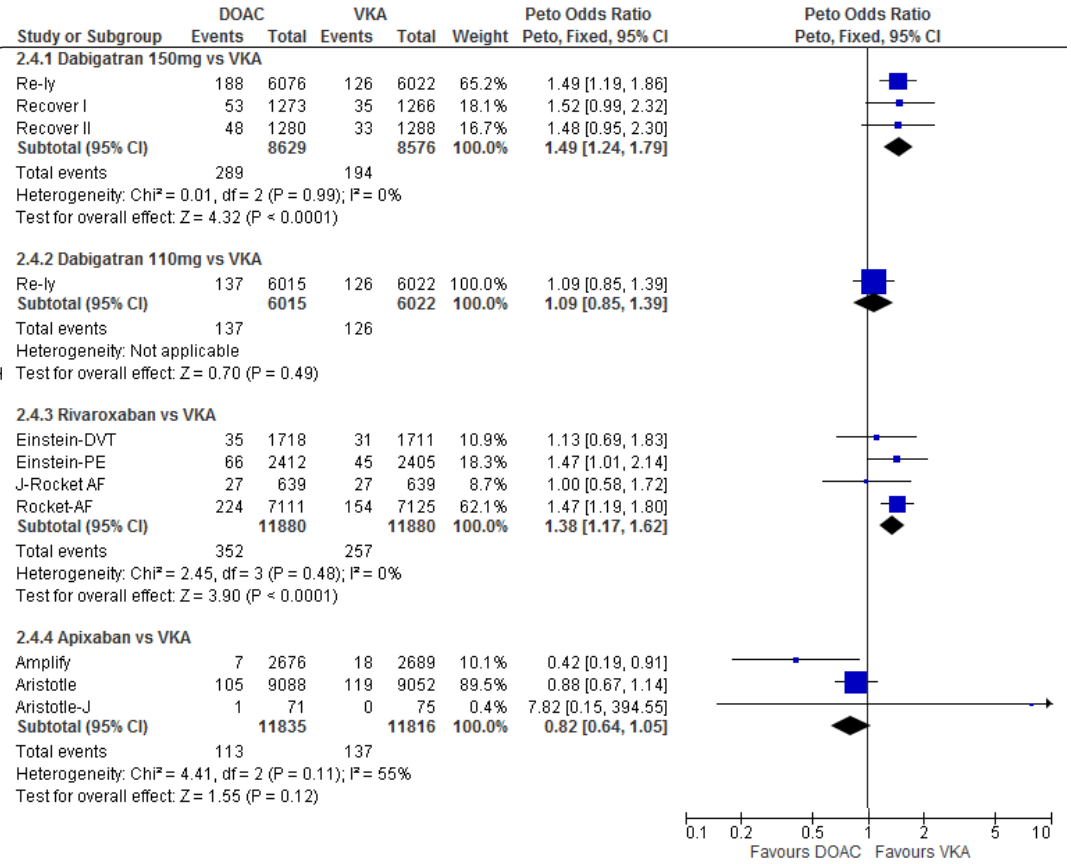


Figure S5. Forest Plots for risk of Gastrointestinal Bleeding in Elderly (left) and Total Population (right).

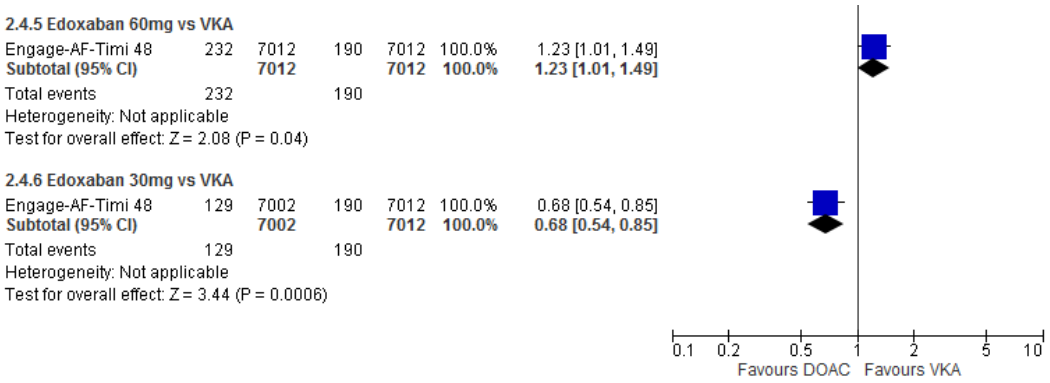


Figure S5. (contd) Forest Plots for risk of Gastrointestinal Bleeding in Total Population (right).

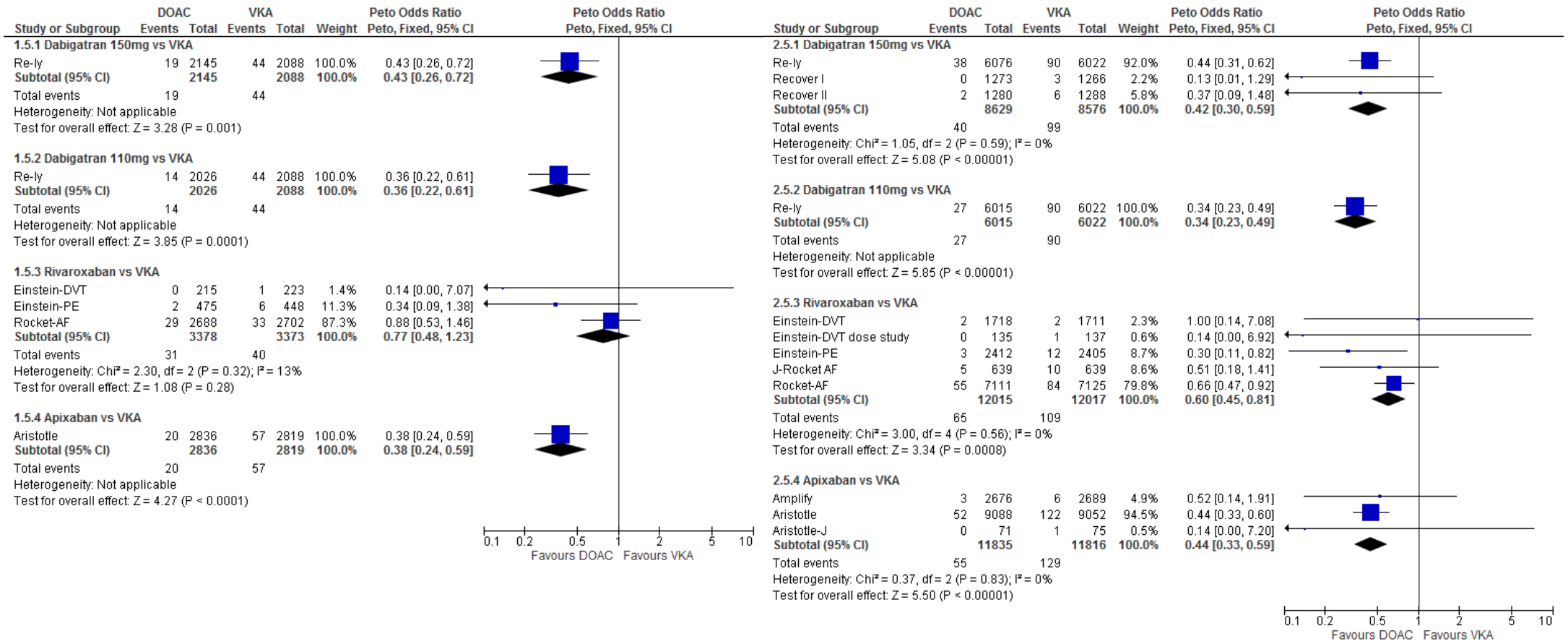


Figure S6. Forest Plots for risk of Intracranial Bleeding in in Elderly (left) and Total Population (right).

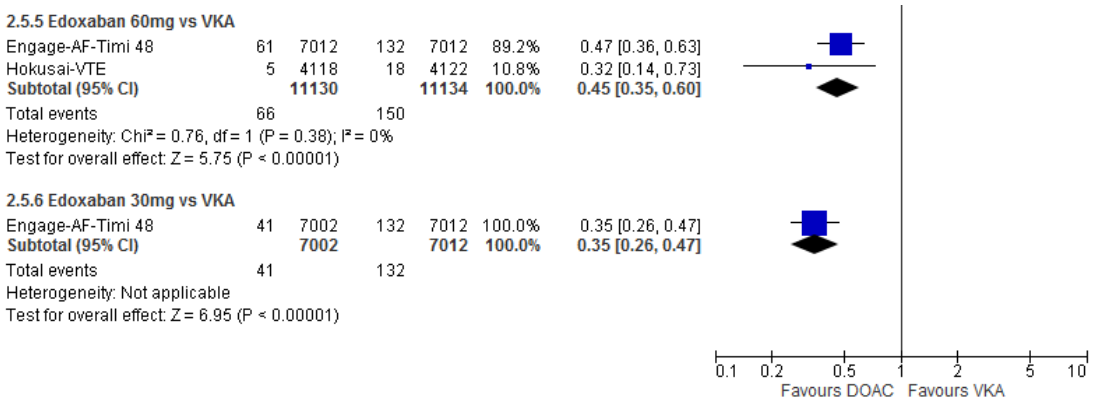
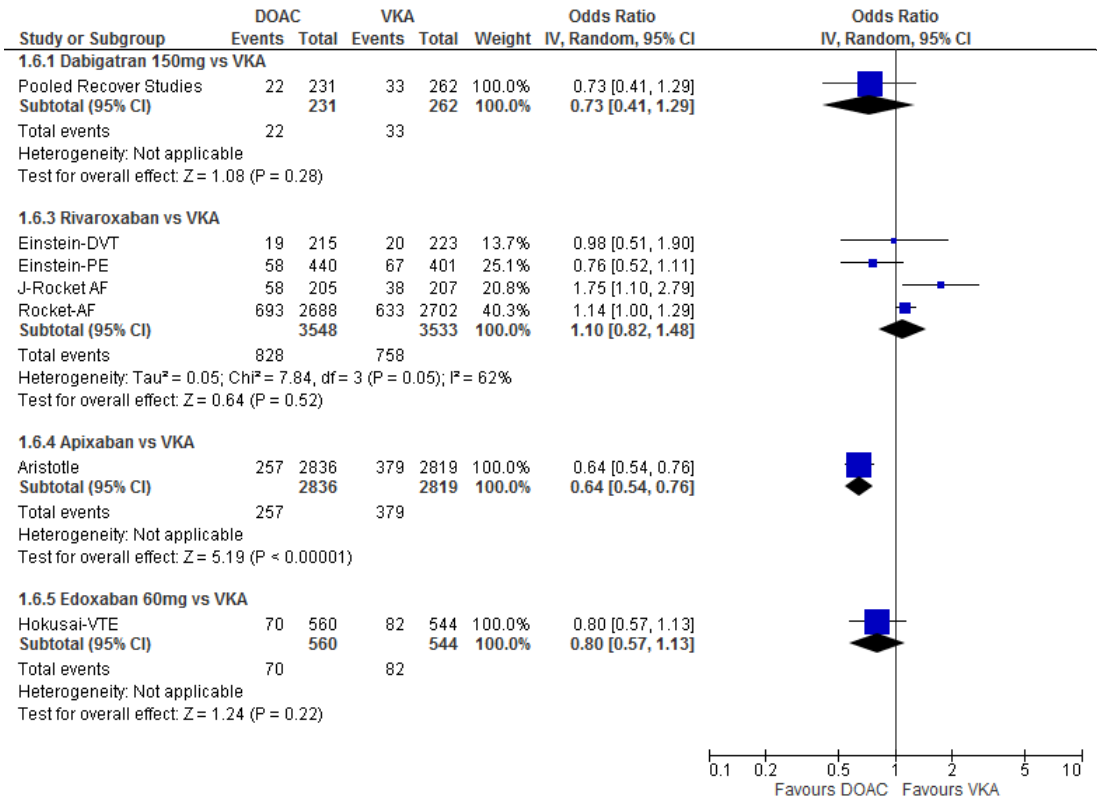


Figure S6. (contd) Forest Plots for risk of Intracranial Bleeding in Total Population (right).



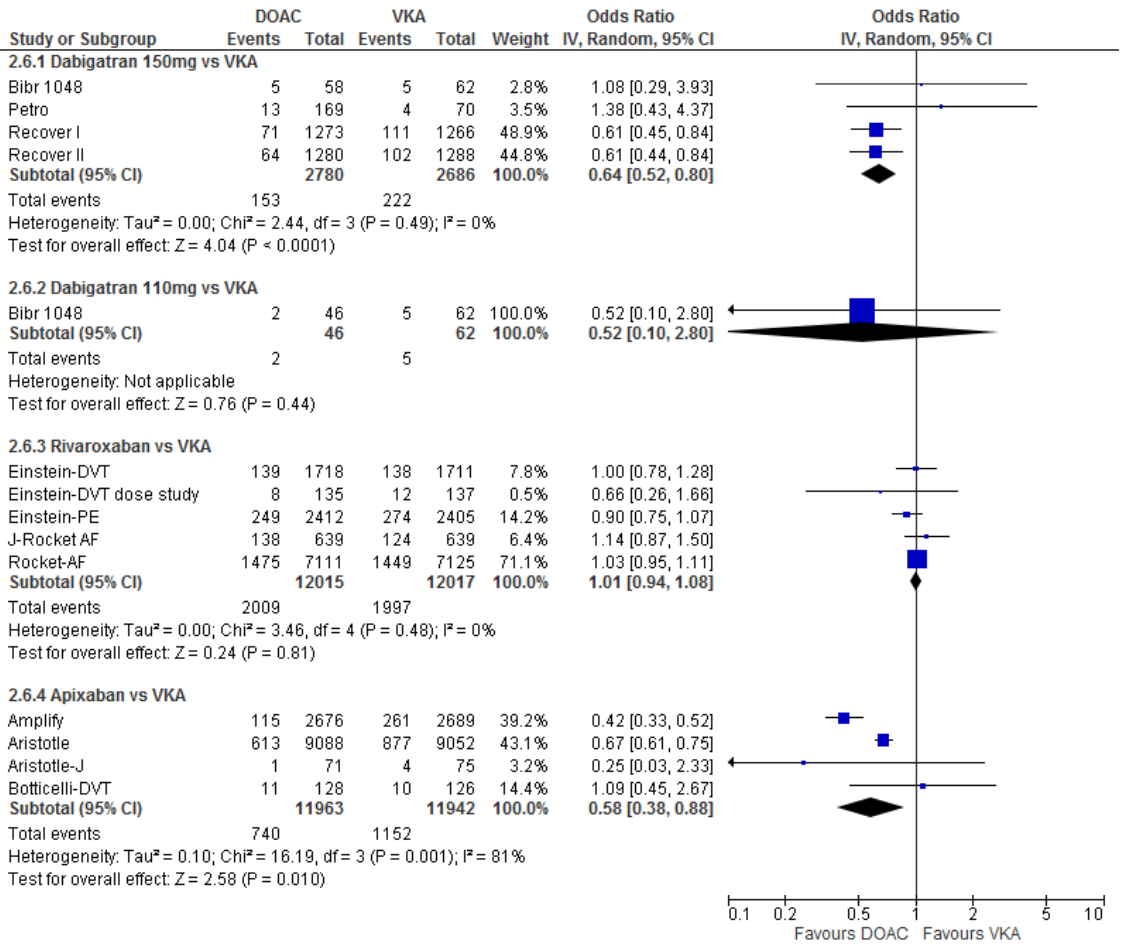


Figure S7. Forest Plots for risk of Clinically Relevant Bleeding in Elderly (left) and Total Population (right) - Random Effects Model

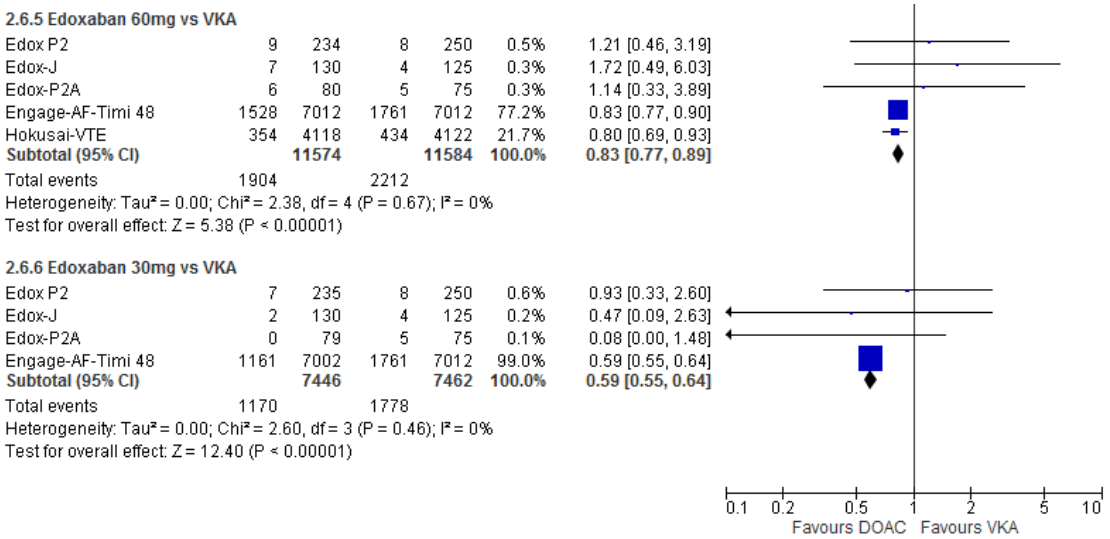
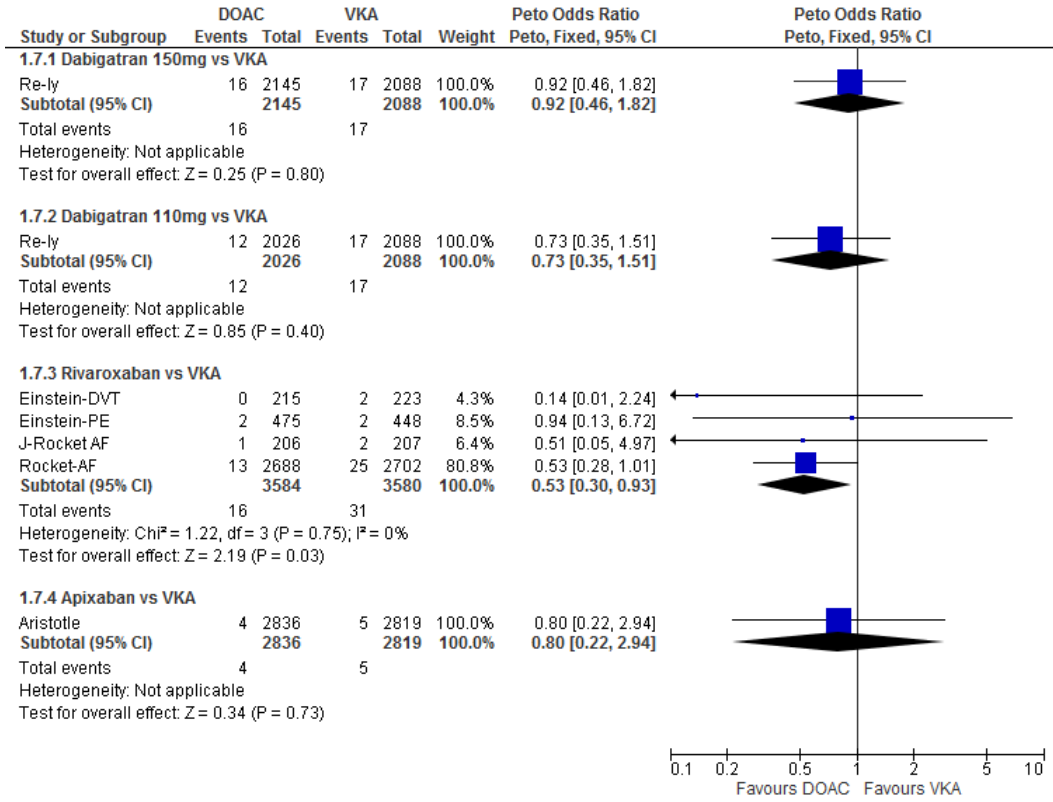


Figure S7. (contd) Forest Plots for risk of Clinically Relevant Bleeding in Total Population (right)- Random Effects Model



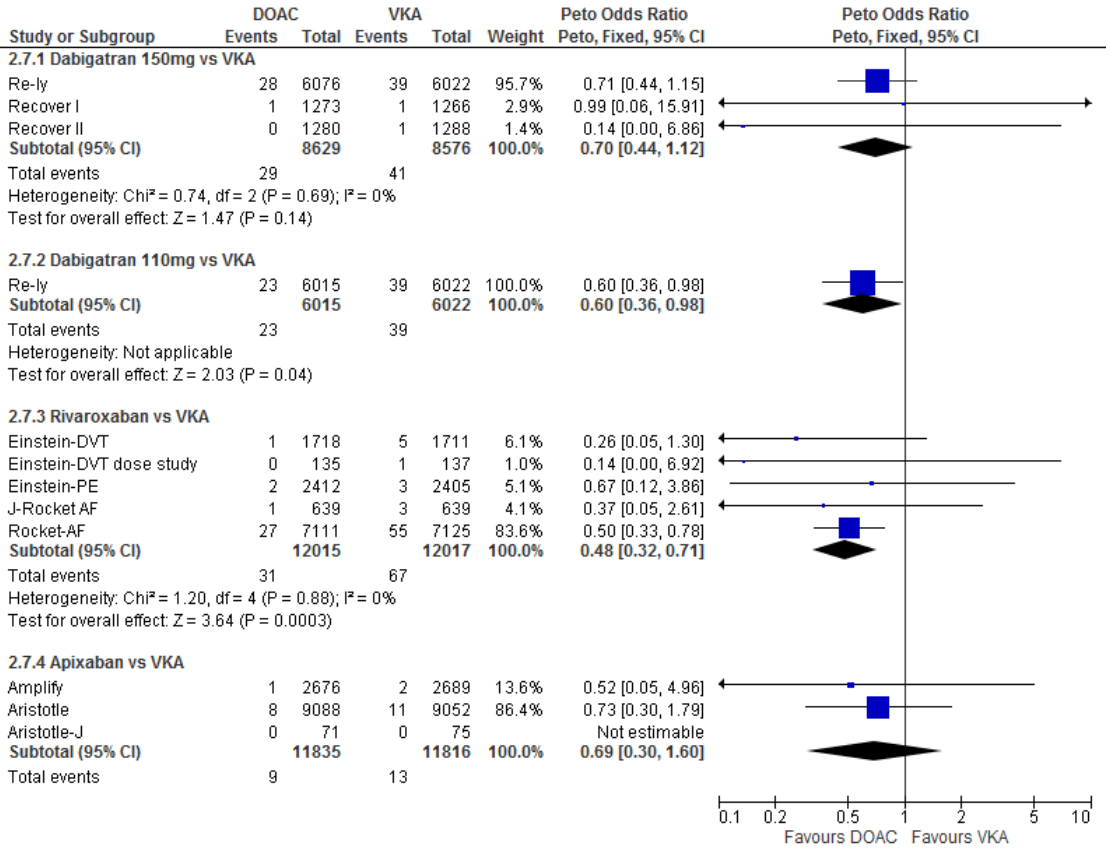


Figure S8. Forest Plots for risk of Fatal Bleeding in Elderly (left) and Total Population (right).

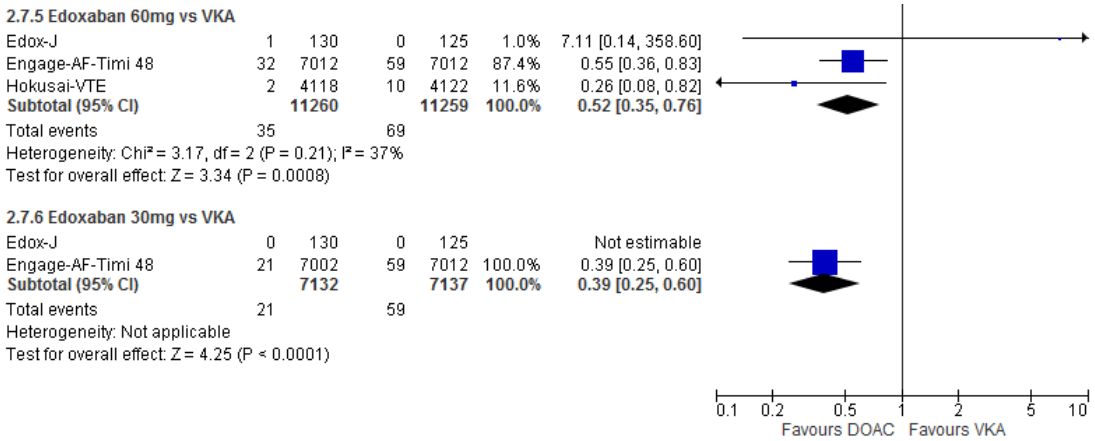
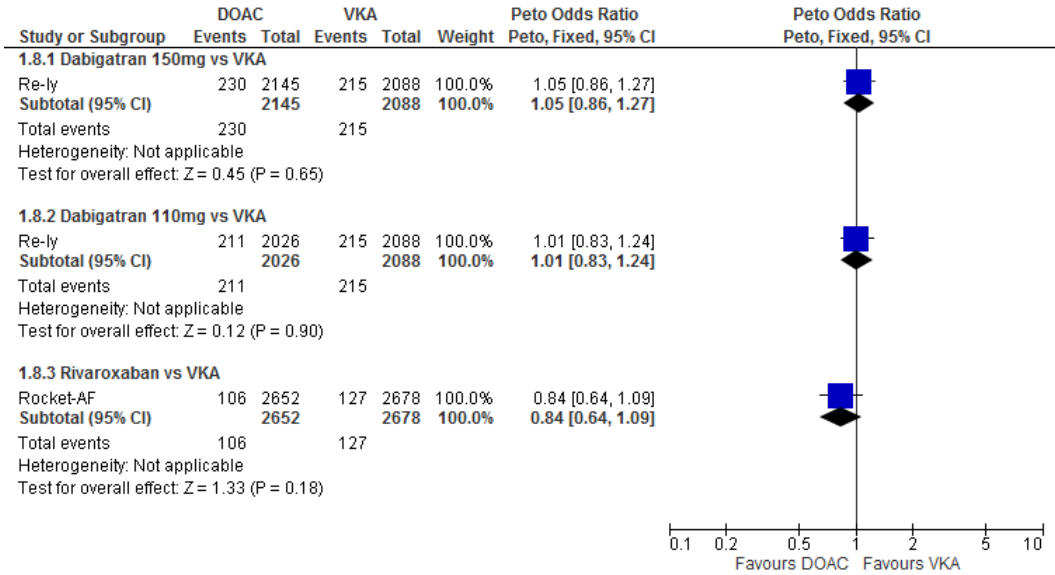


Figure S8. (contd) Forest Plots for risk of Fatal Bleeding in Elderly (left) and Total Population (right).



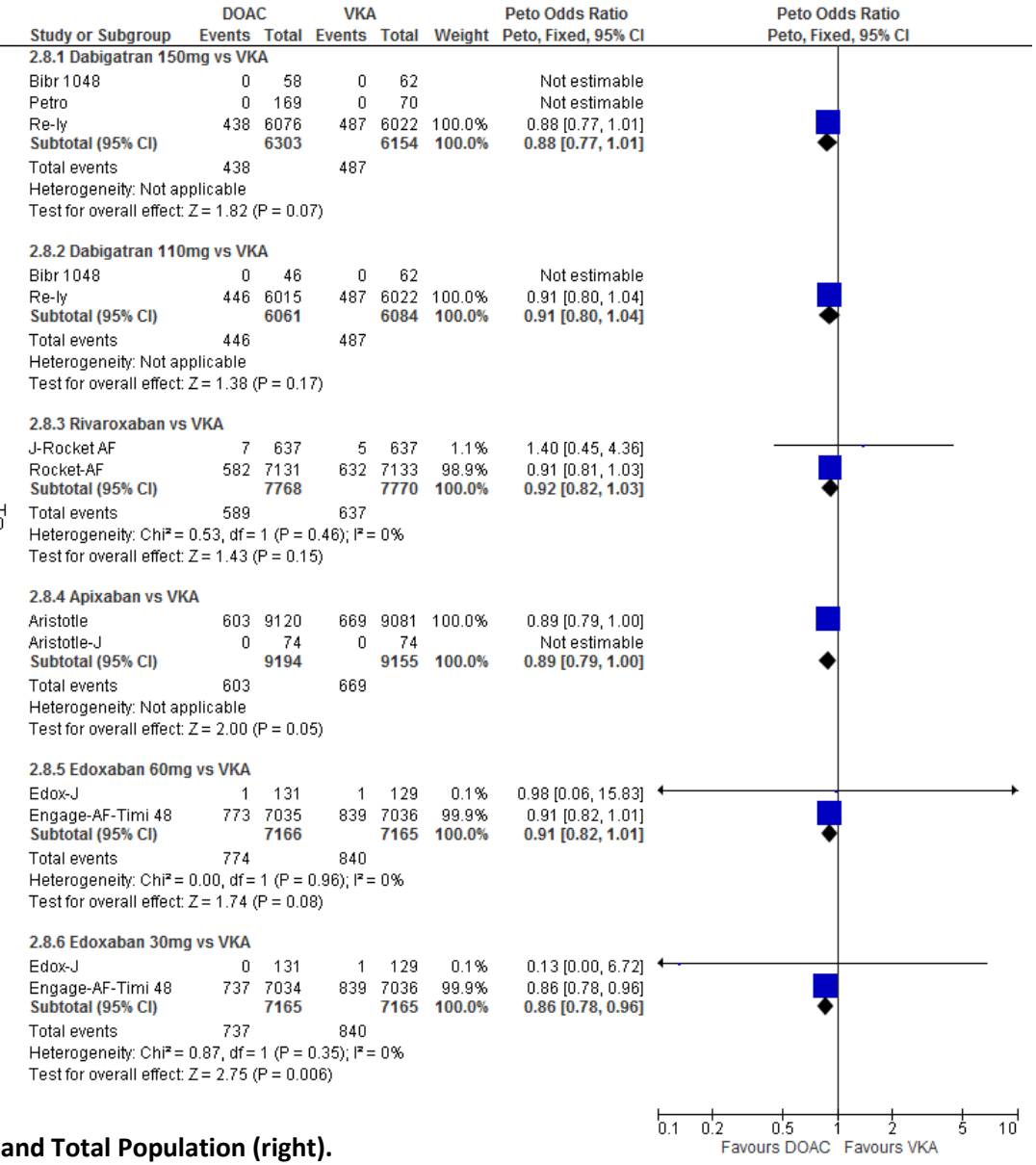


Figure S9. Forest Plots for risk of All Cause Death in Atrial Fibrillation in Elderly (left) and Total Population (right).

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

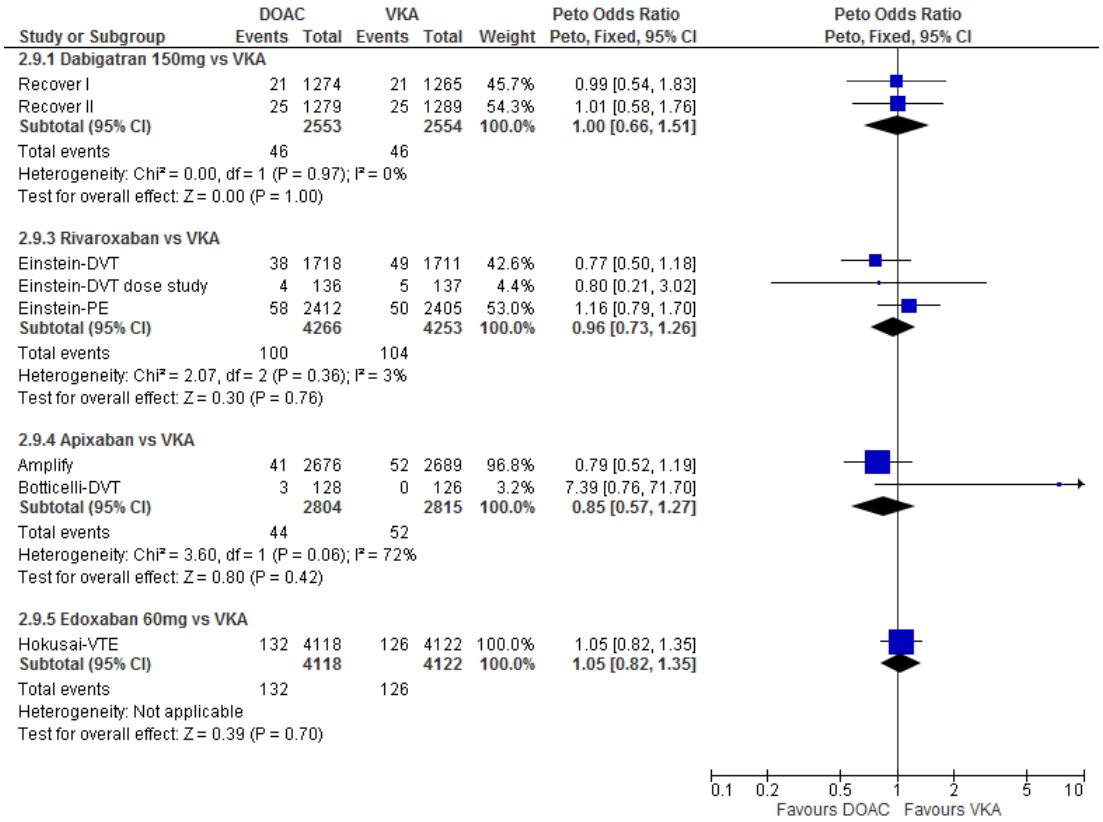
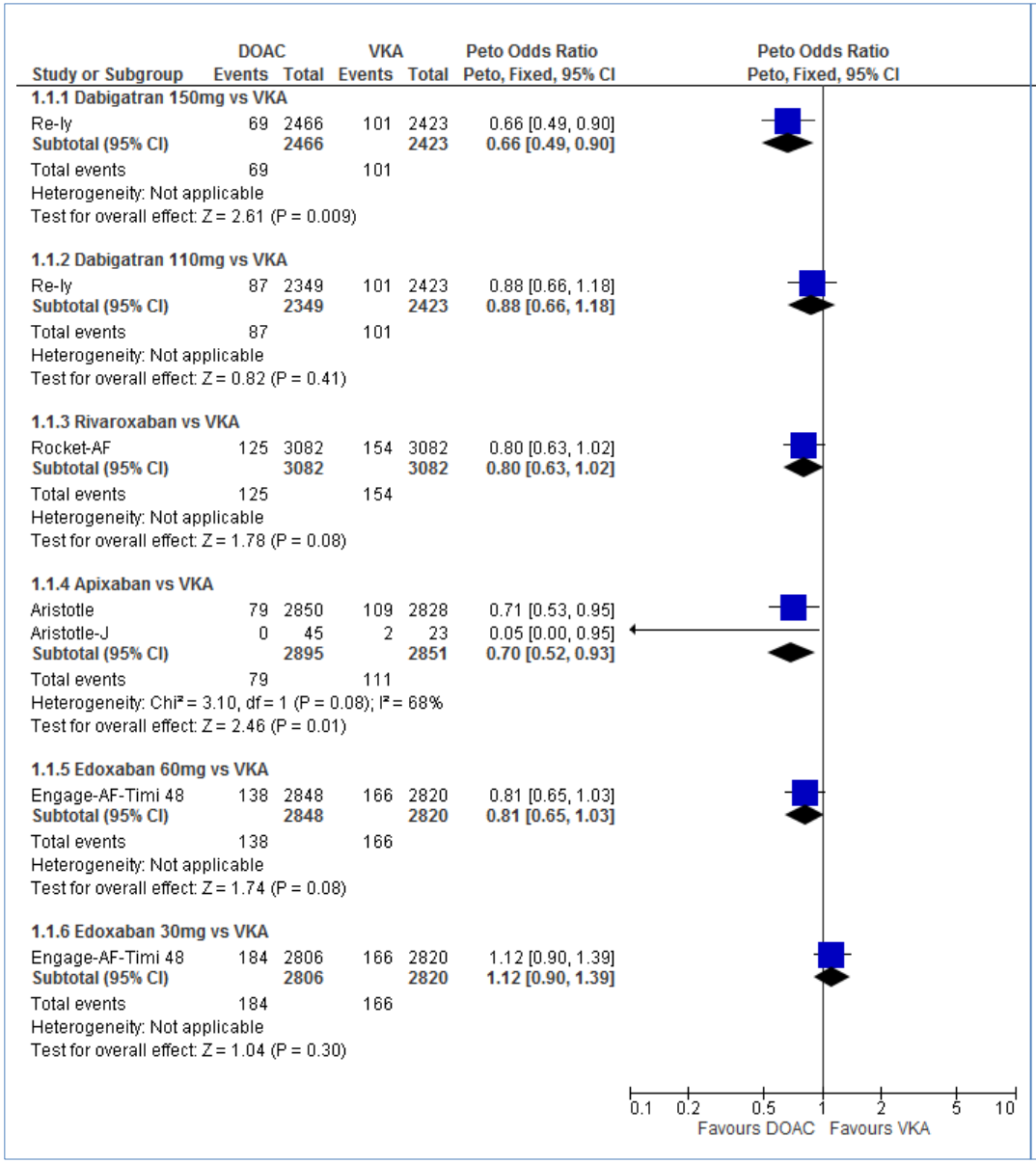


Figure S10. Forest Plots for risk of All Cause Death in Venous thromboembolism in Total Population (right).
*No results available for the elderly for this outcome

Elderly Population aged ≥75



Population aged <75

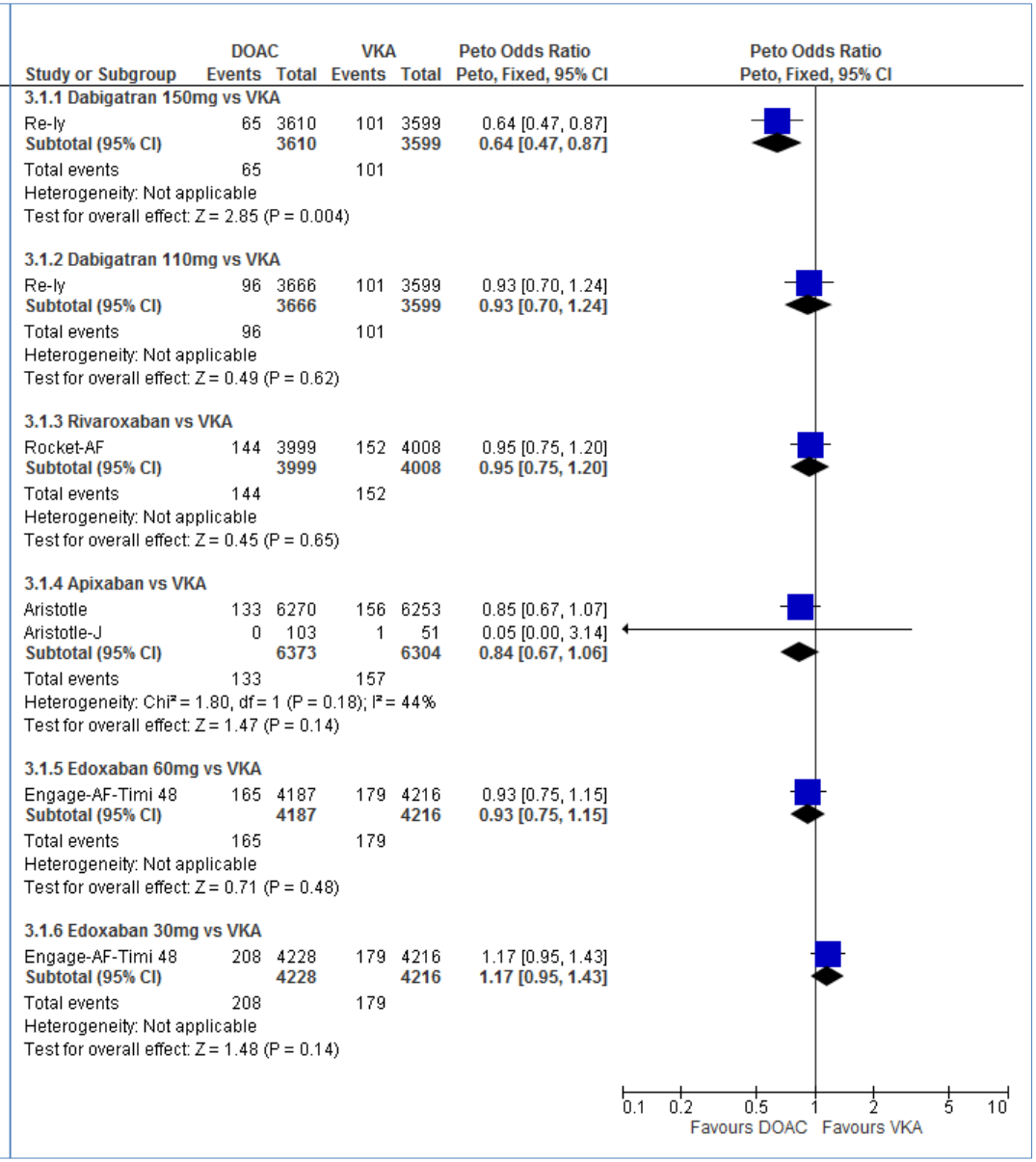
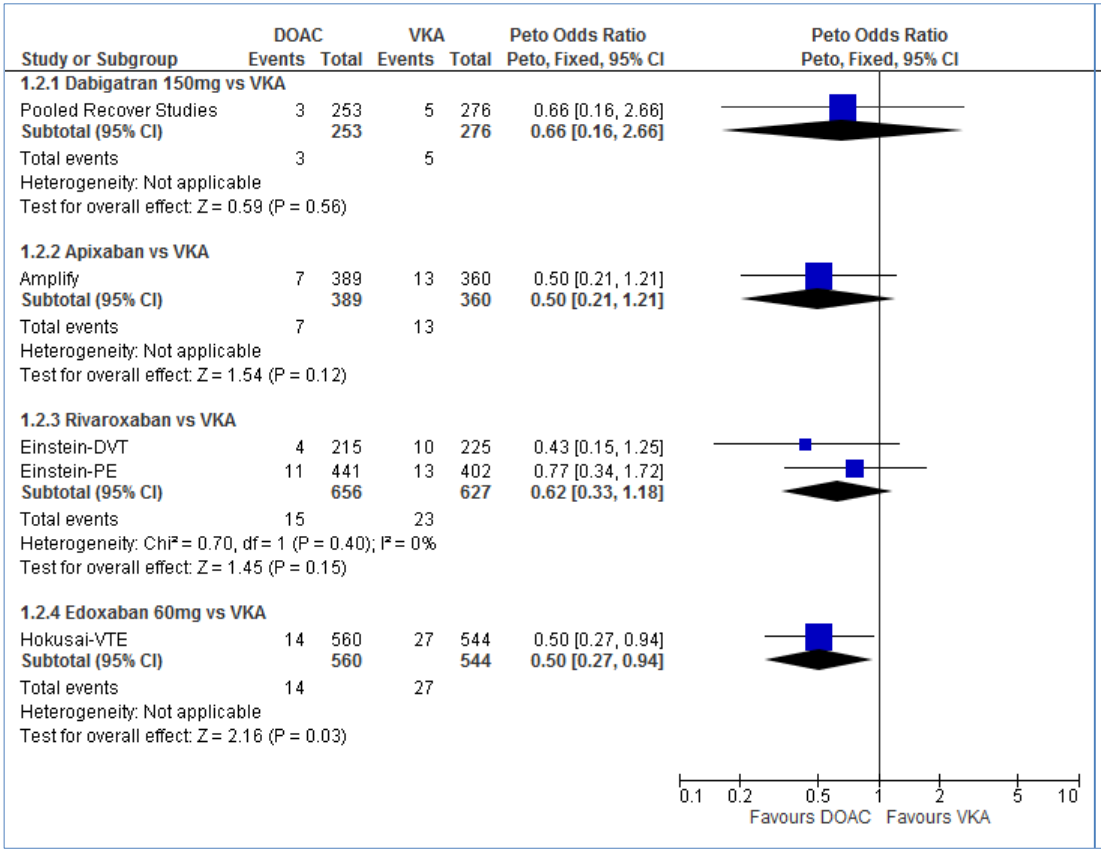


Figure S11. Forest Plots for risk of Stroke or Systemic Embolism in AF in Elderly (left) and <75 Population (right).

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

Elderly Population aged ≥75



Population aged < 75

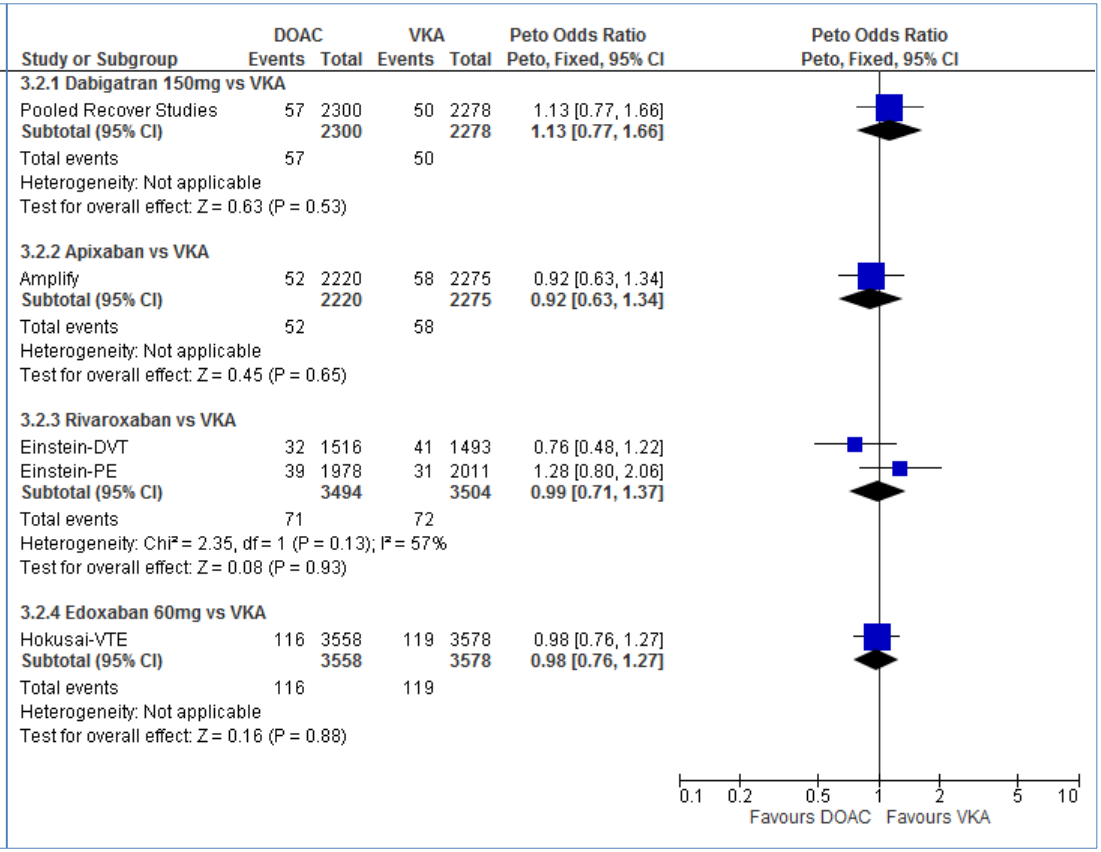


Figure S12. Forest Plots for risk of Venous Thromboembolism in VTE in Elderly (left) and <75 Population (right).

Elderly Population aged ≥75

Population aged <75 years

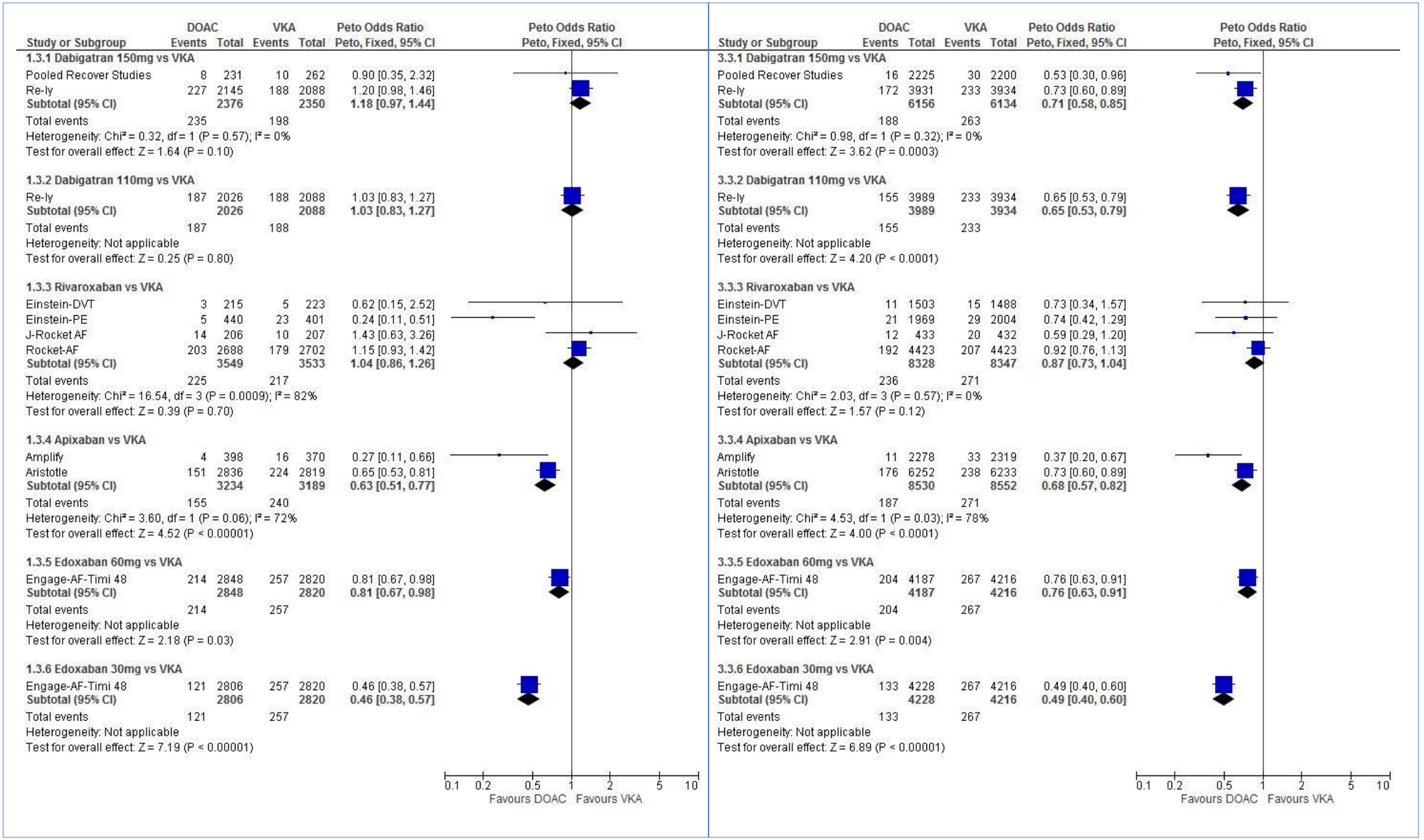
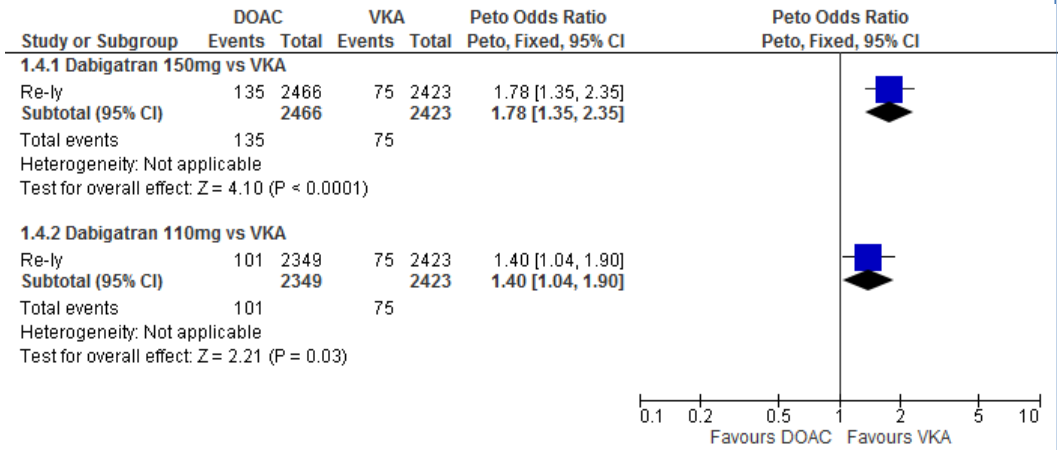


Figure S13. Forest Plots for risk of Major Bleeding in Elderly (left) and <75 Population (right).

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

Elderly Population aged ≥75



Population aged <75 years

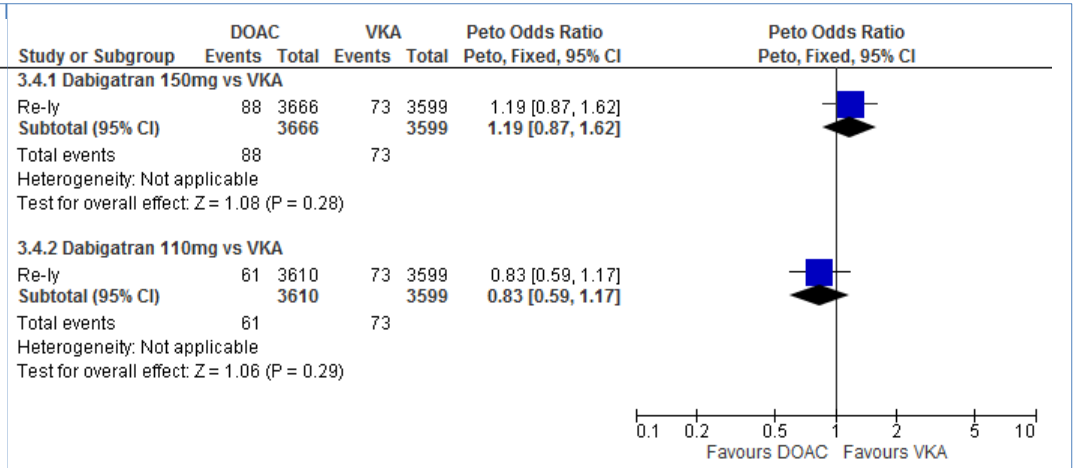
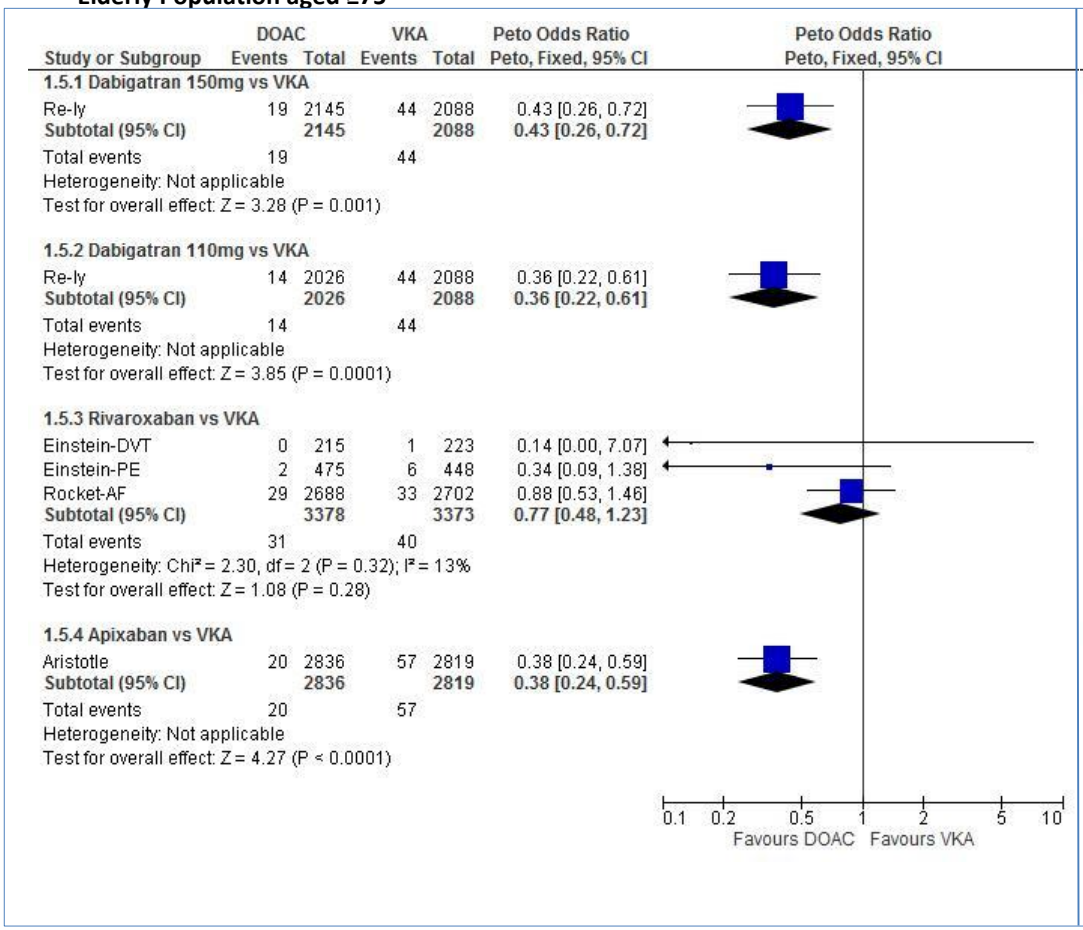


Figure S14. Forest Plots for risk of Gastrointestinal Bleeding in Elderly (left) and <75 Population (right).

Elderly Population aged ≥75



Population aged <75 years

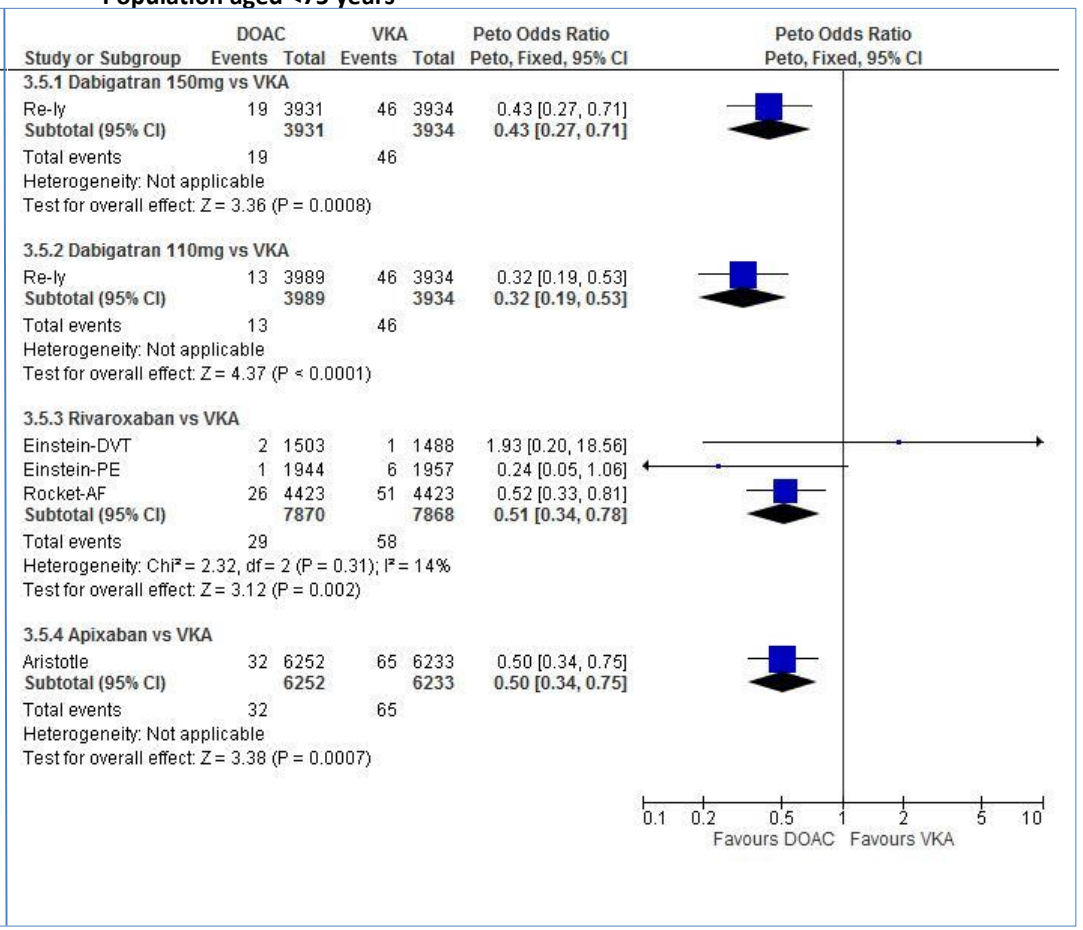
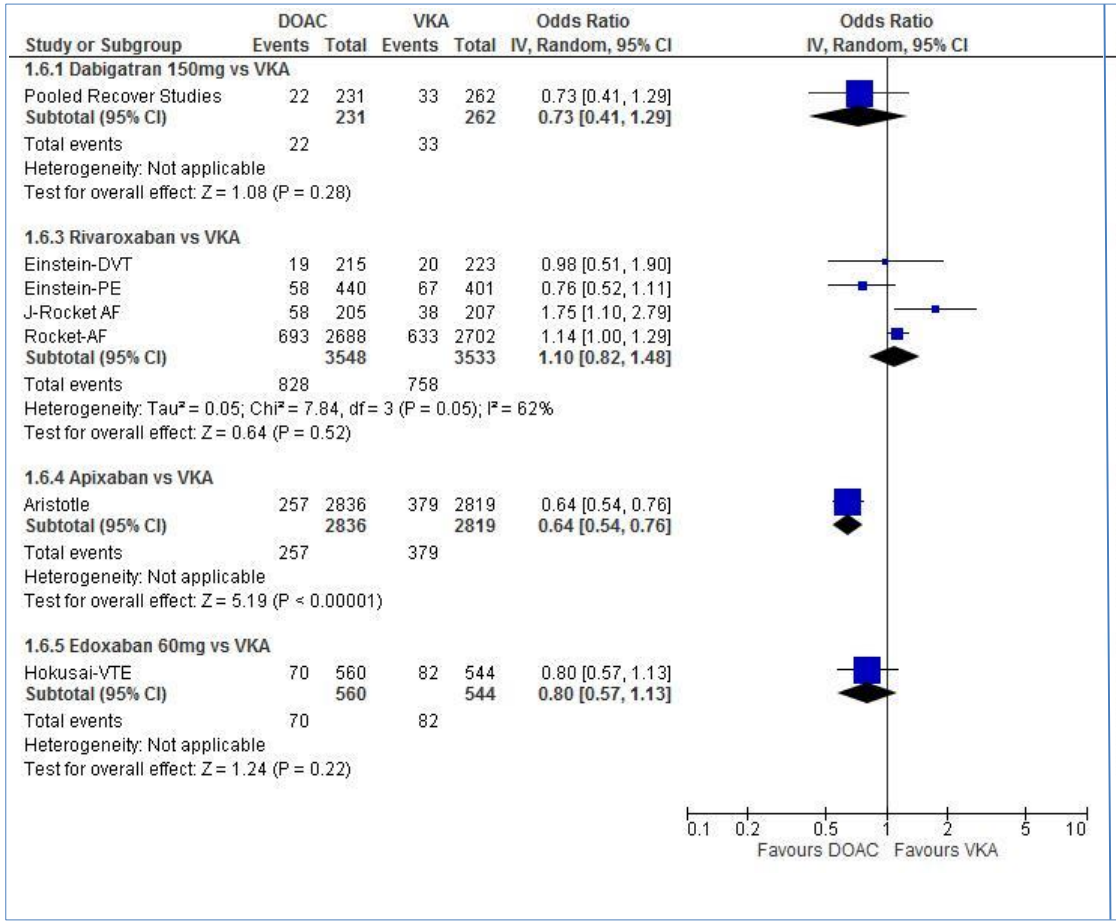


Figure S15. Forest Plots for risk of Intracranial Bleeding in Elderly (left) and <75 Population (right).

Elderly Population aged ≥75



Population aged <75 years

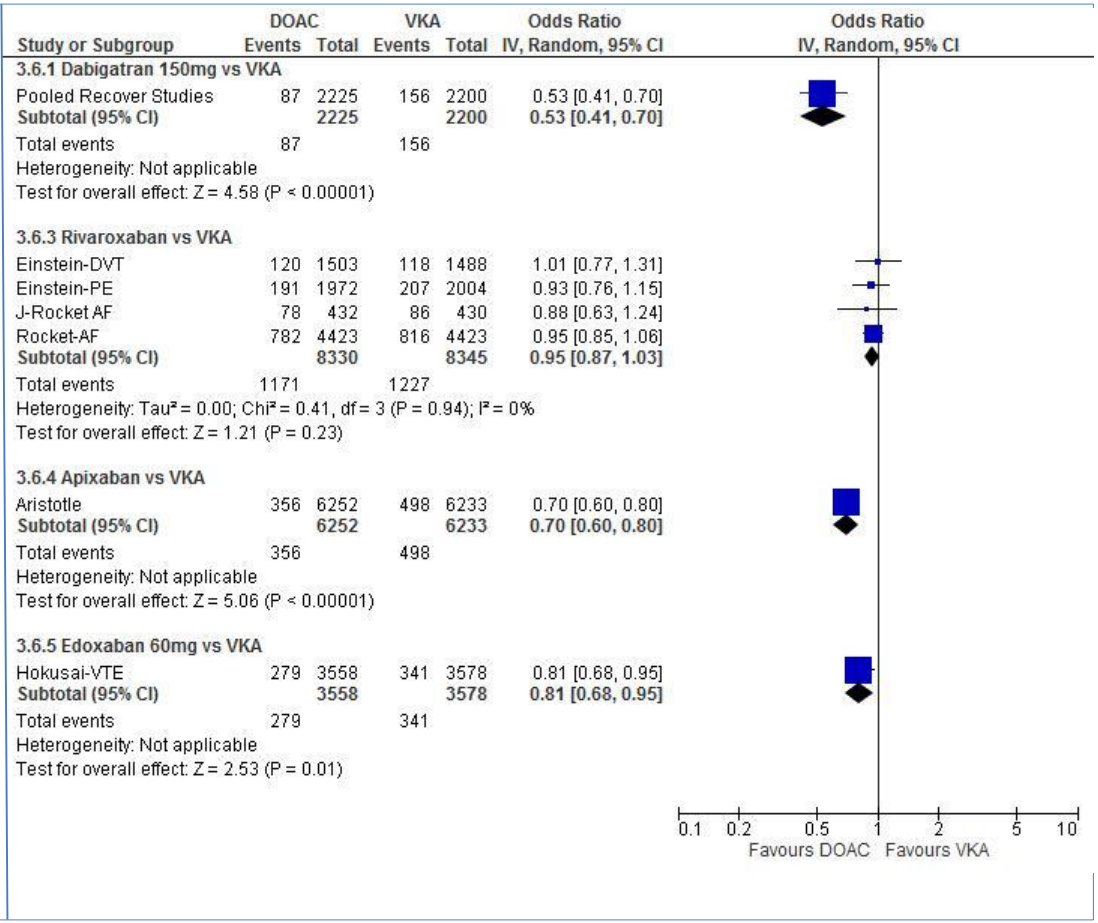
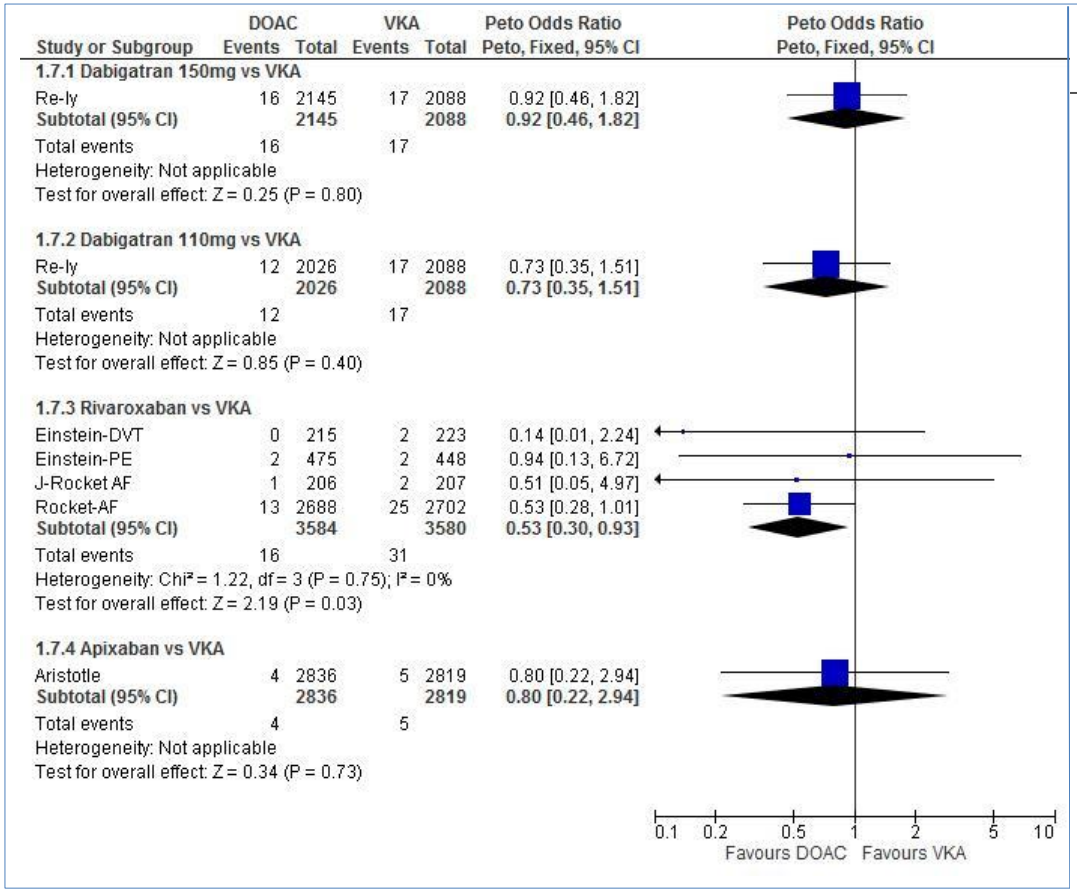


Figure S16. Forest Plots for risk of Clinically Relevant Bleeding in Elderly (left) and <75 Population (right) - Random Effects Model.

Elderly Population aged ≥75



Population aged <75 years

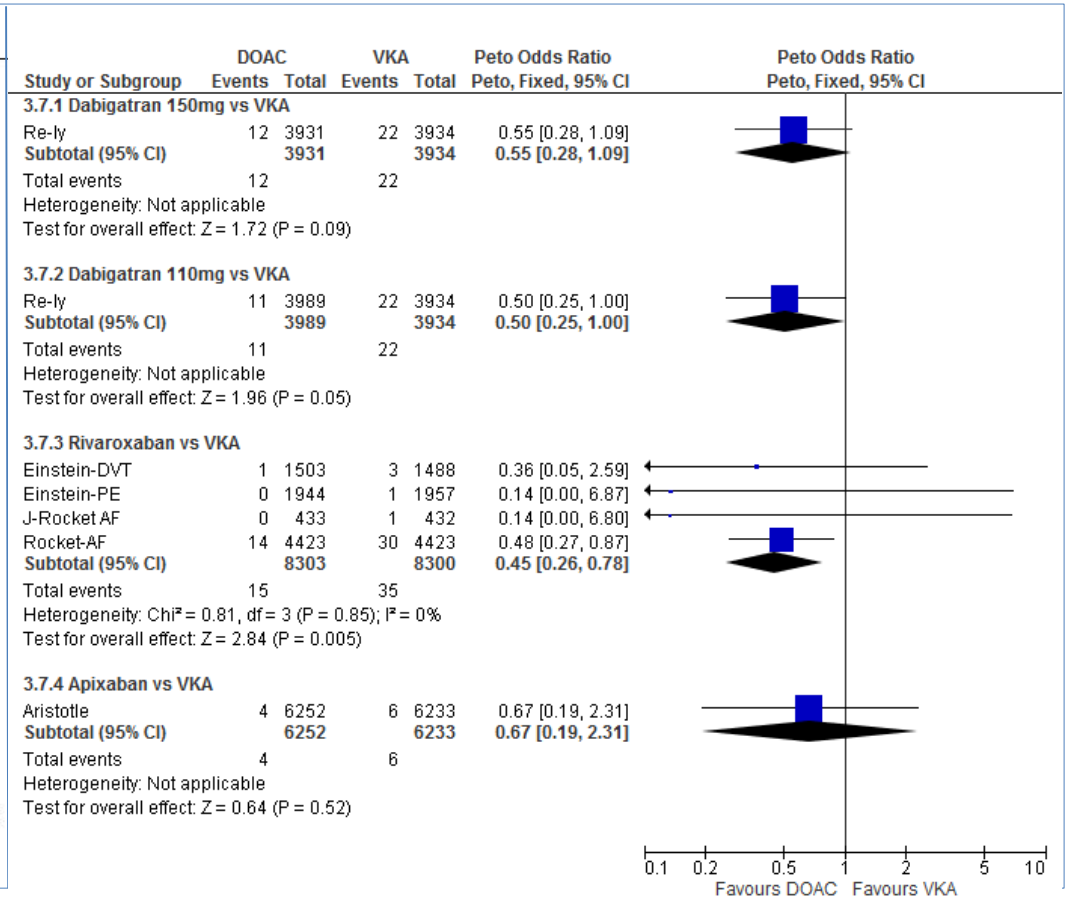
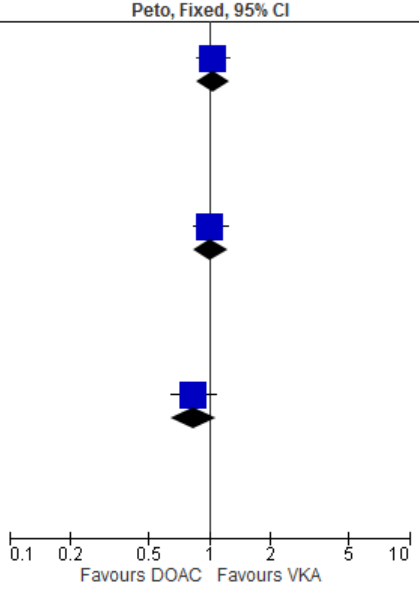


Figure S17. Forest Plots for risk of Fatal Bleeding in Elderly (left) and <75 Population (right).

Elderly Population aged ≥75

Study or Subgroup	DOAC Events	DOAC Total	VKA Events	VKA Total	Peto Odds Ratio Peto, Fixed, 95% CI
1.8.1 Dabigatran 150mg vs VKA					
Re-ly	230	2145	215	2088	1.05 [0.86, 1.27]
Subtotal (95% CI)		**2145**		**2088**	**1.05 [0.86, 1.27]**
Total events	230		215		
Heterogeneity: Not applicable					
Test for overall effect: Z = 0.45 (P = 0.65)					
1.8.2 Dabigatran 110mg vs VKA					
Re-ly	211	2026	215	2088	1.01 [0.83, 1.24]
Subtotal (95% CI)		**2026**		**2088**	**1.01 [0.83, 1.24]**
Total events	211		215		
Heterogeneity: Not applicable					
Test for overall effect: Z = 0.12 (P = 0.90)					
1.8.3 Rivaroxaban vs VKA					
Rocket-AF	106	2652	127	2678	0.84 [0.64, 1.09]
Subtotal (95% CI)		**2652**		**2678**	**0.84 [0.64, 1.09]**
Total events	106		127		
Heterogeneity: Not applicable					
Test for overall effect: Z = 1.33 (P = 0.18)					



Population aged <75 years

Study or Subgroup	DOAC Events	DOAC Total	VKA Events	VKA Total	Peto Odds Ratio Peto, Fixed, 95% CI
3.8.1 Dabigatran 150mg vs VKA					
Re-ly	208	3931	272	3934	0.75 [0.63, 0.91]
Subtotal (95% CI)		**3931**		**3934**	**0.75 [0.63, 0.91]**
Total events	208		272		
Heterogeneity: Not applicable					
Test for overall effect: Z = 3.01 (P = 0.003)					
3.8.2 Dabigatran 110mg vs VKA					
Re-ly	235	3989	272	3934	0.84 [0.70, 1.01]
Subtotal (95% CI)		**3989**		**3934**	**0.84 [0.70, 1.01]**
Total events	235		272		
Heterogeneity: Not applicable					
Test for overall effect: Z = 1.86 (P = 0.06)					
3.8.3 Rivaroxaban vs VKA					
Rocket-AF	112	4409	131	4404	0.85 [0.66, 1.10]
Subtotal (95% CI)		**4409**		**4404**	**0.85 [0.66, 1.10]**
Total events	112		131		
Heterogeneity: Not applicable					
Test for overall effect: Z = 1.24 (P = 0.21)					

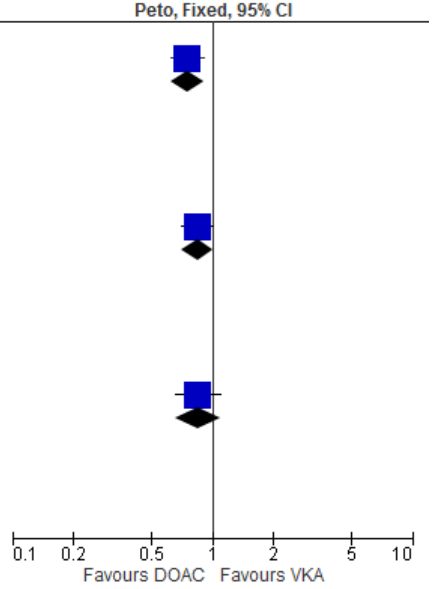


Figure S18. Forest Plots for risk of All Cause Death in AF in Elderly (left) and <75 Population (right).

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

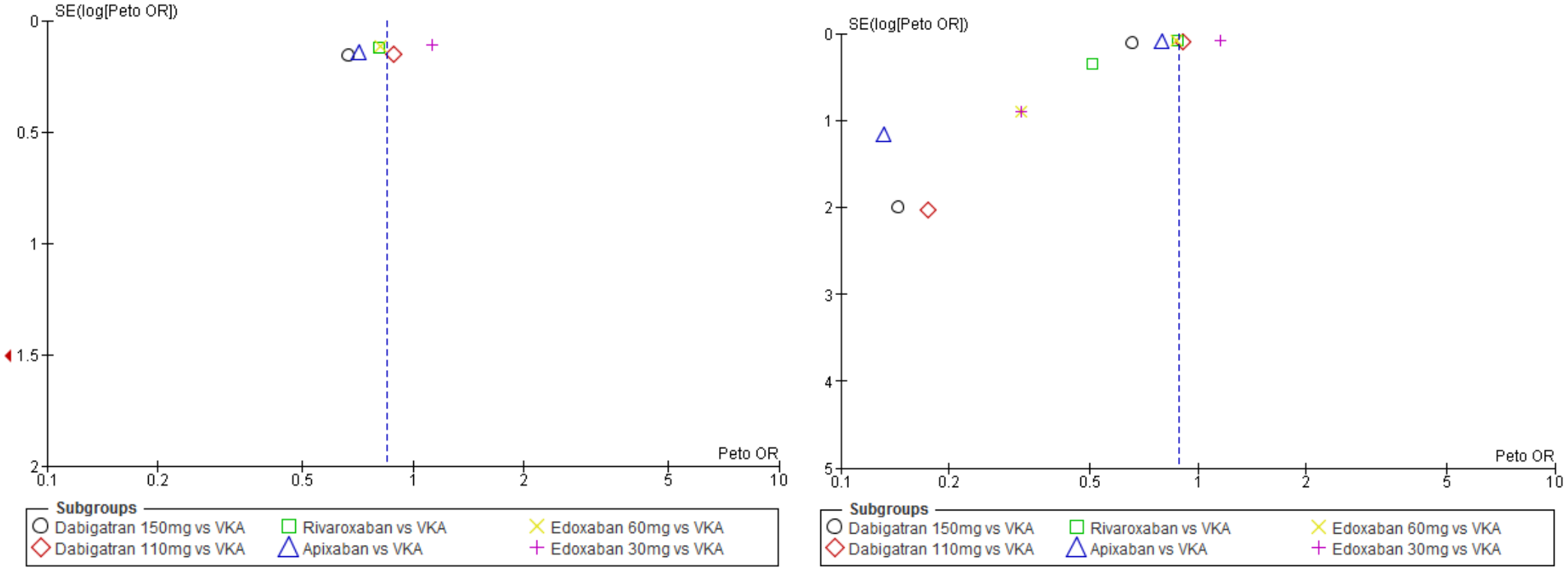


Figure S19. Funnel Plots for Stroke or Systemic Embolism in AF in Elderly (left) and Total population (right).

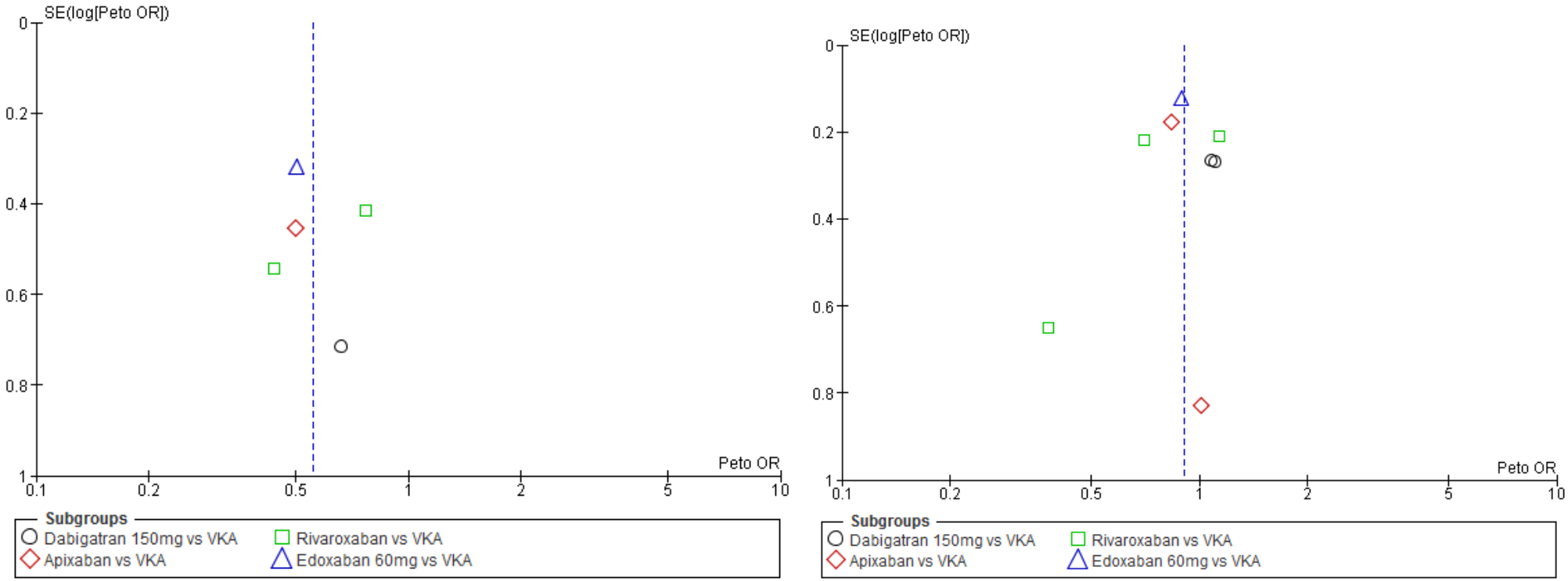


Figure S20. Funnel Plots for risk of Recurrent Venous Thromboembolism in VTE in Elderly (left) and Total population (right).

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