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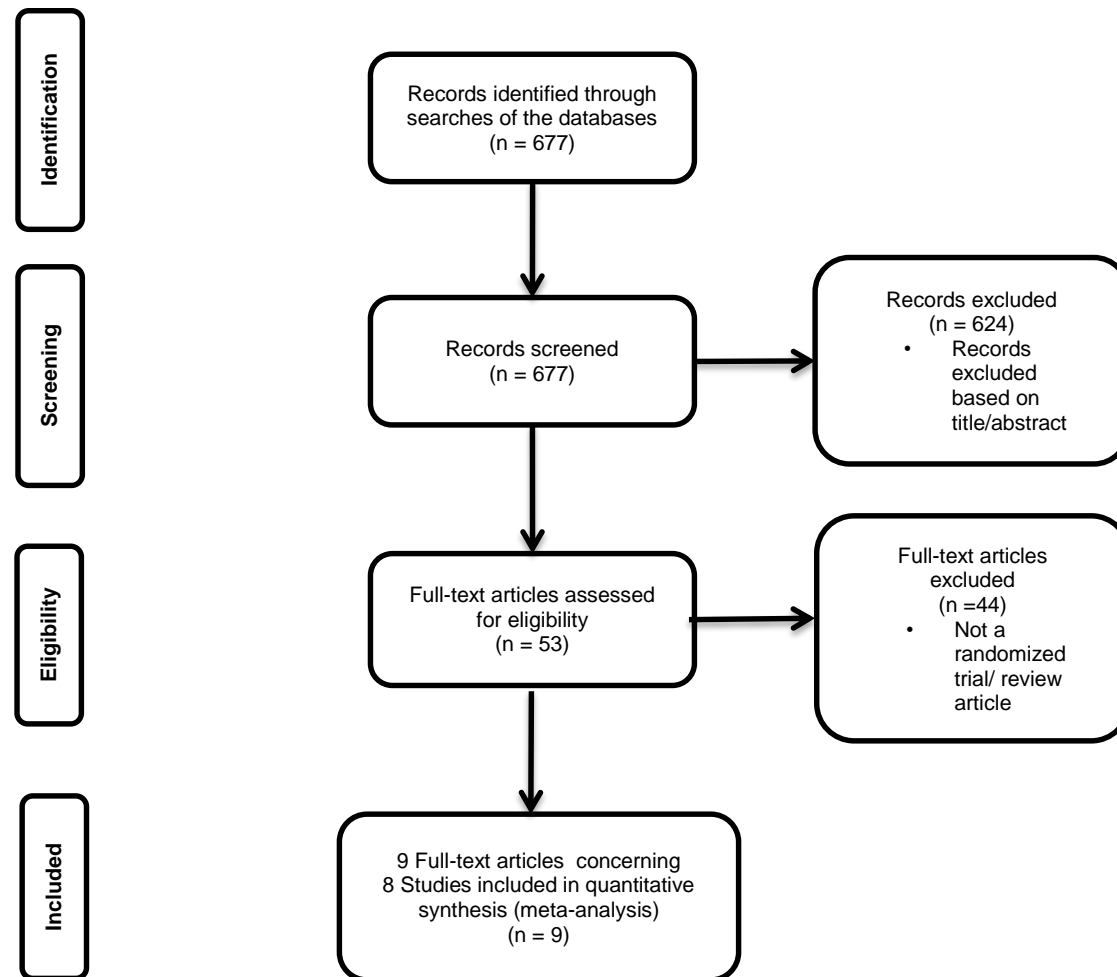
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**Figure S1. Flowchart of literature search.**



## Detailed statistical methods: data synthesis and analysis

The methodological quality of randomized studies was assessed using the Cochrane Collaboration tool for assessing risk of bias. For each clinical trial, bias was assessed qualitatively as low, unclear or high (Table S2). The assessment was made independently by two authors (SG and MM). A meta-analysis comparing the results of individual NOACs vs. warfarin was performed using a random model, which considered between-study variance-tau-squared. Random effects models are more conservative, leading the estimates with wider confidence intervals. In case the  $\tau^2$  were zero, the pooled estimate of the random model would correspond to those from the fixed-effect model. As a measure of the effect, the Mantel-Haenszel relative risk (RR) with 95% confidence interval was used. A sensitivity analysis was performed by excluding the results of 30mg edoxaban from the ENGAGE AF-TIMI study [26].

Furthermore, in case we took under consideration three arms studies (two different doses and control group), the analysis was performed twice: first, performing the analysis separately to different dosages, which required doubling the events and sample size of the control group. Due to this approach, we could get an estimate of a particular dose. In the second approach, we combined the results of different dosages into one group vs. control. This approach maintained a real number of events in the control group, but as a result, the obtained estimate reflects artificial dosage (non-existing one). Both results are presented in the supplementary material. If results remain consistent across the different models then, the results can be considered robust. Additionally, a difference between the effects obtained from drug's classes comparison - Direct Thrombin Inhibitors (DTI) vs warfarin and factor Xa inhibitors (FXa inhibitors) vs warfarin - was analyzed. The calculations were performed using Review Manager (RevMan 5.3 Cochrane Community, Copenhagen: The Nordic Cochrane Centre, The Cochrane Collaboration, 2014).

For comparisons between individual drugs as well as each of them with warfarin, we used a network meta-analysis (network plot) (Fig.S44) We analyzed endpoints for which at least two direct studies of the particular drug vs. warfarin were available. Therefore, network analysis was not used for edoxaban 30mg and for risk assessment of CVD and ST. The RR values for MI are presented in Fig.5. Calculations were performed three times; based on data from the original RELY study [23] and after data correction in the intention-to-treat and on-treatment analysis [27].

Indirect analysis of the 'star' type network was performed using the Busher's method. Network meta-analysis was performed with mvmet command (STATA). We then estimated the relative probability of ranking each therapy and obtained a hierarchy of competing treatments using SUCRA (surface under the cumulative ranking) with the method proposed by G. Salanti [31], which requires estimation of the probability of being the best for a particular therapy. The probability is estimated based on the Bayesian model. We assume uniform distribution as a priori distribution. As a result, we get a posterior normal distribution with mean and variance, where estimators of normal distribution parameters are estimated based on frequentist inference.

The SUCRA (Surface Under the Cumulative Ranking) score is a metric to evaluate which treatment in a network is likely to be the most efficacious in the context of network meta-analyses. The SUCRA score is calculated in the function using the formula described by G. Salanti et al. [31]:

$$SUCRA_j = \frac{\sum_{b=1}^{a-1} cum_{jb}}{a-1}$$

Where j is some treatment, a are all competing treatments, b are the b=1,2,...,a-1 best treatments, and cum represents the cumulative probability of a treatment being among the b best treatments.

Calculations were made with STATA 15.1 software (StataCorp LLC, College Station, Texas, United States).

**Table S1a. The characteristics of studies included in meta-analysis.**

Study	RE-LY, 2009 [23]  n=18113	ROCKET AF, 2011, [24]  n=14264	ENGAGE AF-TIMI 48, 2013 [26]  n=21105	ARISTOTLE, 2011 [25]  n=18201	PIONEERAF-PCI, 2016 [3]  n=2124	RE-DUAL PCI, 2017 [4]  n=2725	AUGUSTUS, 2019 [5]  n=4614	ENTRUST-AF - PCI, 2019 [6]  n=1506
Inclusion criteria	AF and one of: previous stroke or transient	AF and history of stroke, TIA, or systemic	AF and CHADS2 >2, and anticoagulation	AF and one of : age of at least 75 years; previous stroke, TIA,	AF and PCI	AF and successful PCI	AF and planned use of OAC ; recent ACS or PCI; and planned use	AF and PCI for ACS or SCC



	<p>ischemic attack, LVEF &lt; 40%, NYHA II or higher, HF symptoms within 6 months before screening, and an age of at least 75 years or an age of 65 to 74 years plus DM, HA, or CAD</p>	<p>embolism or at least two of the following risk factors: HF or LVEF of 35% or less, HA, an age of 75 years or more, or the presence of DM</p>	<p>therapy planned for the duration of the trial</p>	<p>or systemic embolism; symptomatic heart failure within the previous 3 months or LVEF &lt; 40%; DM or HA</p>		<p>within the previous 120 hours; ACS or SCC</p>	<p>of a P2Y12 inhibitor for at least 6 months</p>	
Exclusion criteria	<p>severe heart-valve disorder, stroke within 14 days or severe stroke within 6 months before screening, increased the risk of</p>		<p>reversible cause of AF; severe renal insufficiency; a high risk of bleeding; use of dual antiplatelet therapy; moderate-to severe</p>	<p>reversible cause of AF, moderate or severe mitral stenosis, conditions other than atrial fibrillation that required anticoagulation, stroke</p>	<p>history of stroke or transient ischemic attack, gastrointestinal bleeding, severe renal insufficiency, anemia, increased</p>	<p>bioprosthetic or mechanical heart valves, severe renal insufficiency or other major coexisting conditions.</p>	<p>OAC for other indication, severe renal insufficiency, intracranial hemorrhage, CABG, coagulopathy, bleeding, contraindication for study therapy</p>	

	hemorrhage, severe renal insufficiency, active liver disease, and pregnancy.		mitral stenosis; other indications for anticoagulation therapy; ACS, coronary revascularization, or stroke within 30 days before randomization; and an inability to adhere to study procedures.	within the previous 7 days, a need for aspirin at a dose of >165 mg a day or for both aspirin and clopidogrel, and severe renal insufficiency	risk of bleeding			
Mean follow up	2 years	707 days	2.8 years	1.8 years	3 years	14 months	7 months	12 months
Primary Outcomes	Stroke or systemic embolism	Stroke and systemic embolism	Stroke or systemic embolism	Stroke or systemic embolism	Clinically significant bleeding	Major or clinically relevant bleeding	Major or clinically relevant bleeding	Major or clinically relevant bleeding,
Secondary Outcomes	Stroke, systemic embolism and death	Stroke, systemic embolism, death from	Stroke, systemic embolism, or death from cardiovascular	Death from any cause, MI	Bleeding, death from cardiovascular causes, MI, stroke, stent thrombosis	MI, stroke, systemic embolism, death, unplanned revascularization	Death, hospitalization, stroke, MI, sent thrombosis, urgent revascularization	Efficacy – cardiovascular death, stroke, systemic embolic

		cardiovascular causes, MI	causes, MI, death from any cause					event, MI definite stent thrombosis
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\*From Hohnloser SH et al. [27]

<sup>a</sup> From Connolly SJ et al. [23] and Hohnloser SH et al. [27]

AF – atrial fibrillation, ACS – acute coronary syndrome, CABG – coronary artery bypass grafting, CAD – coronary artery disease, DM – diabetes mellitus, HA – arterial hypertension, HF – heart failure, LVEF – left ventricle ejection fraction, MI – myocardial infarction, NYHA – New York Heart Association classification, OAC – oral anticoagulants, PCI – percutaneous angioplasty, SCC – stable coronary syndrome, TIA – transient ischaemic attack,

**Table S1b . MACE (++) and thromboembolic or ischemic end points (+)**

Study	RE-LY	ROCKET AF	ENGAGE AF TIMI 48	ARISTOTLE	PIONEER-AF PCI	RE-DUAL PCI	AUGUSTUS	ENTRUST-AF -PCI
Endpoint								
Overall mortality	+	+	+	++	++	++	++	+
Cardiovascular mortality	+	++	++		+		+	++
Cardiac death	++*							
Cardiac arrest	++*							
Myocardial infarction	++ (a)	++	++	++	++	++	++	++
Unstable angina	++*							
Stroke	++	++	++	++	++	++	++	++
Stent thrombosis					+	+	+	++

Systemic embolism	++*	++	++	++		++		++
Revascularisation	++*					++	+	

\*From Hohnloser SH et al. [27]

<sup>a</sup> From Connolly SJ et al. [23] and Hohnloser SH et al. [27]

**Table S1c. Characteristics of patients in clinical trials included in the meta-analysis – RE-LY, ROCKET AF, ENGAGE AF TIMI 48, ARISTOTLE**

Characteristics	RE-LY			ROCKET AF		ENGAGE AF TIMI 48			ARISTOTLE	
Treatment/dose	Dabigatran 110 mg (n =6015)	Dabigatran 150 mg (n =6076)	Warfarin (n=6022)	Rivaroxaban 20 mg or 15 mg daily if CrCl 30-49 ml/min (n =7131)	Warfarin (n =7133)	High Dose Edoxaban (n =7035)	Low Dose Edoxaban (n =7034)	Warfarin (n =7036)	Apixaban 5mg twice daily or 2.5mg twice daily (n=9120)	Warfarin (n =9081)
Age, y, mean (SD) or median	Mean (SD) 71.4 (8.6)	Mean (SD) 71.5 (8.8)	Mean (SD) 71.6 (8.6)	Median 73	Median 73	Median 72	Median 72	Median 72	Median 70	Median 70
Female, n (%)	2150 (35.7)	2236 (36.8)	2213 (36.7)	2831 (39.7)	2832 (39.7)	2669 (37.9)	2730 (38.8)	2641 (37.5)	3234 (35.5)	3182 (35.0)

Renal function, n (%) or as indicated otherwise	NA	NA	NA	Median CrCl 67 ml/min	Median CrCl 67 ml/min	CrCl ≤50 ml/min 1379 (19.6)	CrCl ≤50 ml/min 1334 (19.0)	CrCl ≤50 ml/min 1361 (19.3)	CrCl ≤50 ml/min 1502 (16.5)	CrCl ≤50 ml/min 1515 (16.7)
CHA <sub>2</sub> DS <sub>2</sub> VASc, mean (SD)	2.1 (1.1)	2.2 (1.2)	2.1 (1.1)	3.48 (0.94)	3.46 (0.95)	2.8 (1.0)	2.8 (1.0)	2.8 (1.0)	2.1 (1.1)	2.1 (1.1)
HAS-BLED, mean (SD) or <3 vs ≥3	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
Hypertension, n (%)	4738 (78.8)	4795 (78.9)	4750 (78.9)	6436 (90.3)	6474 (90.8)	6591 (93.7)	6575 (93.5)	6588 (93.6)	7962 (87.3)	7954 (87.6)
Diabetes mellitus, n (%)	1409 (23.4)	1402 (23.1)	1410 (23.4)	2878 (40.4)	2817 (39.5)	2559 (36.4)	2544 (36.2)	2521 (35.8)	2284 (25.0)	2263 (24.9)
History of stroke or TIA, n	1195 (19.9)	1233 (20.3)	1195 (19.8)	3916 (54.9)	3895 (54.6)	1976 (28.1)	2006 (28.5)	1991 (28.3)	1748 (19.2)	1790 (19.7)

(%) or systemic embolism										
History of myocardial infarction, n (%)	1008 (16.8)	1029 (16.9)	968 (16.1)	1182 (16.6)	1286 (18.0)	NA	NA	NA	1319 (14.5)	1266 (13.9)
History of CABG, n (%)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
History of PCI, n (%)	NA	NA	NA	NA	NA	NA	NA	NA	NA	NA
ASA	2404 (40.0)	2352 (38.7)	2442 (40.6)	2586 (36.3)	2619 (36.7)	2070 (29.4)	2018 (28.7)	2092 (29.7)	2859 (31.3)	2773 (30.5)

ASA – aspirin, CABG – coronary artery bypass grafting, CrCl – creatinine clearance, PCI – percutaneous angioplasty, TIA – transient ischemic attack,



**Table S1d. Characteristics of patients in clinical trials included in the meta-analysis – PIONEER-AF PCI, RE-DUAL PCI, AUGUSTUS, ENTRUST-AF-PCI**

Characteristics	PIONEER-AF PCI, 2016		RE-DUAL PCI, 2017				AUGUSTUS, 2019		ENTRUST-AF –PCI 2019	
Therapy	DT (n = 709)  Rivaroxaban (15 mg) + P2Y <sub>12</sub> inhibitor (clopidogrel, 75 mg, or ticagrelor, 2 × 90 mg, or prasugrel, 10 mg)	TT (n = 706)  VKA + ASA (75– 100 mg) + P2Y <sub>12</sub> inhibitor (clopidogrel, 75 mg, or ticagrelor, 2 × 90 mg, or prasugrel, 10 mg)	DT (n = 981)  Dabigatran (2 × 110 mg) + P2Y <sub>12</sub> inhibitor (clopidogrel, 75 mg, or ticagrelor, 2 × 90 mg)	DT (n = 763)  Dabigatran (2 × 150 mg) + + P2Y <sub>12</sub> inhibitor (clopidogrel, 75 mg, or ticagrelor, 2 × 90 mg)	TT (n = 981)  VKA + ASA (<100 mg) + P2Y <sub>12</sub> inhibitor (clopidogrel, 75 mg, or ticagrelor, 2 × 90 mg)	TT (n=764)  Corresponding TT  VKA	DT/TT (n = 2306)  Apixaban (2 × 5 mg or 2 × 2.5 mg) + P2Y <sub>12</sub> inhibitor + ASA, 81 mg/placebo	DT/TT (n = 2308)  VKA + P2Y <sub>12</sub> inhibitor + ASA, 81 mg/placebo	DT (n=751)  Edoxaban (60mg/ or 30 mg in specific indication) + P2Y <sub>12</sub> inhibitor	TT (n=755)  VKA + P2Y <sub>12</sub> inhibitor + ASA (100mg, for 1-12 months)
Age, y, mean (SD)	70.4 (9.1)	69.9 (8.7)	71.5 (8.9)	68.6 (7.7)	71.7 (8.9)	68.8 (7.7)	70.4	70.9	69	70

Female sex, n (%)	181 (25.5)	188 (26.6)	253 (25.8)	171 (22.4)	231 (23.5)	170 (22.3)	670 (29.1)	667 (28.9)	194 (26)	192 (25)
Renal function, n (%) or as indicated otherwise	Mean (SD) CrCl, 78.3 (31.3) ml/min	Mean (SD) CrCl, 80.7 (30) ml/min	Mean (SD) CrCl, 76.3 (28.9) ml/min	Mean (SD) CrCl, 83.7 (31) ml/min	Mean (SD) CrCl, 75.4 (29.1) ml/min	Mean (SD) CrCl, 81.3 (29.6) ml/min	creat ≥ 1.5 mg/dl 173 (7.6)	creat ≥ 1.5 mg/dl 207 (9.2)	Mean 71.8 ml/min	Mean 71.7 ml/min
Type of index event, n (%)	NSTEMI, 130 (18.5) STEMI, 86 (12.3) UA, 145 (20.7)	NSTEMI, 123 (17.8) STEMI, 74 (10.7) UA, 164 (23.7)	ACS, 509 (51.9) CCS, 433 (44.1) Staged PCI 156 (15.9) Other 43 (4.4)	ACS, 391 (51.2) CCS, 320 (41.9) Staged PCI, 138 (18.1) Other, 65 (8.5)	ACS, 475 (48.4) CCS, 429 (43.7) Staged PCI, 168 (17.1) Other, 62 (6.3)	ACS 369 (48.3), CCS 339 (44.4), Staged PCI 134 (17.5), other 50 (6.5)	ACS and PCI, 873 (38) ACS - medical therapy, 547 (23.8) Elective PCI, 877 (38.2)	ACS and PCI, 841 (36.6) ACS -medical therapy, 550 (23.9) Elective PCI, 907 (39.5)	ACS 388 (52), CCS 363 (48)	ACS 389 (52), CCS 366 (48)
CHA <sub>2</sub> DS <sub>2</sub> VASc, mean (SD)	3.7 (1.7)	3.8 (1.6)	3.7 (1.6)	3.3 (1.5)	3.8 (1.5)	3.5 (1.5)	3.9 (1.6)	4.0 (1.6)	4	4

HAS-BLED, mean (SD) or <3 vs ≥3	<3, 28 ≥3, 72	<3, 29 ≥3, 71	2.7 (0.7)	2.6 (0.7)	2.8 (0.8)	2.7 (0.8)	2.9 (1.0)	2.9 (0.9)	3	3
Hypertension, n (%)	NA	NA	NA	NA	NA	NA	2042 (88.6)	2031 (88)	674 (90)	687 (91)
Diabetes mellitus, n (%)	NA	NA	362 (36.9)	260 (34.1)	371 (37.9)	303 (39.7)	842 (36.5)	836 (36.2)	259 (34)	258 (34)
Stroke or TIA, n (%)	NA	NA	74 (7.5)	52 (6.8)	100 (10.2)	77 (10.1)	326 (14.2)	307 (13.4)	97 (13)	92 (12)
History of myocardial infarction, n (%)	20%	22%	237 (24.2)	194 (25.4)	268 (27.3)	211 (27.6)	NA	NA	188 (25)	177 (23)
History of CABG, n (%)	NA	NA	97 (9.9)	79 (10.4)	111 (11.3)	87 (11.4)	NA	NA	46 (6)	49 (6)

History of PCI, n (%)	NA	NA	326 (33.2)	239 (31.3)	347 (35.4)	272 (35.6)	NA	NA	199 (26)	195 (26)
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ASA – aspirin, CABG – coronary artery bypass grafting, CrCl – creatinine clearance, PCI – percutaneous angioplasty, TIA – transient ischemic attack,

**Table S2. The Risk of bias of individual studies by Cochrane risk assessment tool.**

Study	Random sequence generation (Selection bias)	Allocation concealment ( <i>Selection bias</i> )	Blinding of participants and personnel ( <i>Performance bias</i> )	Blinding of outcome assessment personnel ( <i>Detection bias</i> )	Incomplete outcome data ( <i>Attrition bias</i> )	Selective reporting ( <i>Reporting bias</i> )	Other sources of bias
RE-LY	+	+	-	-	+	+	+
RE-DUAL PCI	+	+	-	+	+	+	+
ARISTOTLE	+	+	+	+	+	+	+
AUGUSTUS	+	+	-	+	+	+	+
ENGAGE AF-TIMI	+	+	+	+	+	+	+
ENTRUST-AF PCI	+	+	-	+	+	+	+

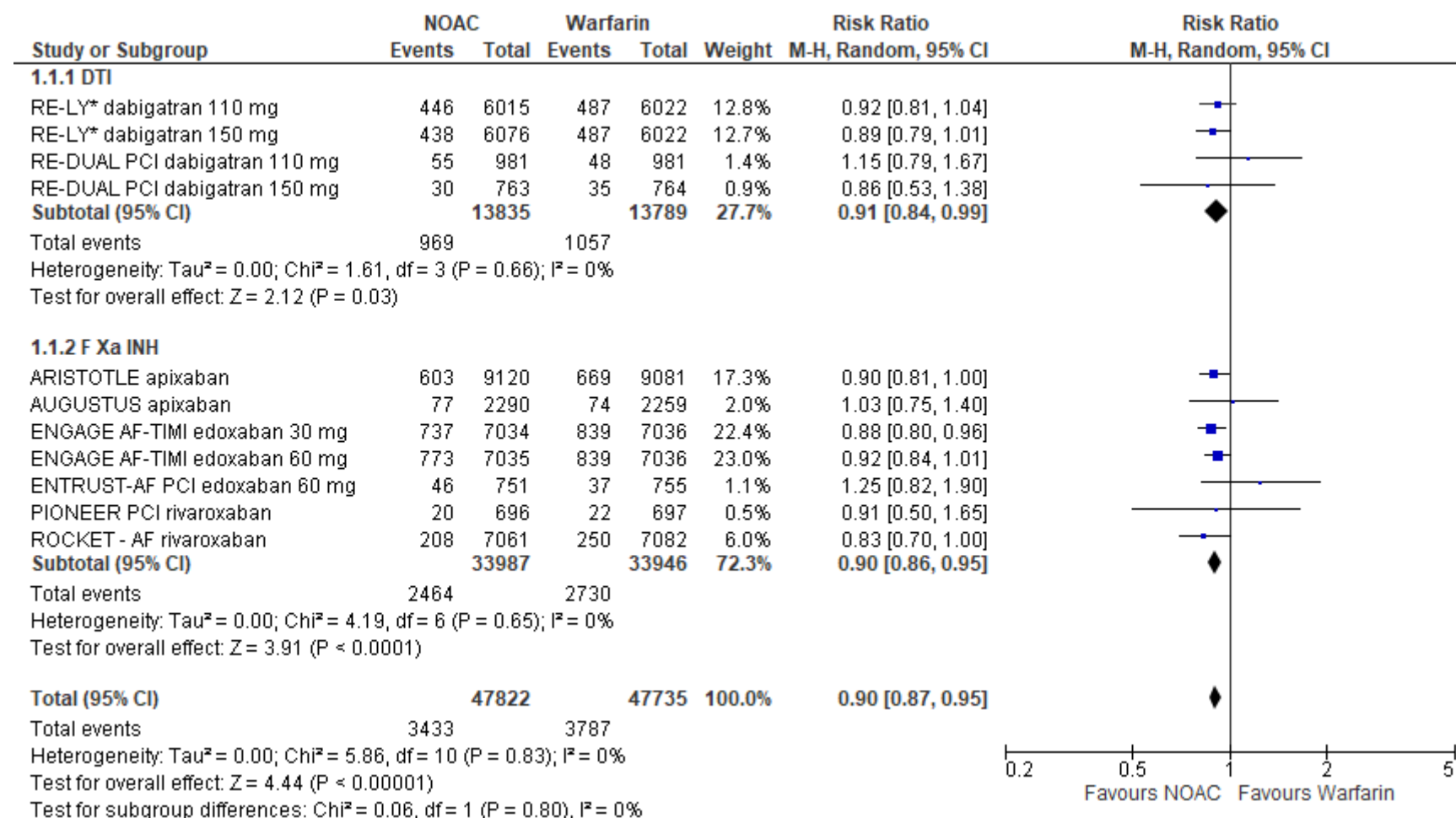
PIONEER PCI							
ROCKET - AF							

**low risk of bias**

**unclear risk of bias**

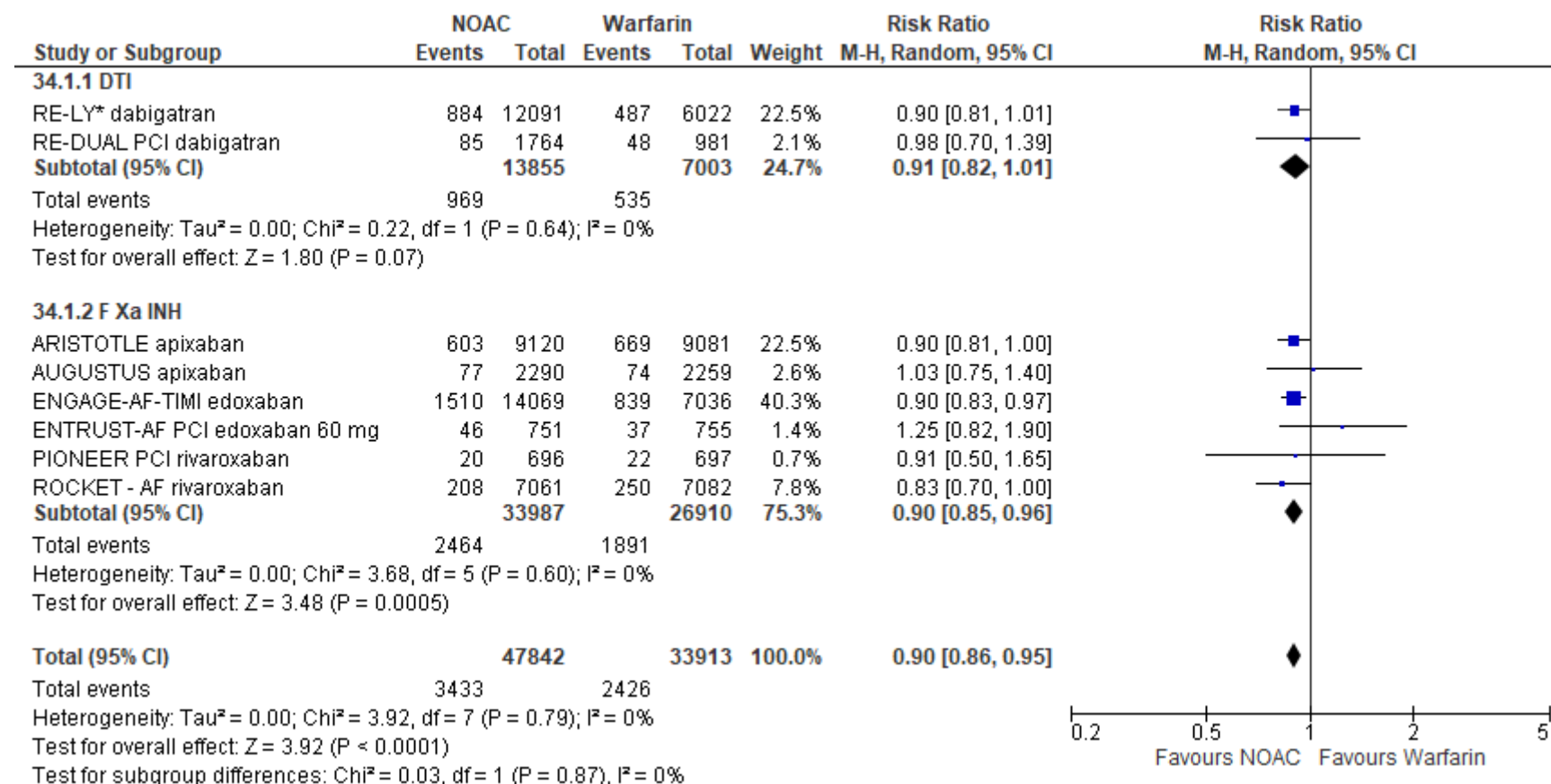
**high risk of bias**

**Figure S2. The meta-analysis results for all-cause mortality.**



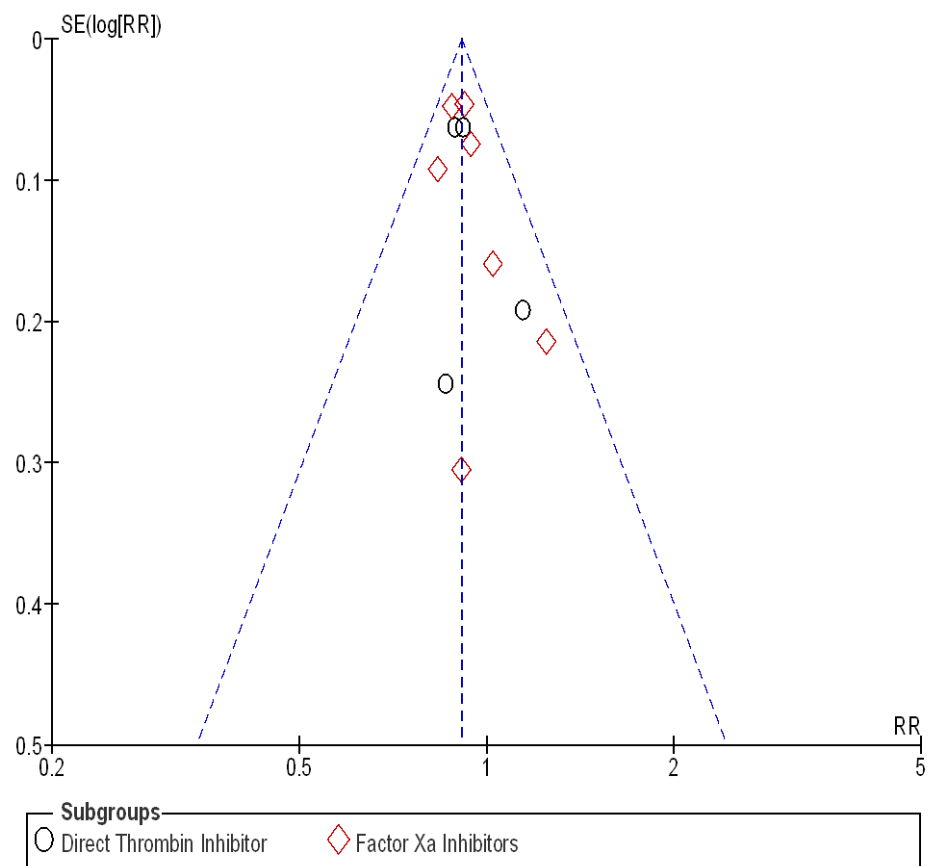
\*- original data from RE-LY study [23]

**Figure S2A. The meta-analysis results for all-cause mortality after combining study data with respect to doses**



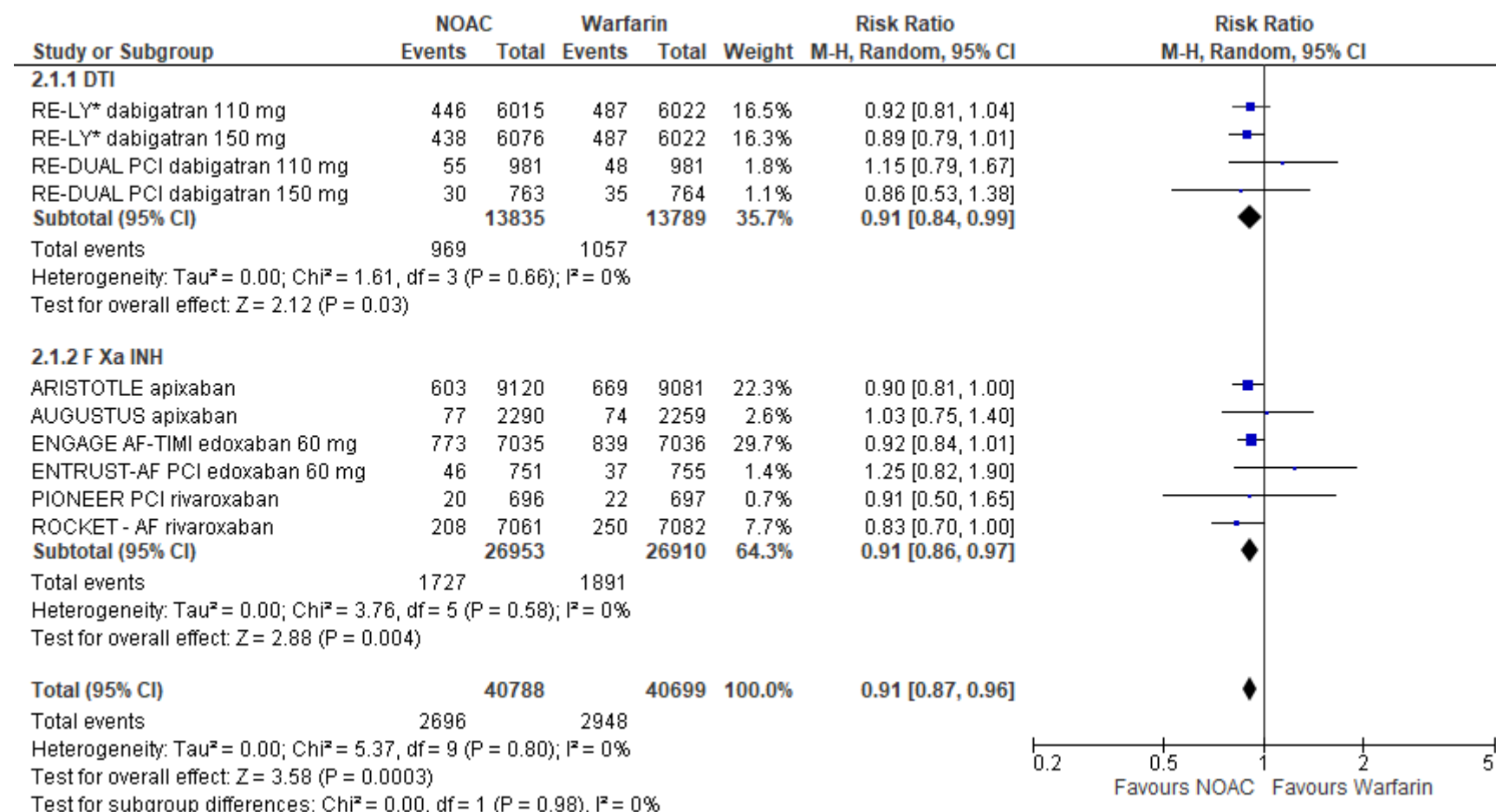
\*- original data from RE-LY study [23]

**Figure S3. The funnel plot for all-cause mortality.**



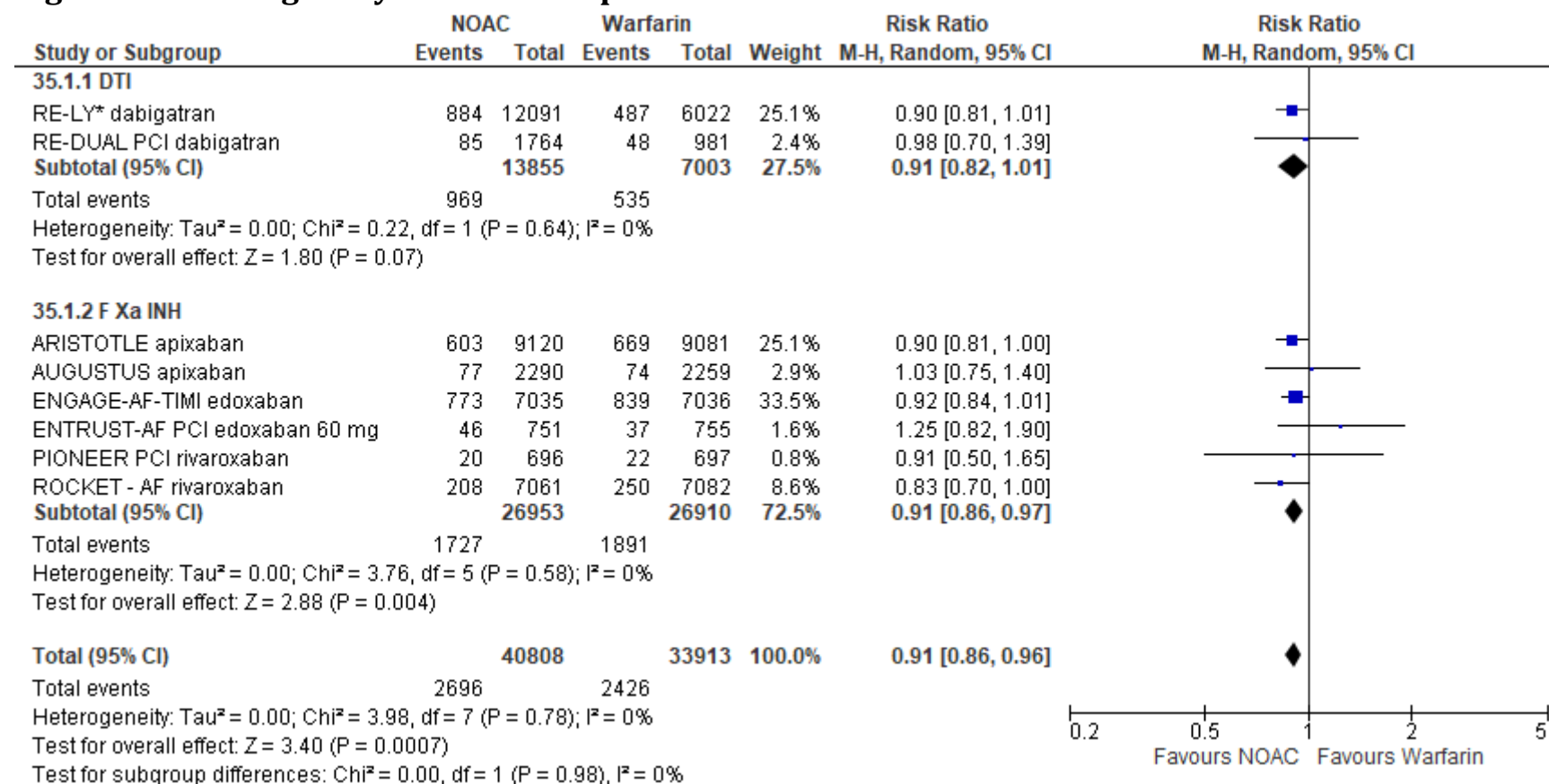


**Figure S4. The meta-analysis results for all-cause mortality after excluding ENGAGE AF-TIMI edoxaban 30 mg.**



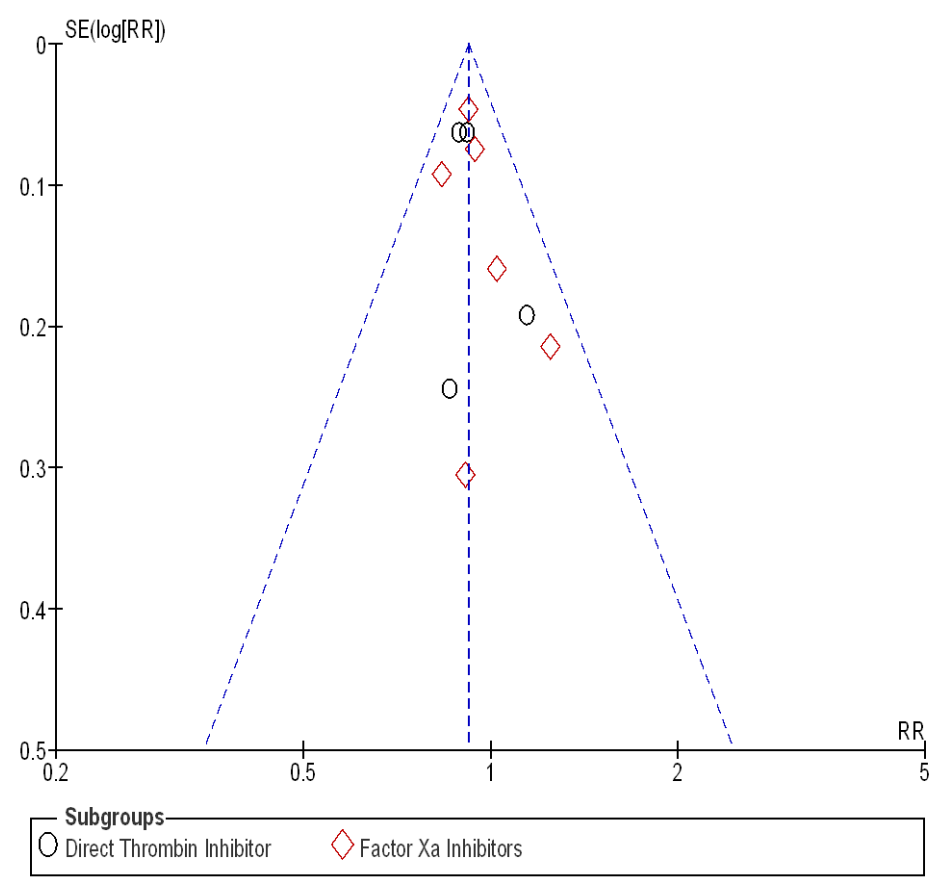
\*- original data from RE-LY study [23]

**Figure S4A. The meta-analysis results for all-cause mortality after excluding ENGAGE AF-TIMI edoxaban 30 mg and combining study data with respect to doses**

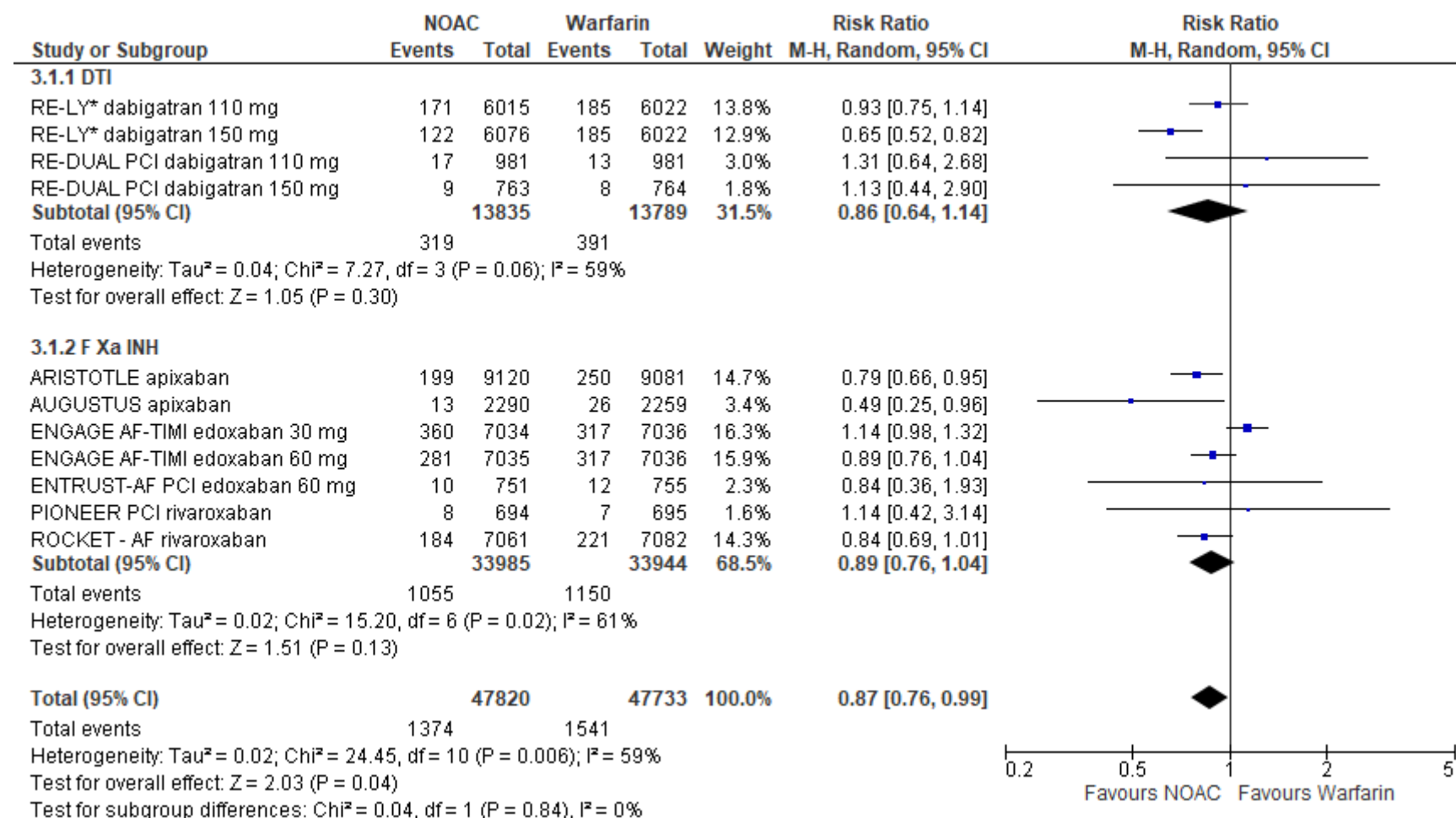


\*- original data from RE-LY study [23]

**Figure S5. The funnel plot for all-cause mortality after excluding ENGAGE AF-TIMI edoxaban 30 mg.**



**Figure S6. The meta-analysis results for stroke.**



\*- original data from RE-LY study [23]

**Figure S6A. The meta-analysis results for stroke after combining study data with respect to doses.**

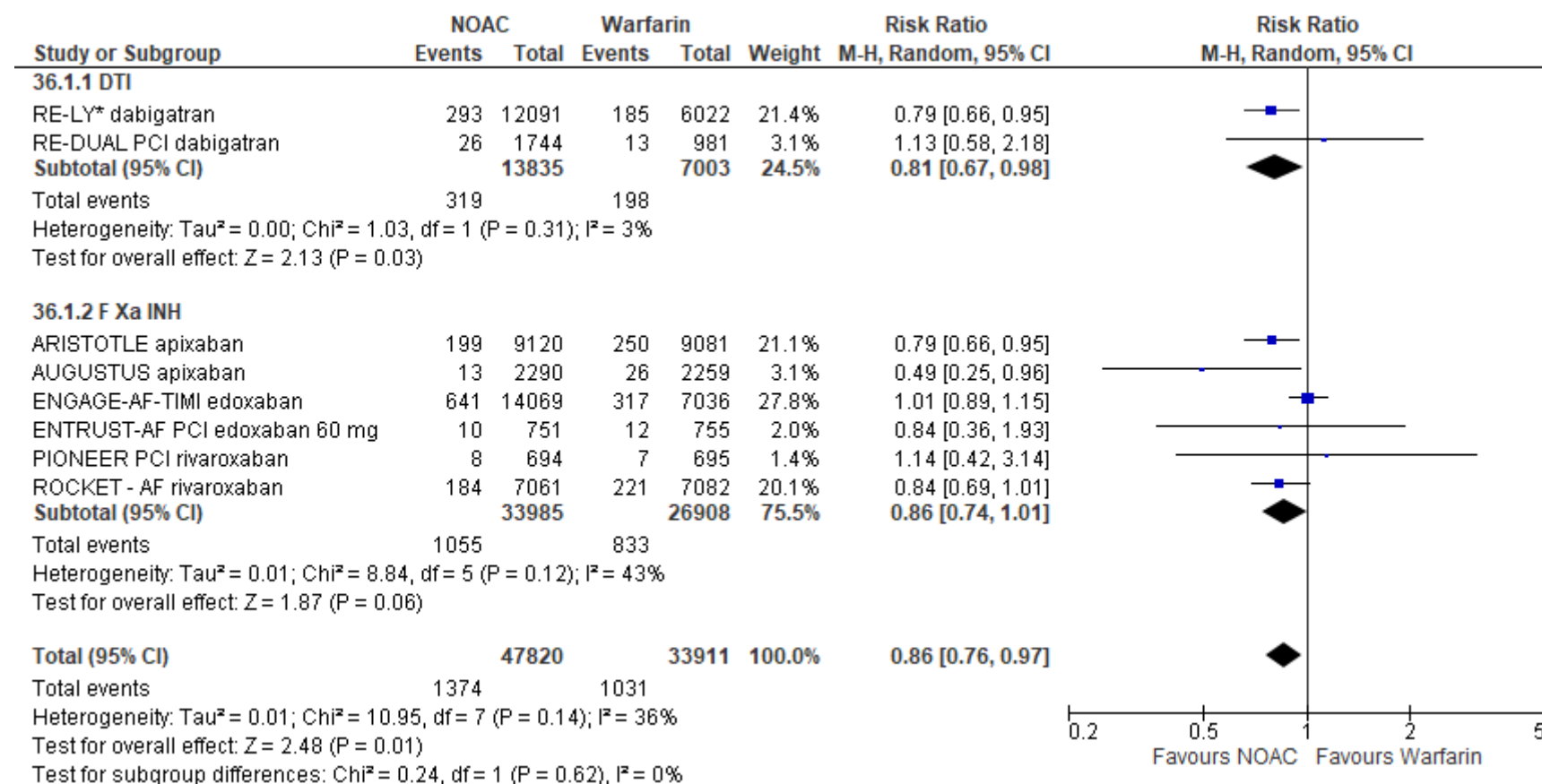
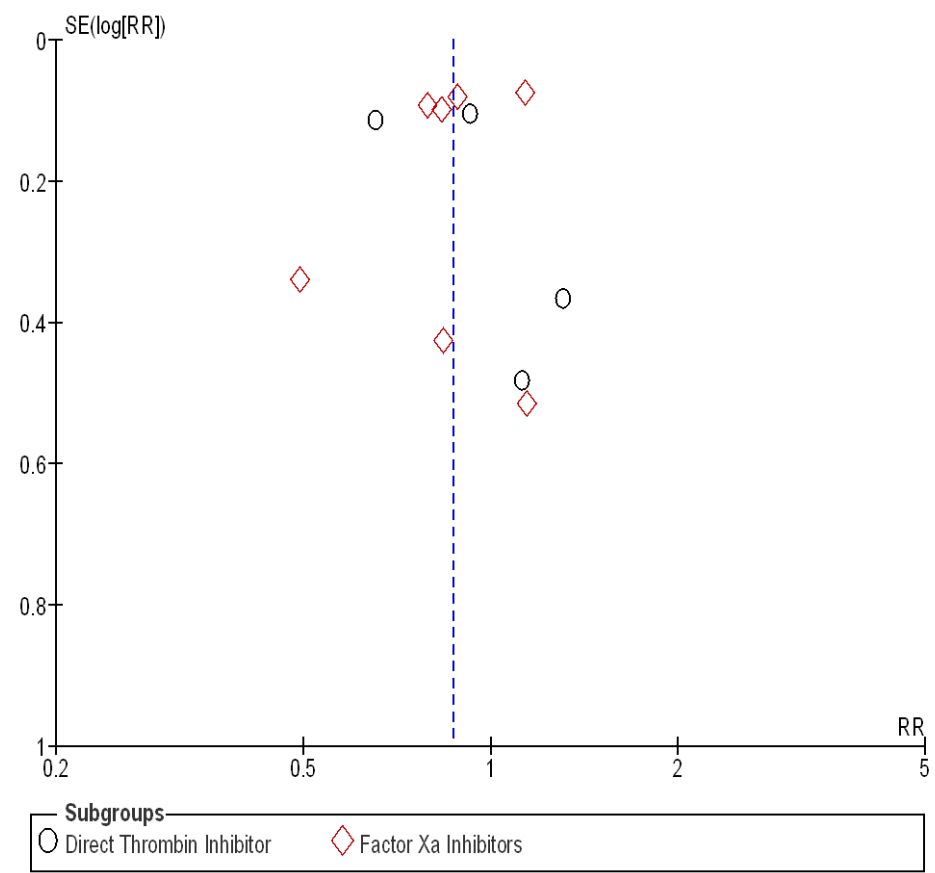
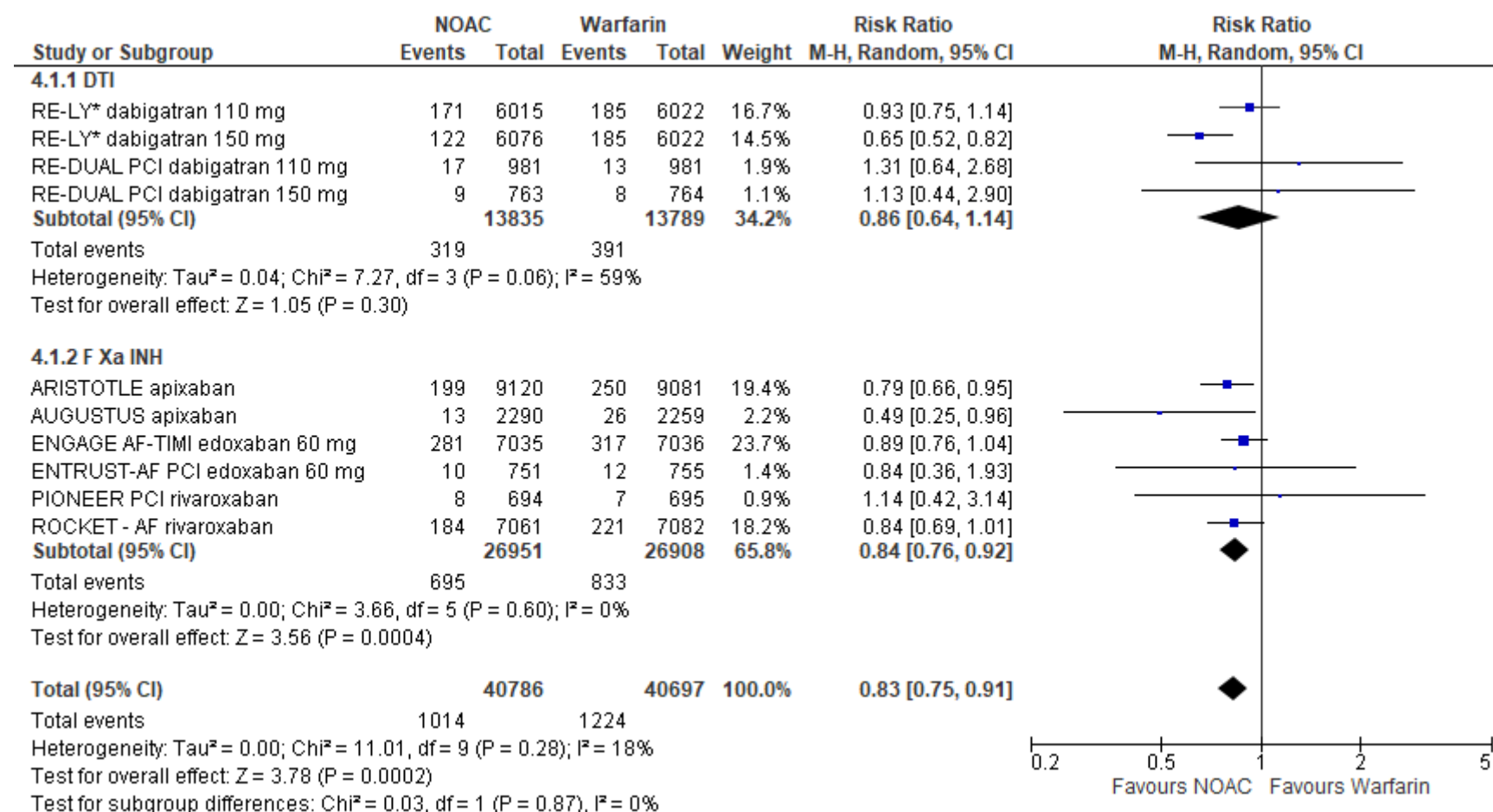


Figure S7. The funnel plot for stroke.

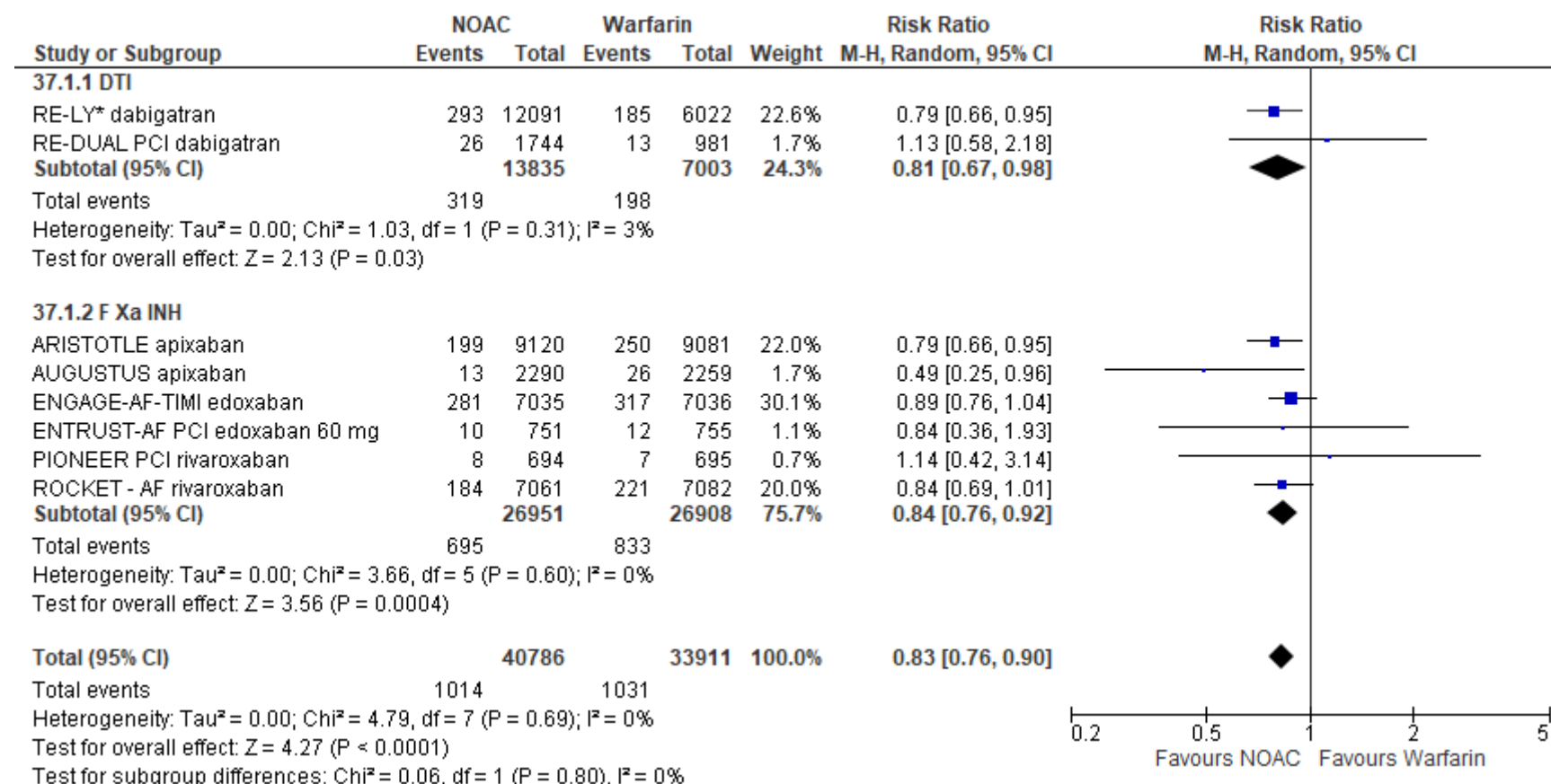


**Figure S8. The meta-analysis results for stroke after excluding ENGAGE AF-TIMI edoxaban 30 mg.**



\*- original data from RE-LY study [23]

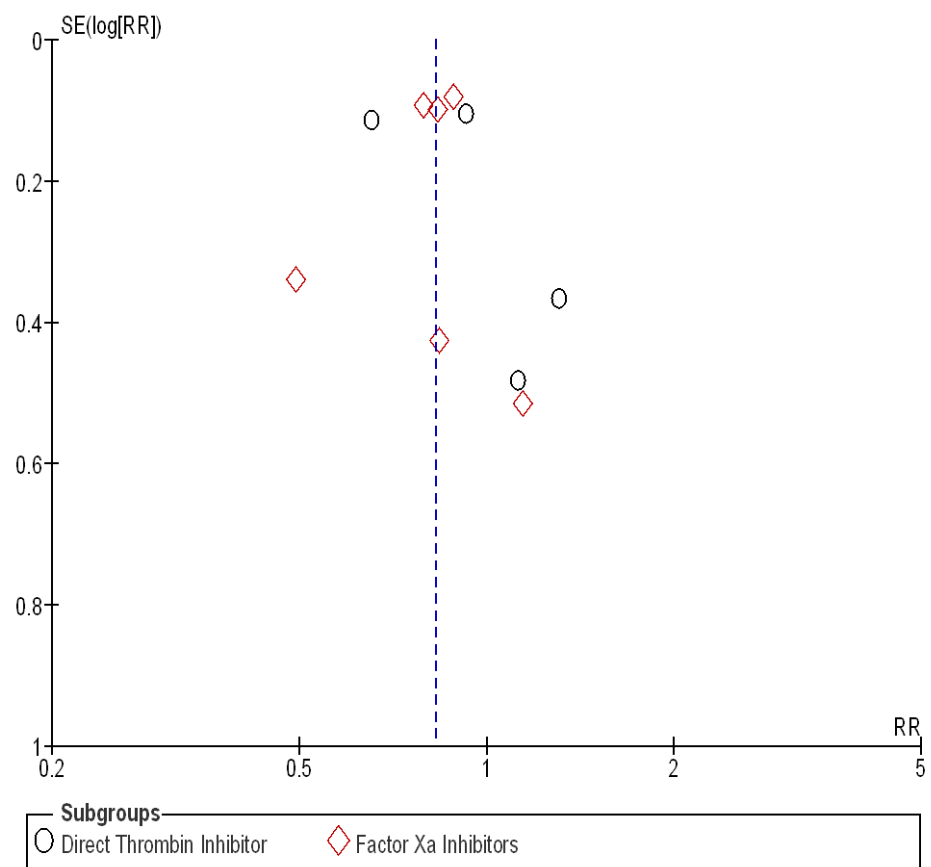
**Figure S8A. The meta-analysis results for stroke after excluding ENGAGE AF-TIMI edoxaban 30 mg and combining study data with respect to doses.**



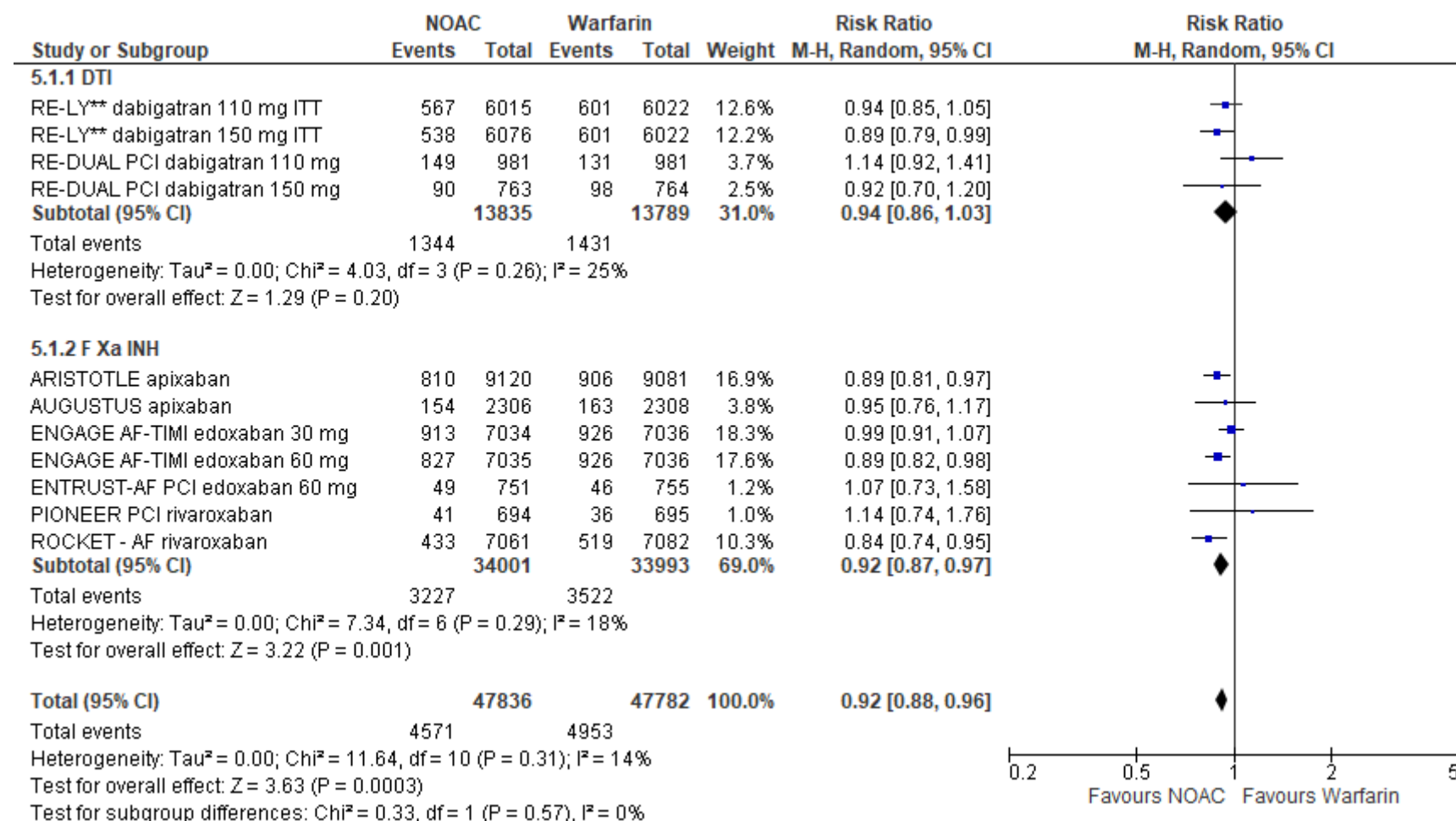
\*- original data from RE-LY study [23]



**Figure S9. The funnel plot for stroke after excluding ENGAGE AF-TIMI edoxaban 30 mg.**

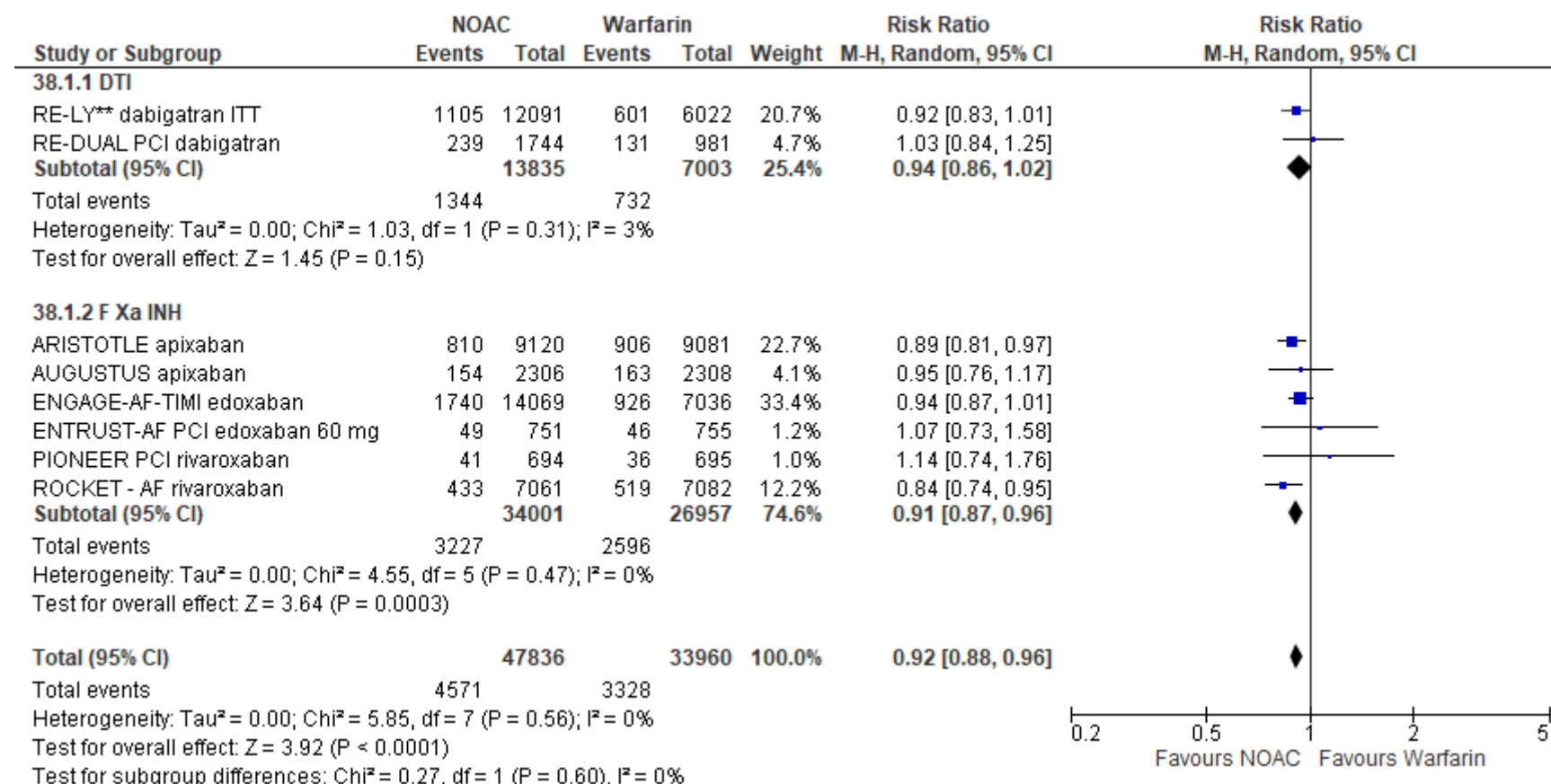


**Figure S10. The meta-analysis results for MACE – reanalysis RE-LY [27] -intention to treat data.**



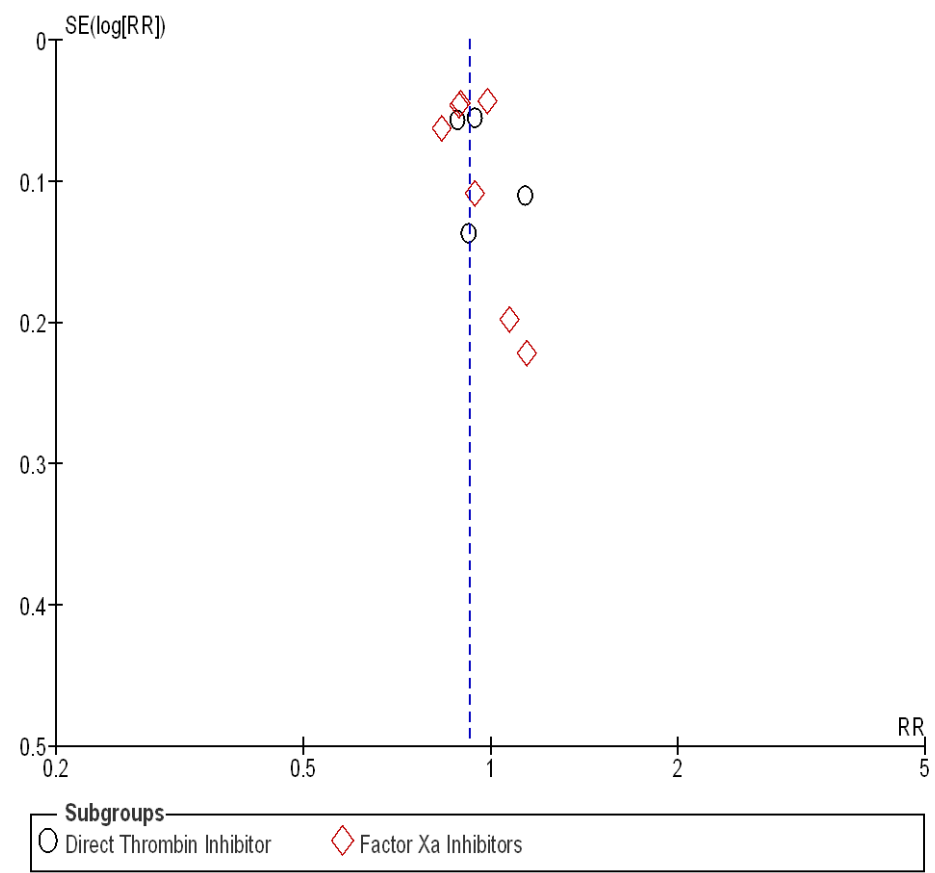
\*\* - results from reanalysis of RE-LY study [27]

**Figure S10A. The meta-analysis results for MACE – reanalysis RE-LY [27] -intention to treat data after combining study data with respect to doses.**

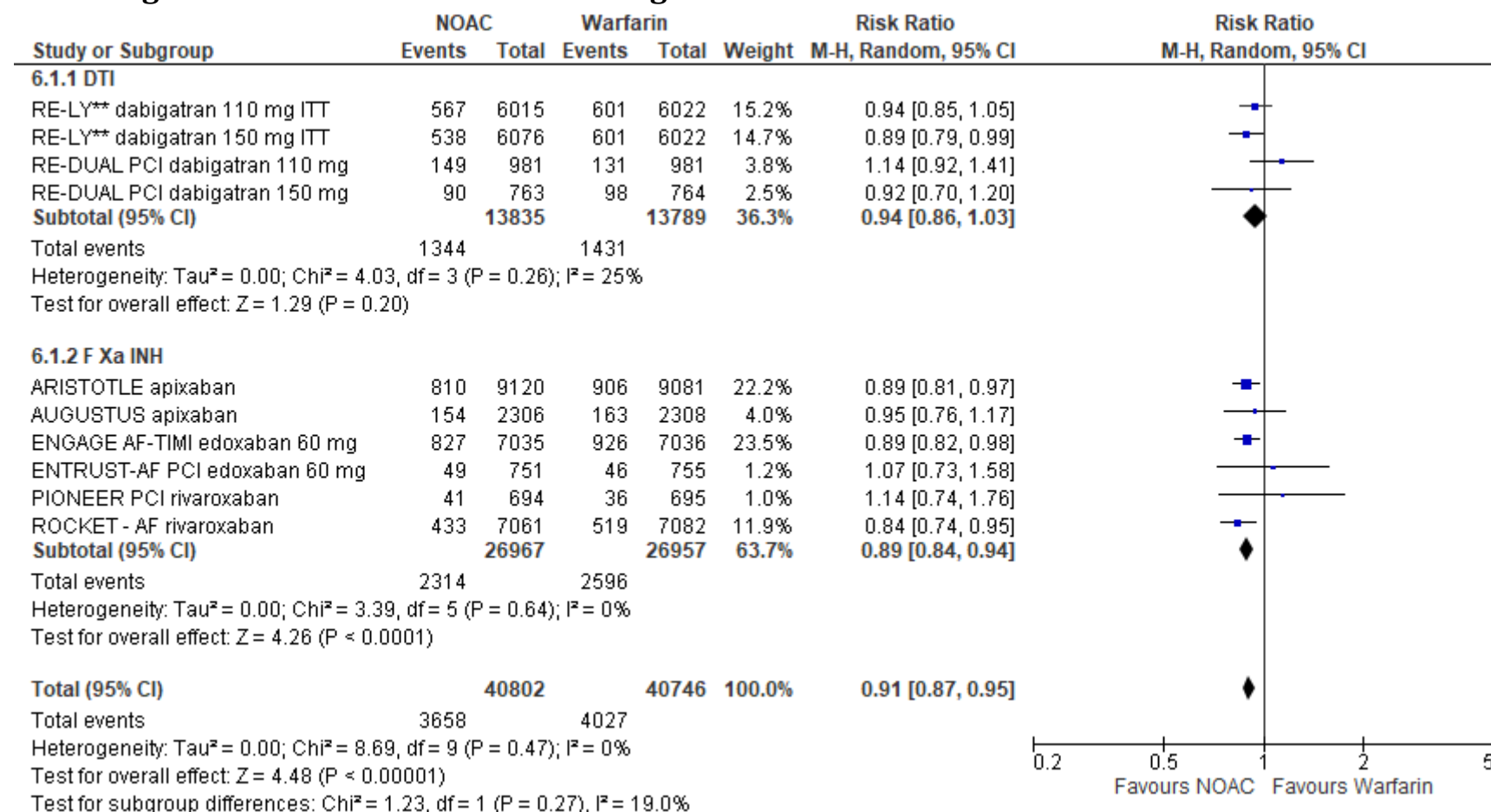


\*\* - results from reanalysis of RE-LY study [27]

**Figure S11. The funnel plot for MACE – re-analysis RE-LY [27] -intention to treat data.**

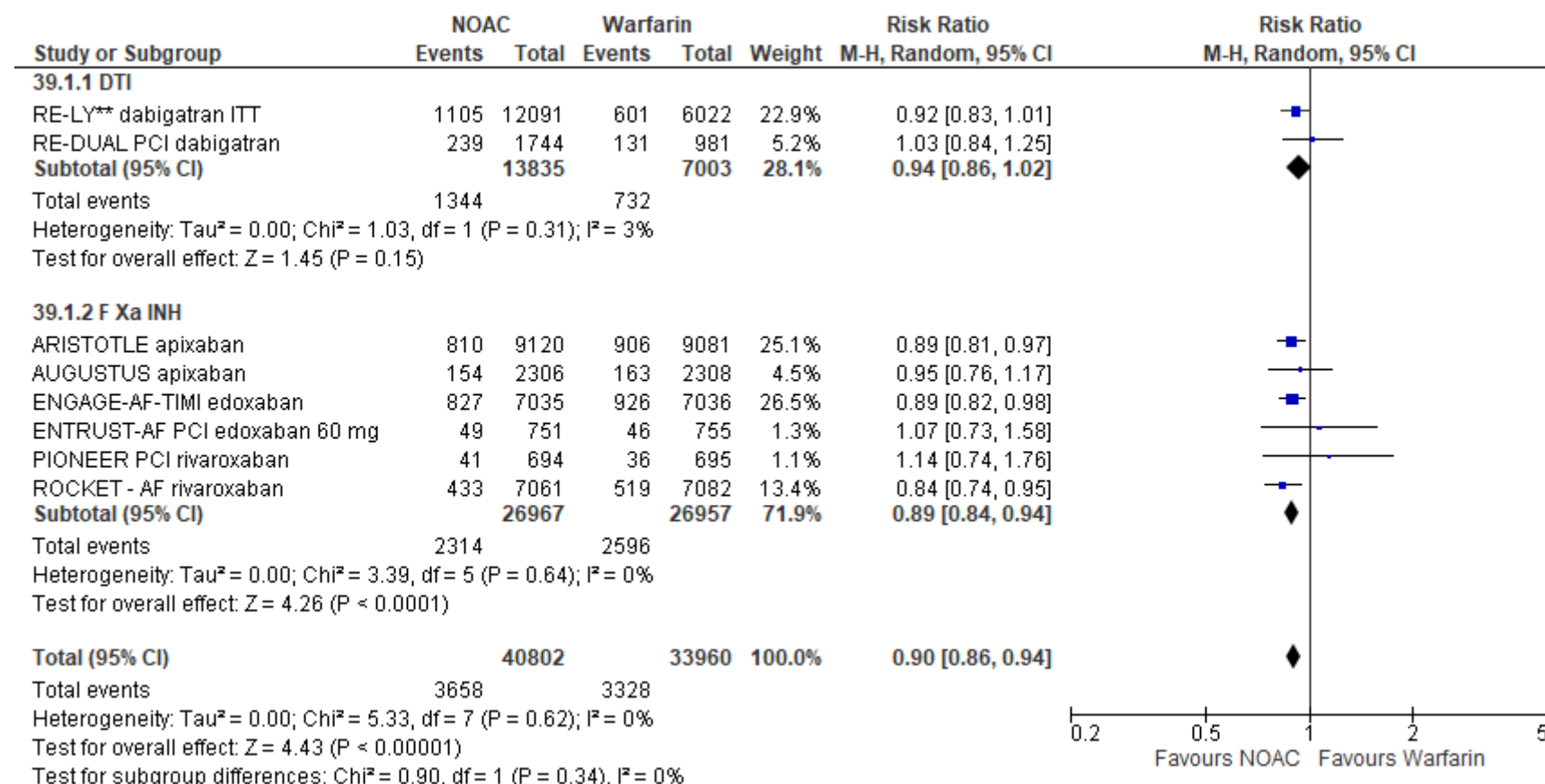


**Figure S12. The meta-analysis results for MACE – reanalysis RE-LY [27] -intention to treat data after excluding ENGAGE AF-TIMI edoxaban 30 mg**



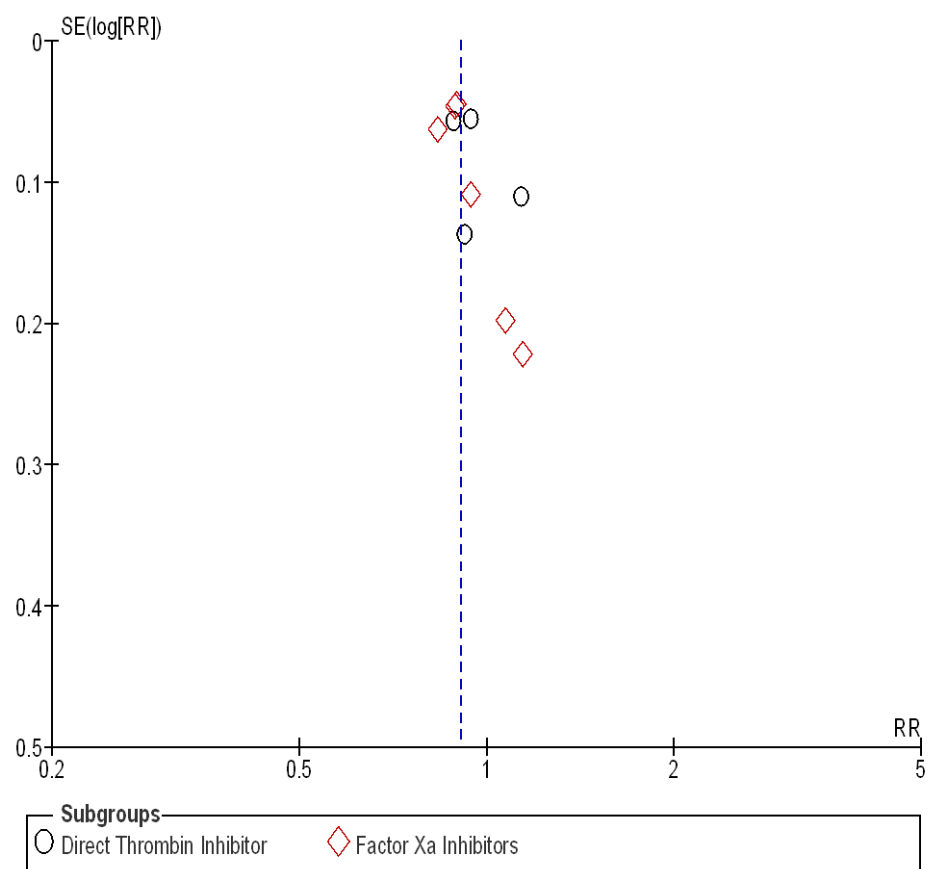
\*\* - results from reanalysis of RE-LY study [27]

**Figure S12A. The meta-analysis results for MACE – reanalysis RE-LY [27] -intention to treat data after excluding ENGAGE AF-TIMI edoxaban 30 mg and combining study data with respect to doses.**

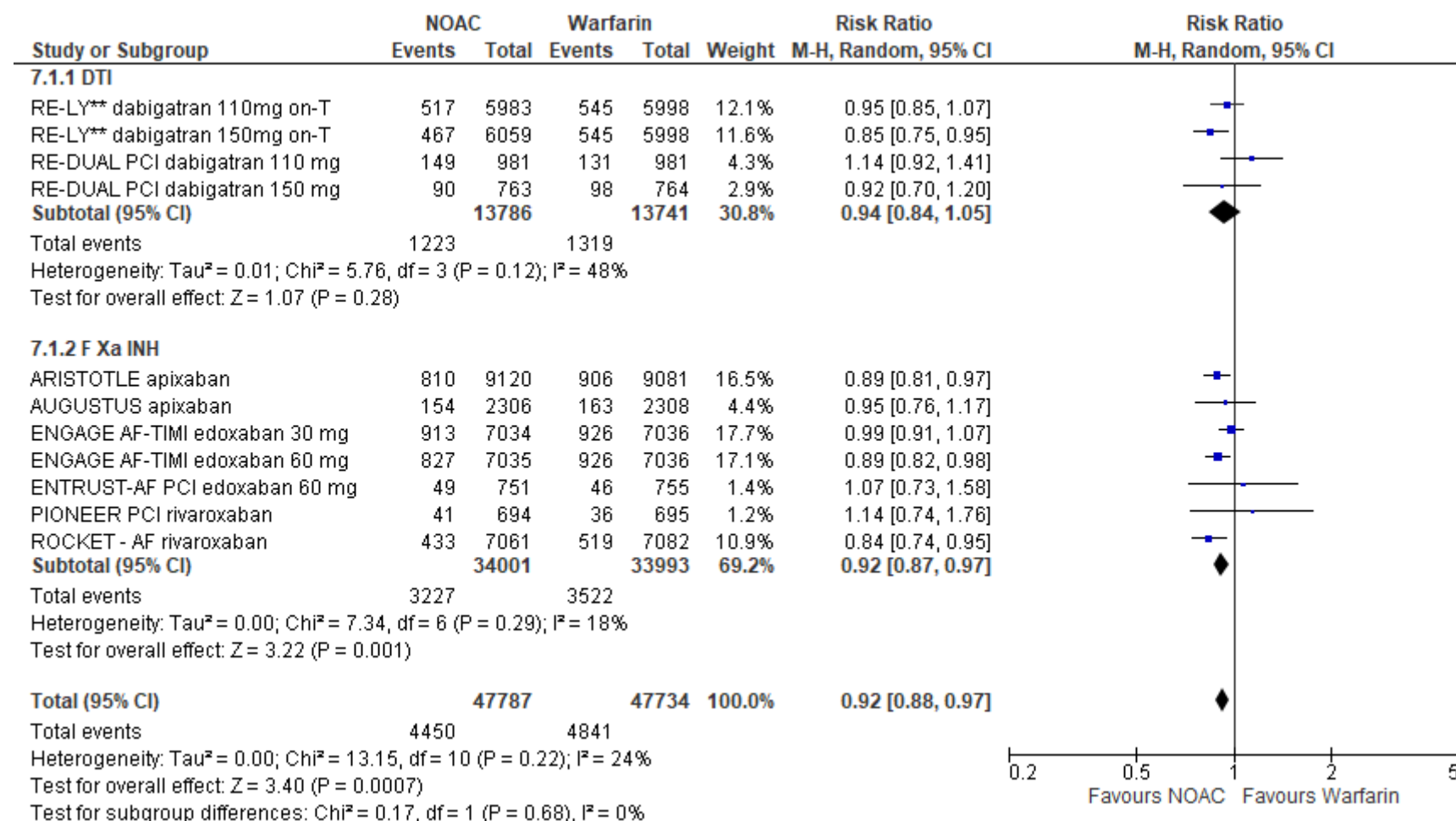


\*\* - results from reanalysis of RE-LY study [27]

**Figure S13. The funnel plot for MACE – reanalysis RE-LY [27] -intention to treat data after excluding ENGAGE AF-TIMI edoxaban 30 mg.**



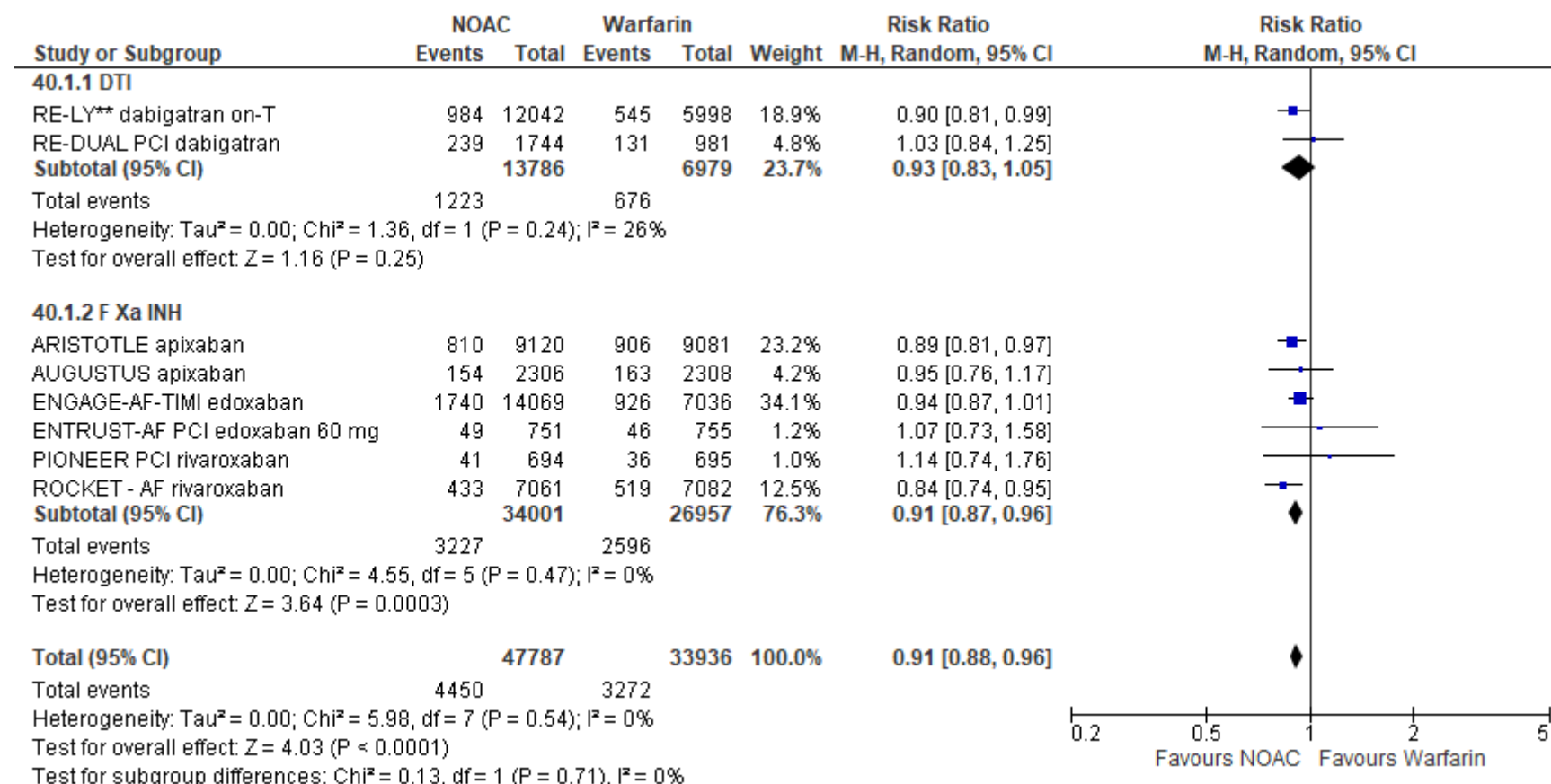
**Figure S14. The meta-analysis results for MACE – reanalysis RE-LY [27] -on treatment data.**



\*\* - results from reanalysis of RE-LY study [27]

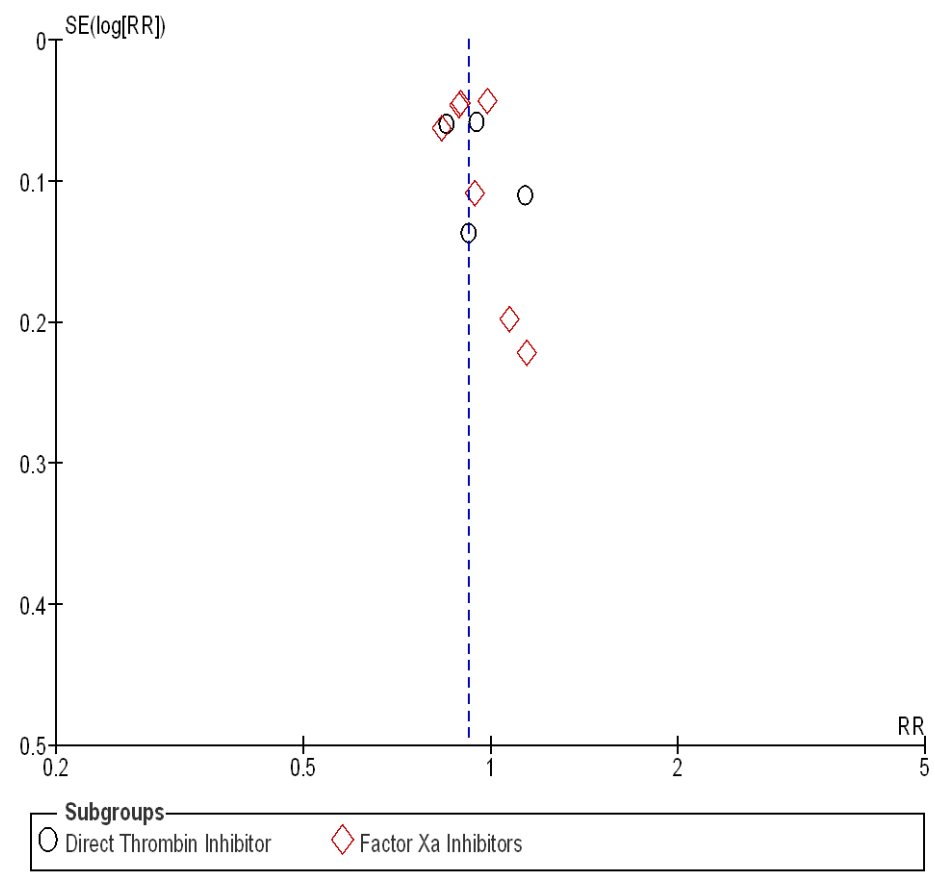


**Figure S14A. The meta-analysis results for MACE – reanalysis RE-LY [27] -on treatment data after combining study data with respect to doses.**

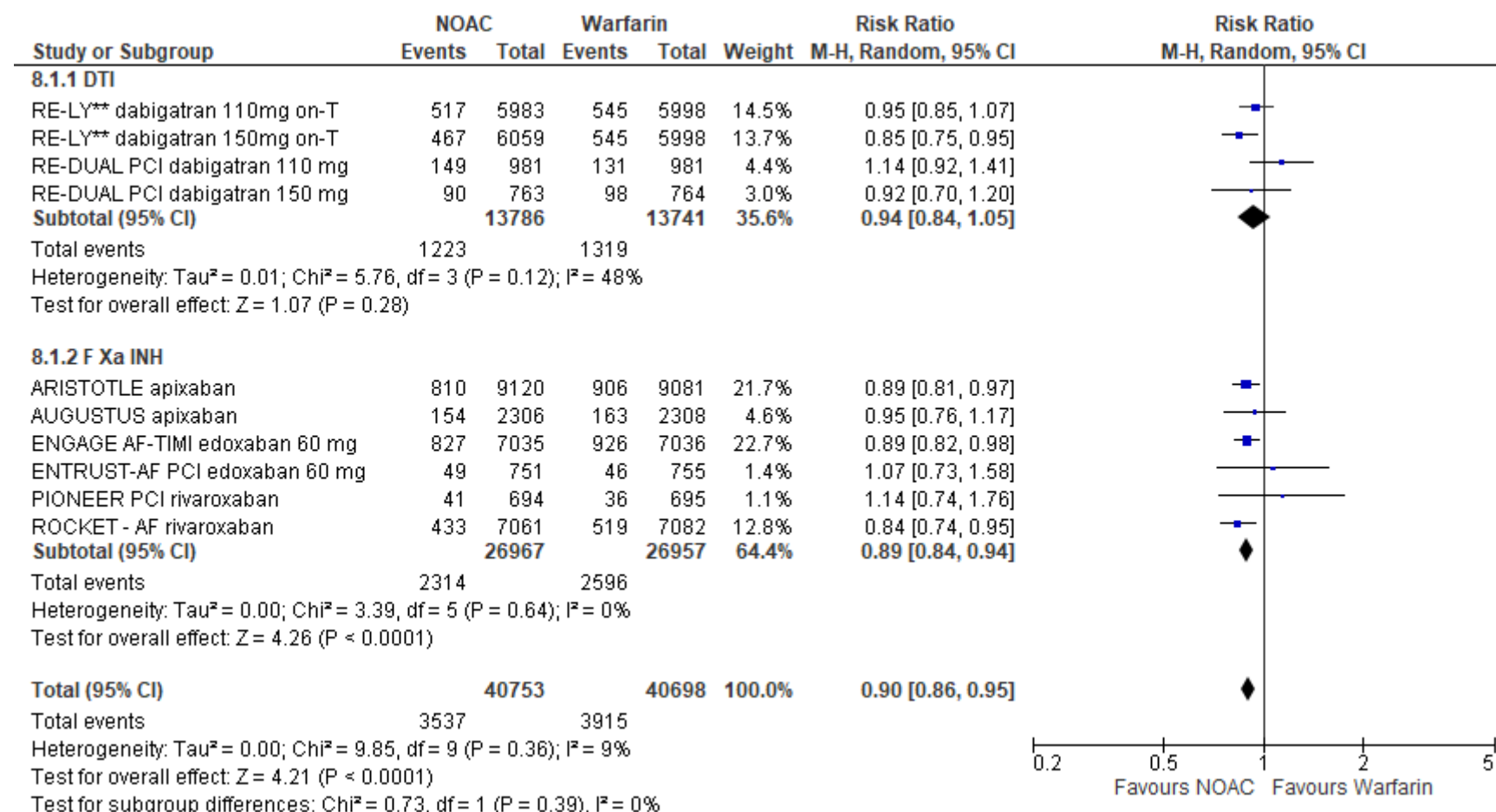


\*\* - results from reanalysis of RE-LY study [27]

**Figure S15. The funnel plot for MACE – reanalysis RE-LY [27] - on treatment data.**

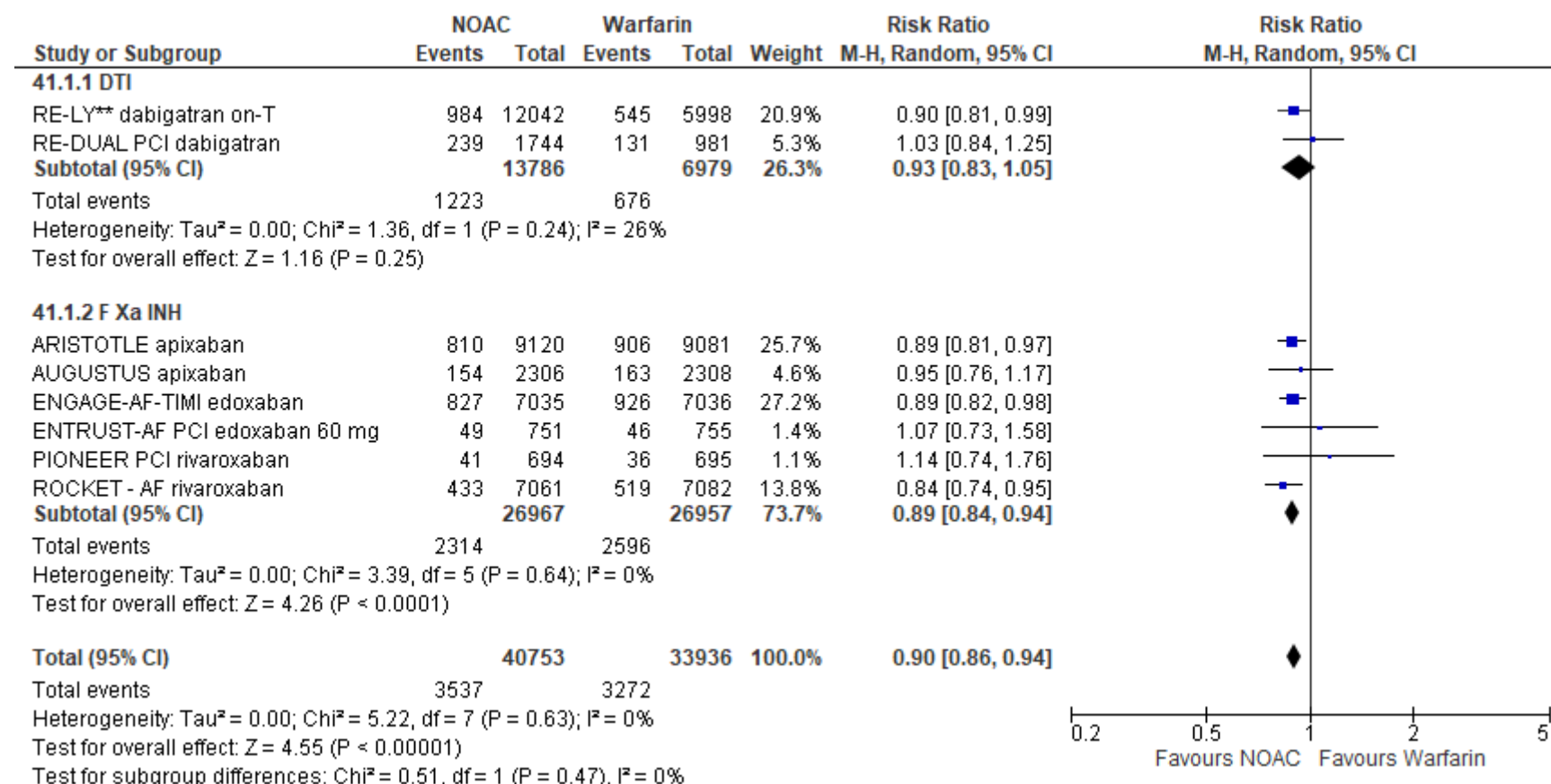


**Figure S16. The meta-analysis results for MACE – reanalysis RE-LY [27] -on treatment data after excluding ENGAGE AF-TIMI edoxaban 30 mg.**



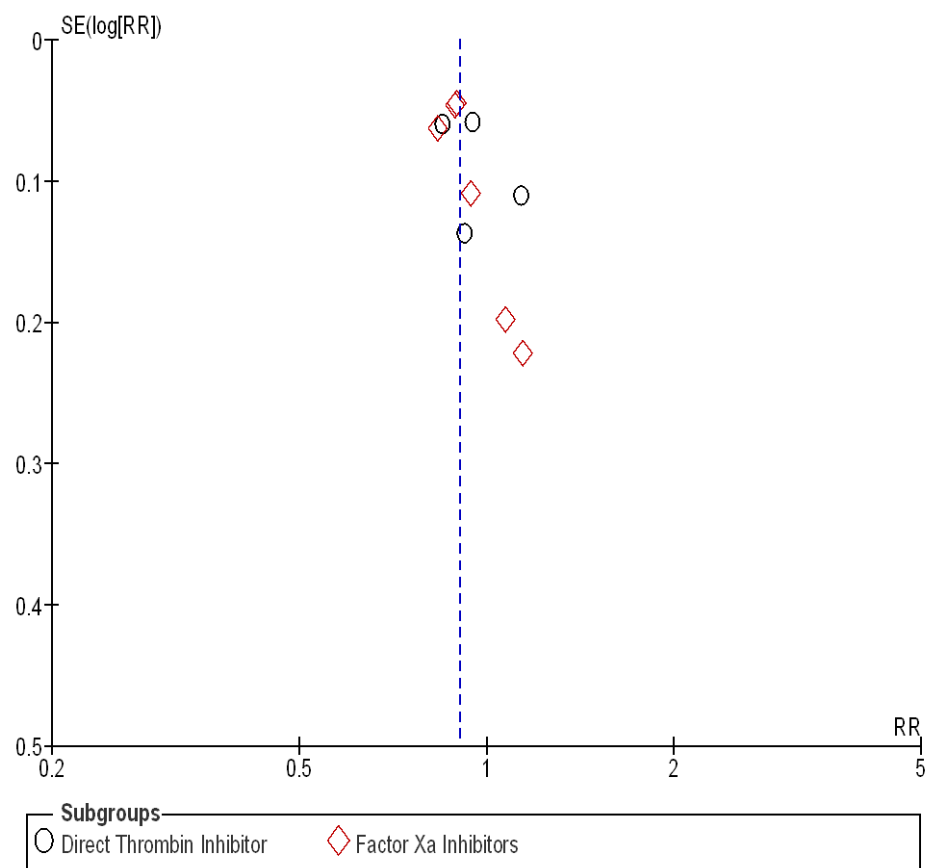
\*\* - results from reanalysis of RE-LY study [27]

**Figure S16A. The meta-analysis results for MACE – reanalysis RE-LY [27] -on treatment data after excluding ENGAGE AF-TIMI edoxaban 30 mg and combining study data with respect to doses.**

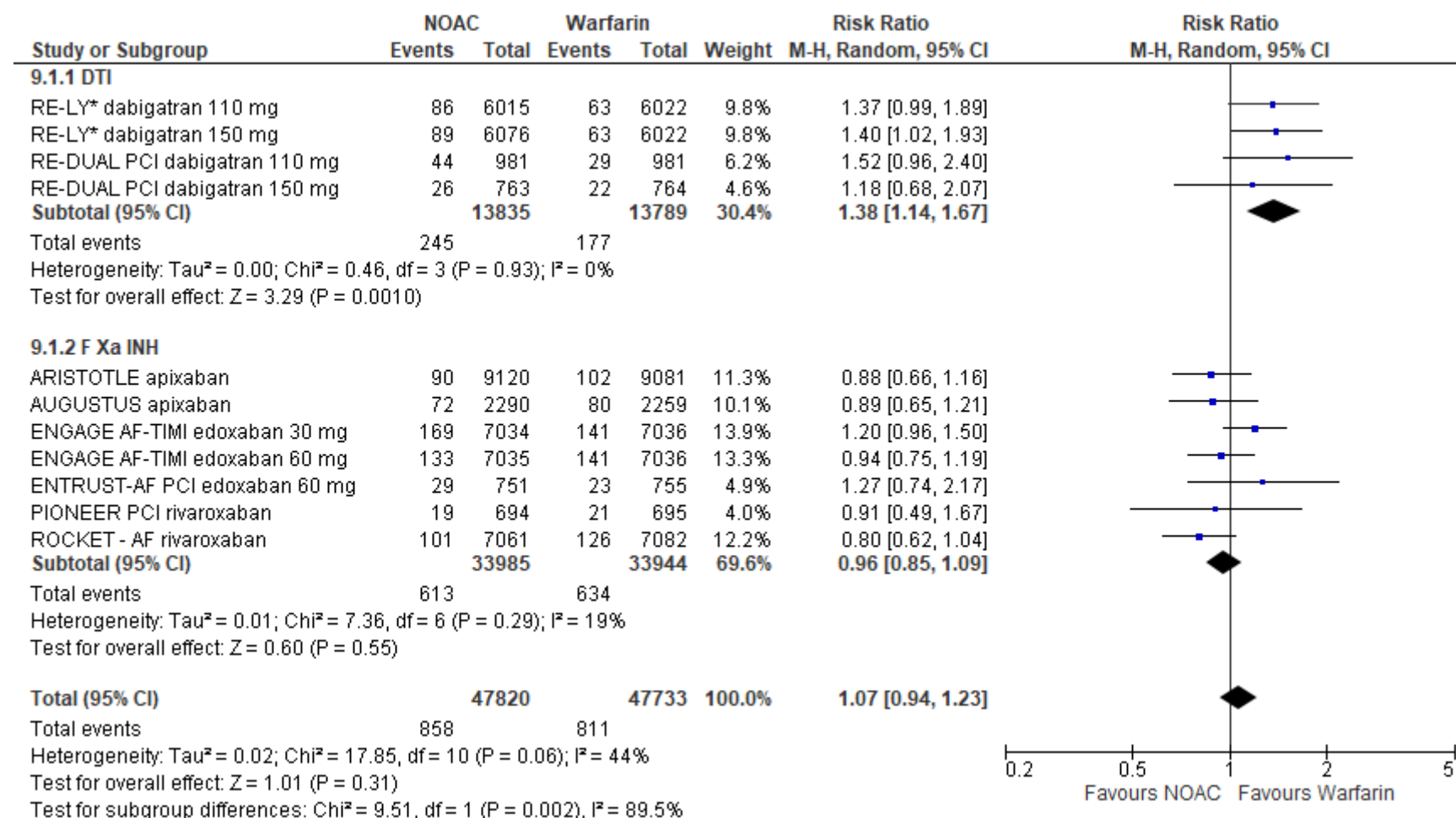


\*\* - results from reanalysis of RE-LY study [27]

**Figure S17. The funnel plot for MACE – reanalysis RE-LY [27] on treatment data after excluding ENGAGE AF-TIMI edoxaban 30 mg.**

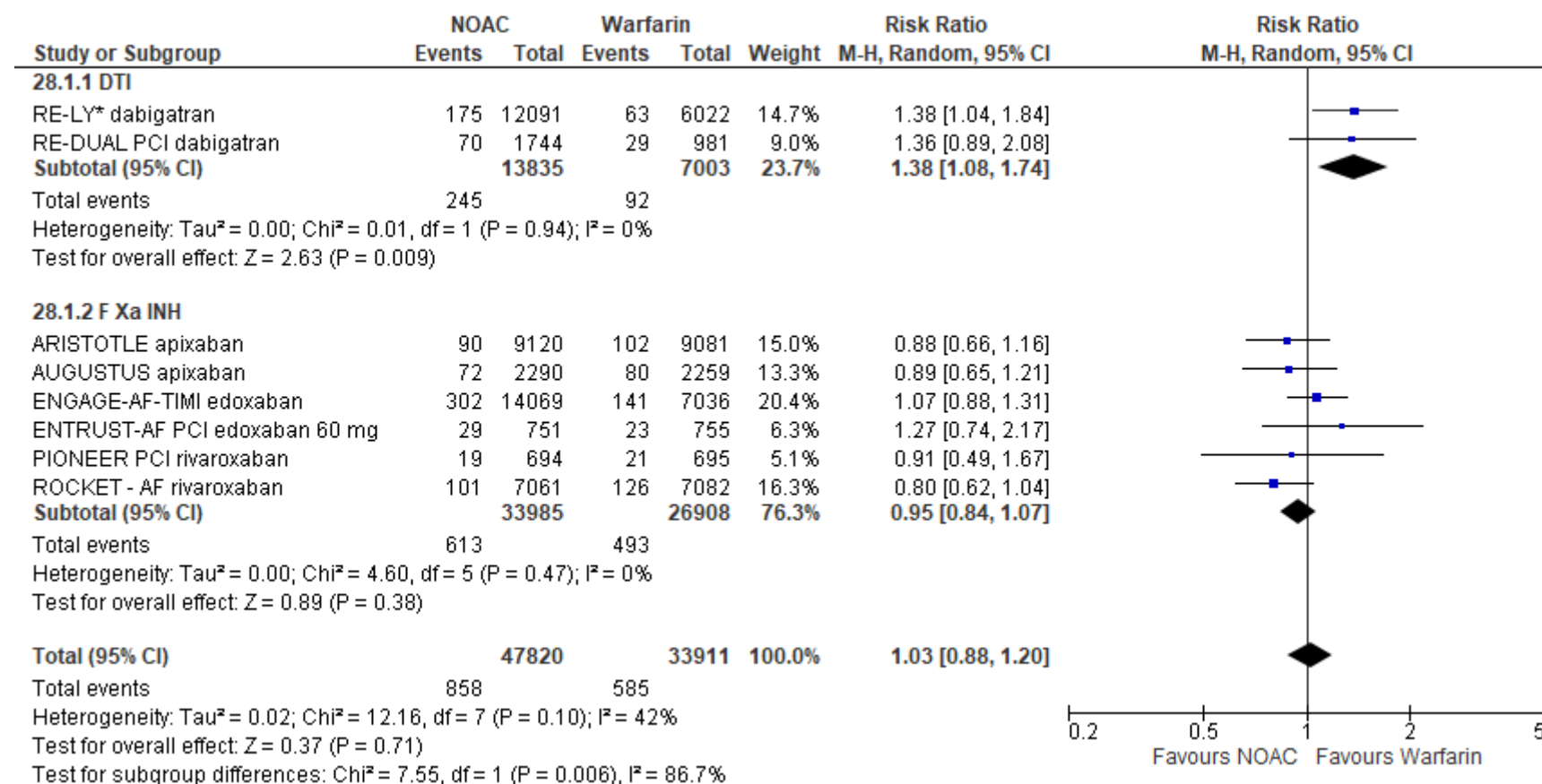


**Figure S18. The meta-analysis results for MI.**



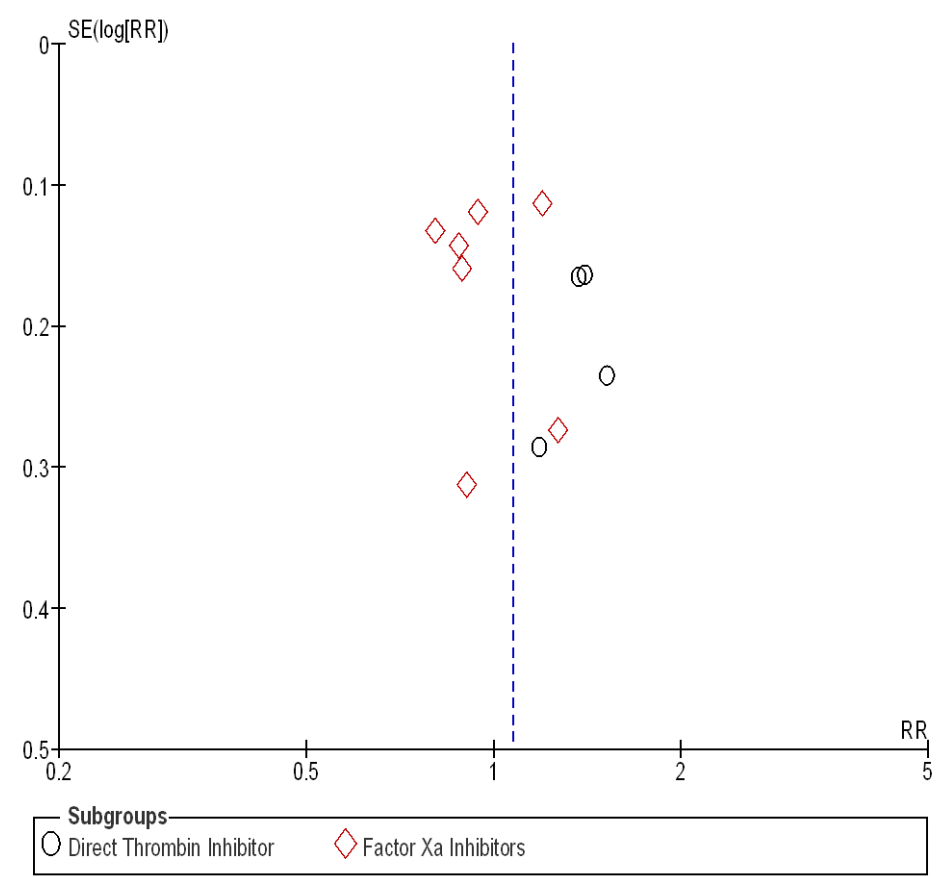
\*- original data from RE-LY study [23]

**Figure S18A. The meta-analysis results for MI after combining study data with respect to doses.**



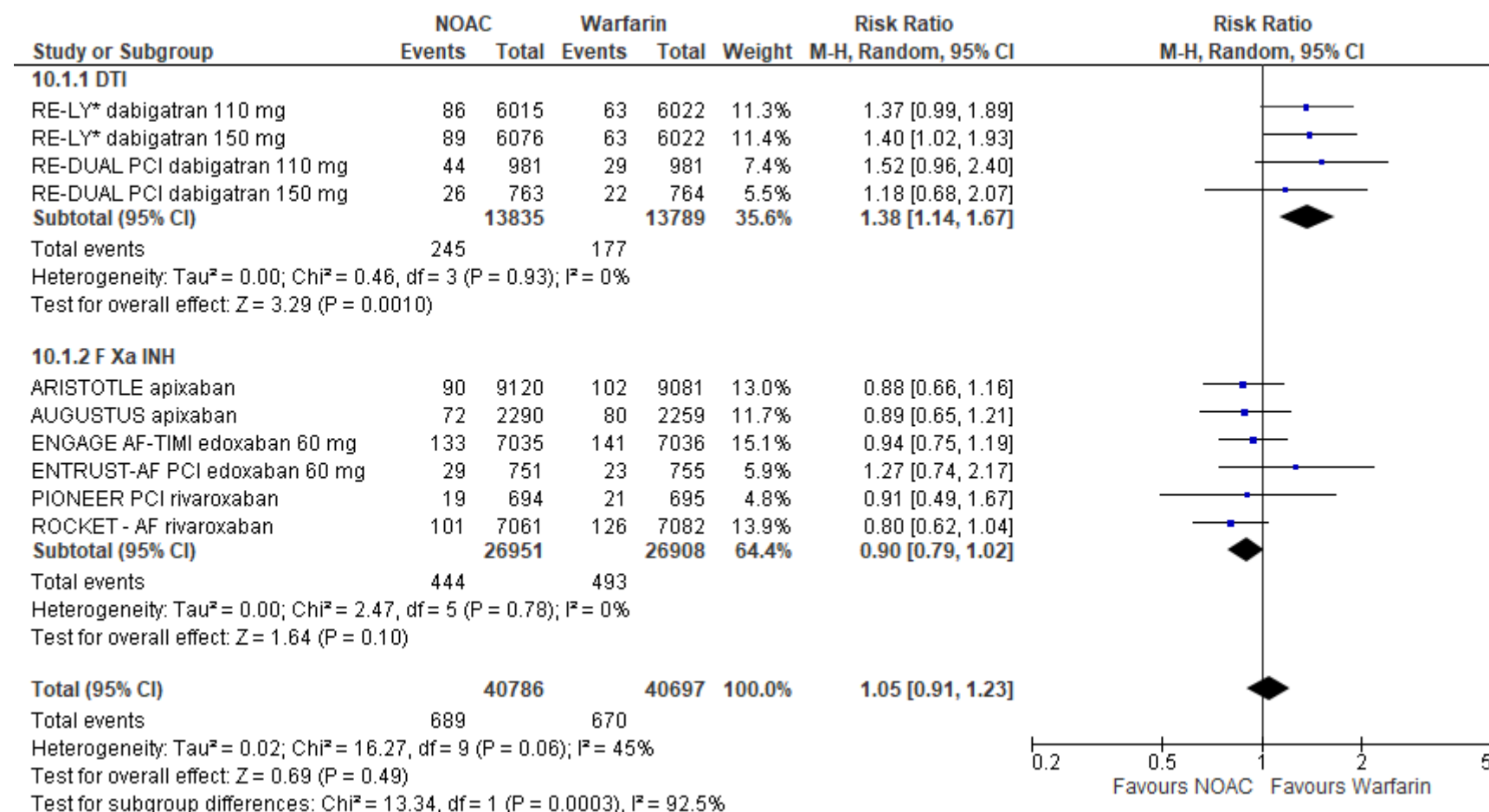
\*- original data from RE-LY study [23]

**Figure S19. The funnel plot for MI.**



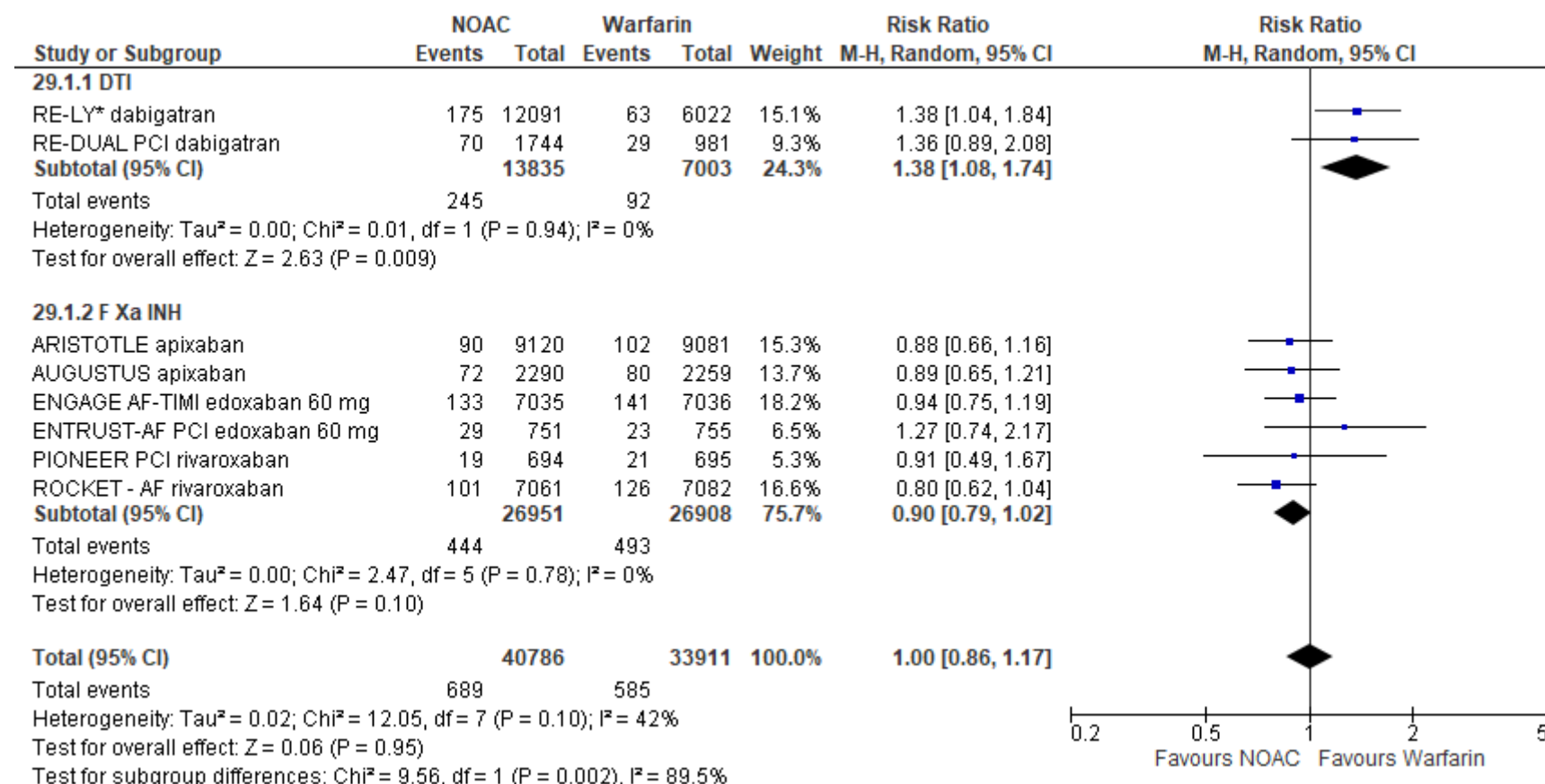


**Figure S20. The meta-analysis results for MI after excluding ENGAGE AF-TIMI edoxaban 30 mg.**



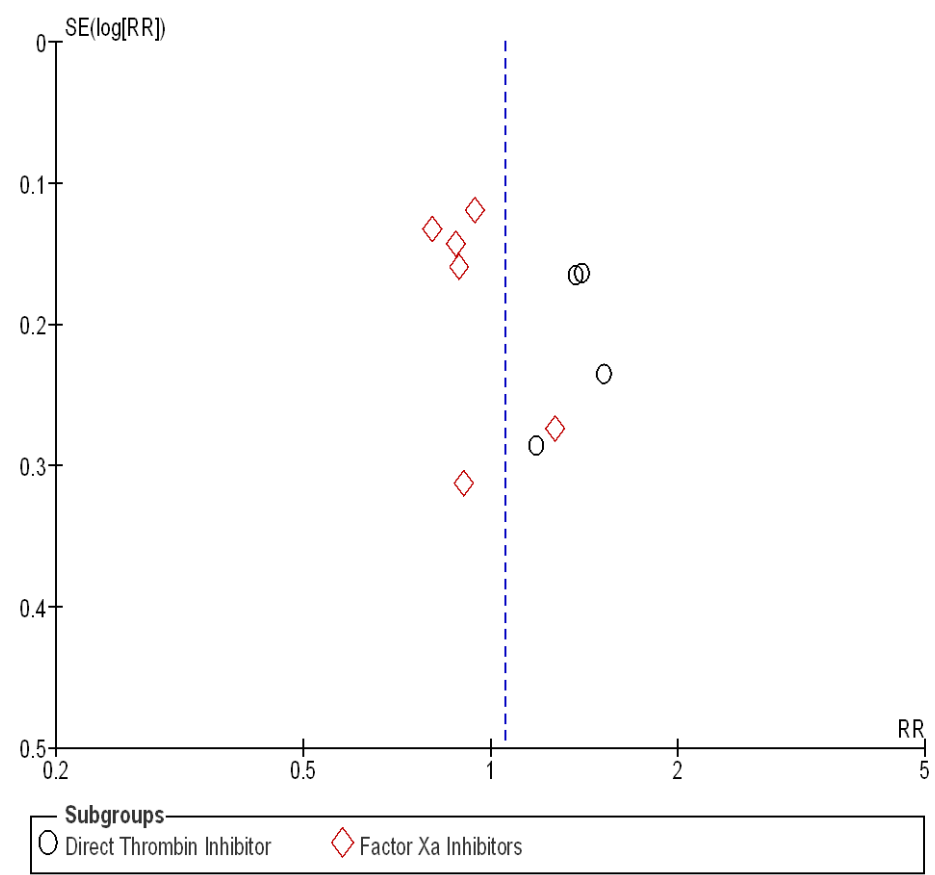
\*- original data from RE-LY study [23]

**Figure S20A. The meta-analysis results for MI after excluding ENGAGE AF-TIMI edoxaban 30 mg and combining study data with respect to doses.**

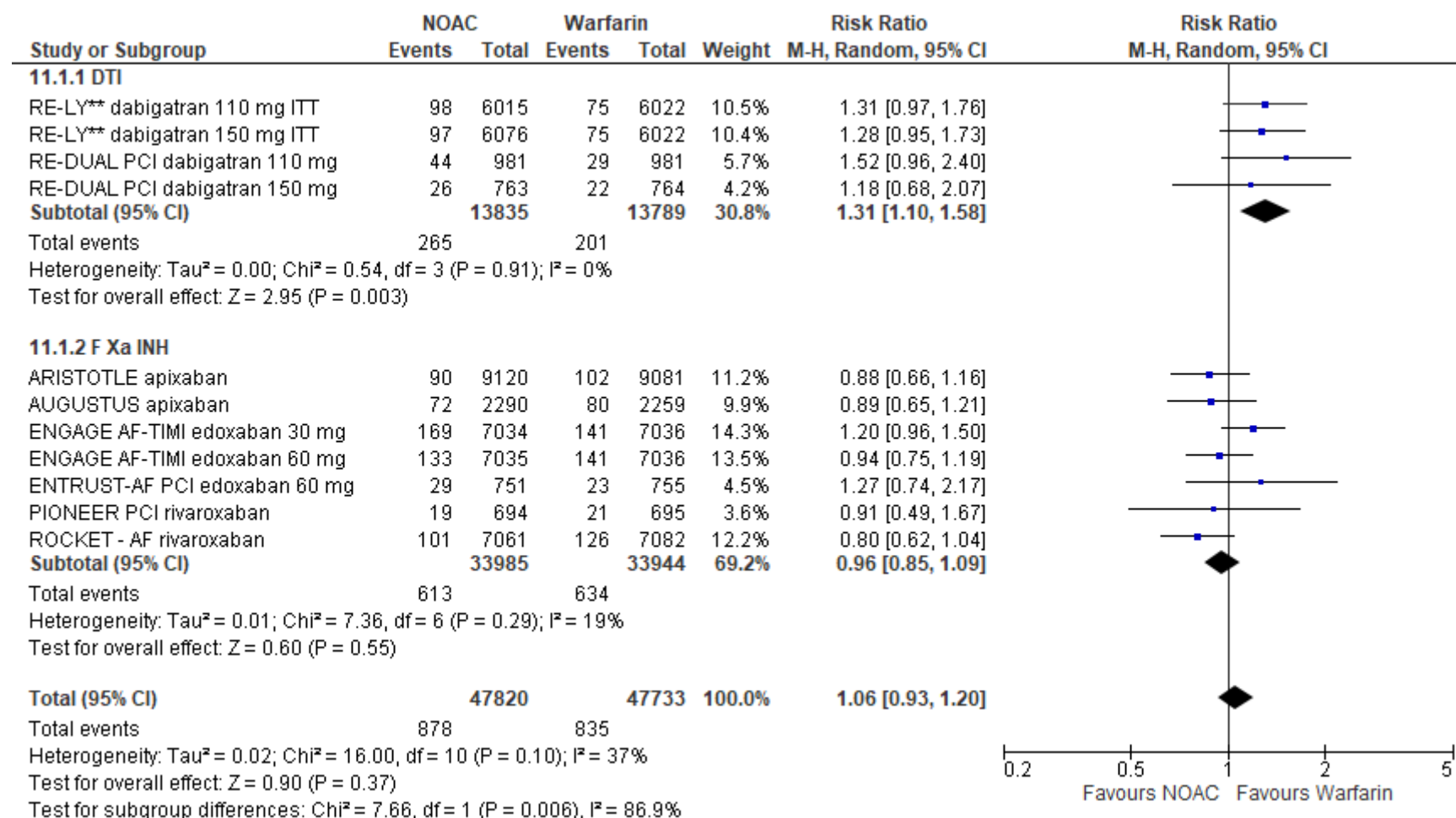


\*- original data from RE-LY study [23]

**Figure S21. The funnel plot for MI after excluding ENGAGE AF-TIMI edoxaban 30 mg.**

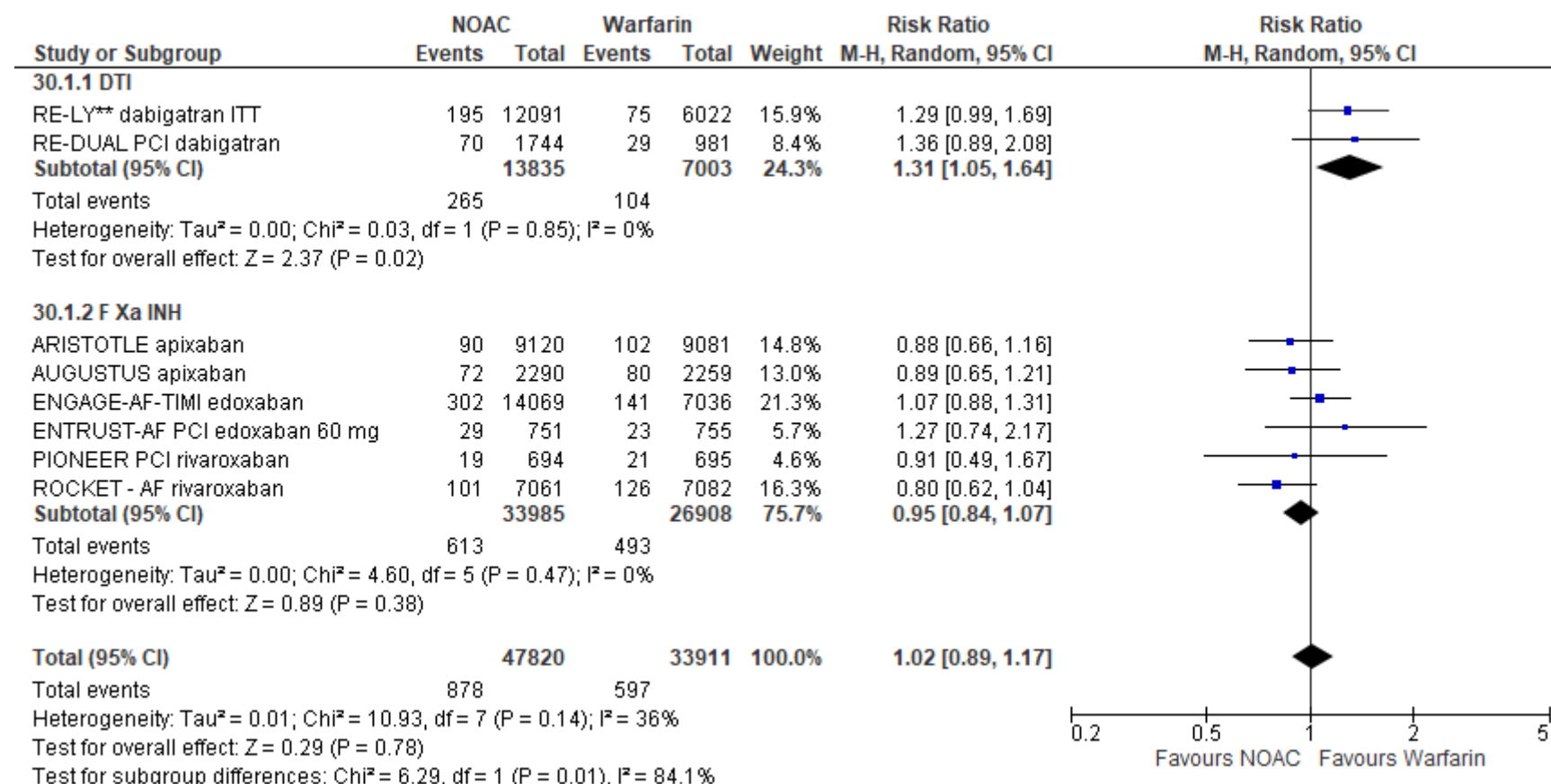


**Figure S22. The meta-analysis results for MI – reanalysis RE-LY [27] -intention to treat data.**



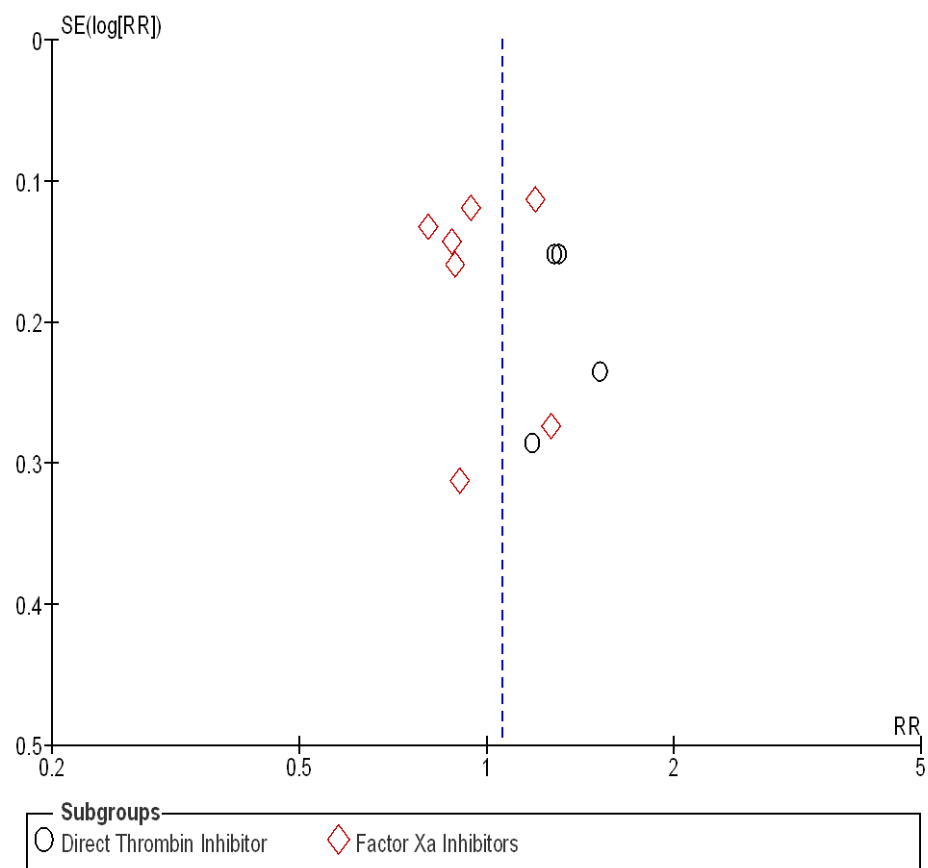
\*\* - results from reanalysis of RE-LY study [27]

**Figure S22A. The meta-analysis results for MI – reanalysis RE-LY [27] -intention to treat data after combining study data with respect to doses.**

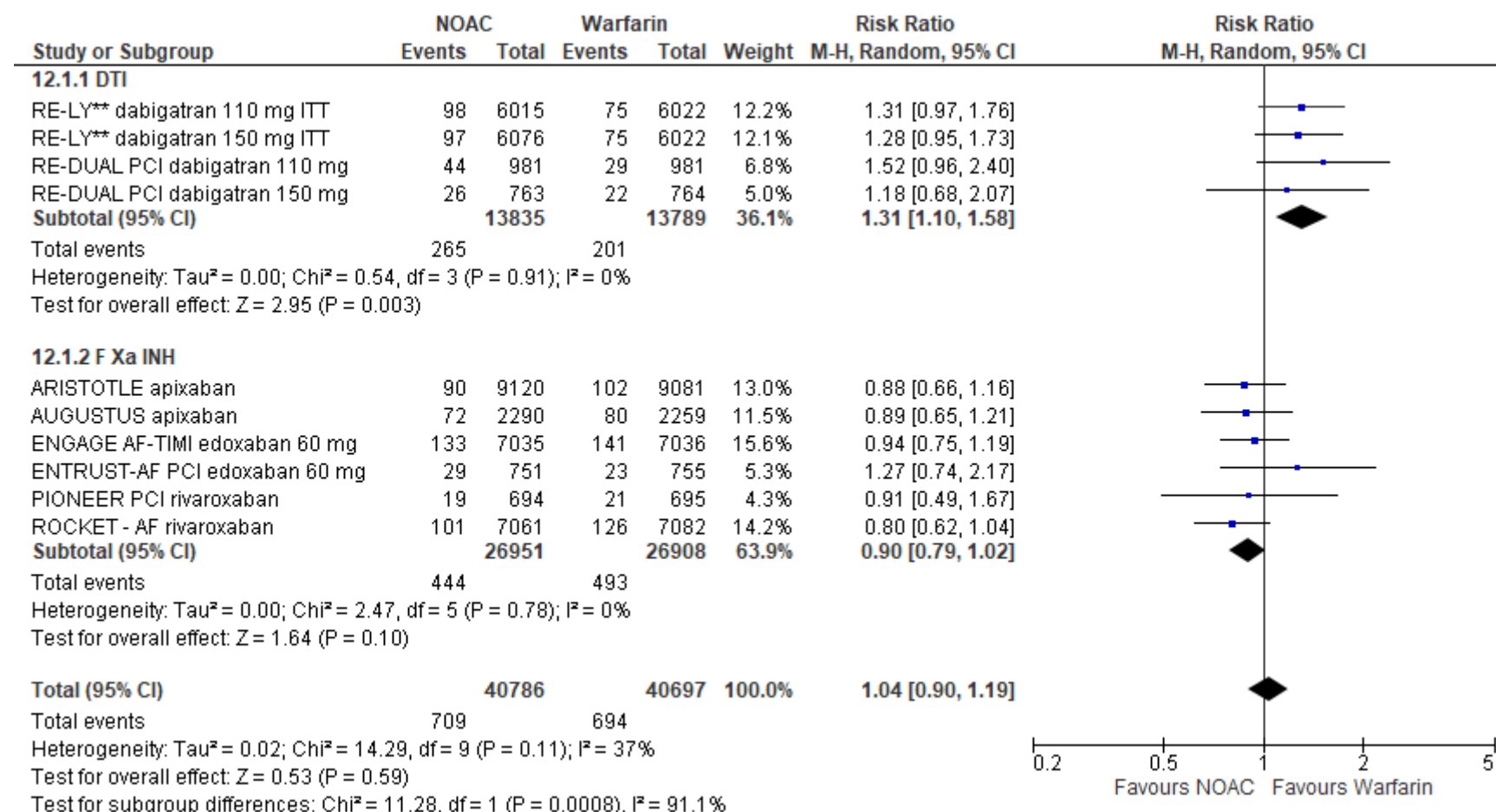


\*\* - results from reanalysis of RE-LY study [27]

**Figure S23. The funnel plot for MI – reanalysis RE-LY [27] -intention to treat data.**

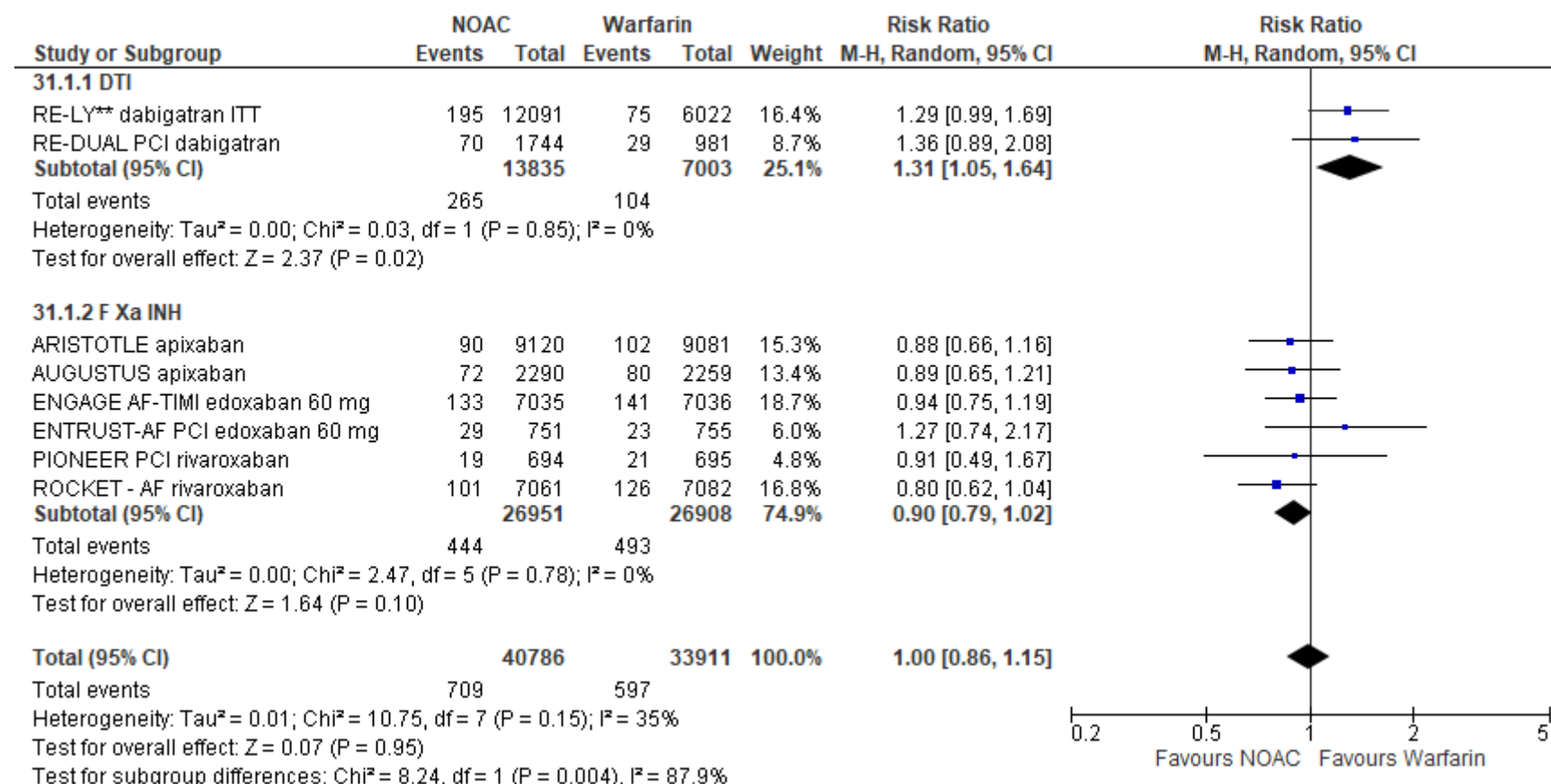


**Figure S24. The meta-analysis results for MI – reanalysis RE-LY [27] - intention to treat data after excluding ENGAGE AF-TIMI edoxaban 30 mg.**



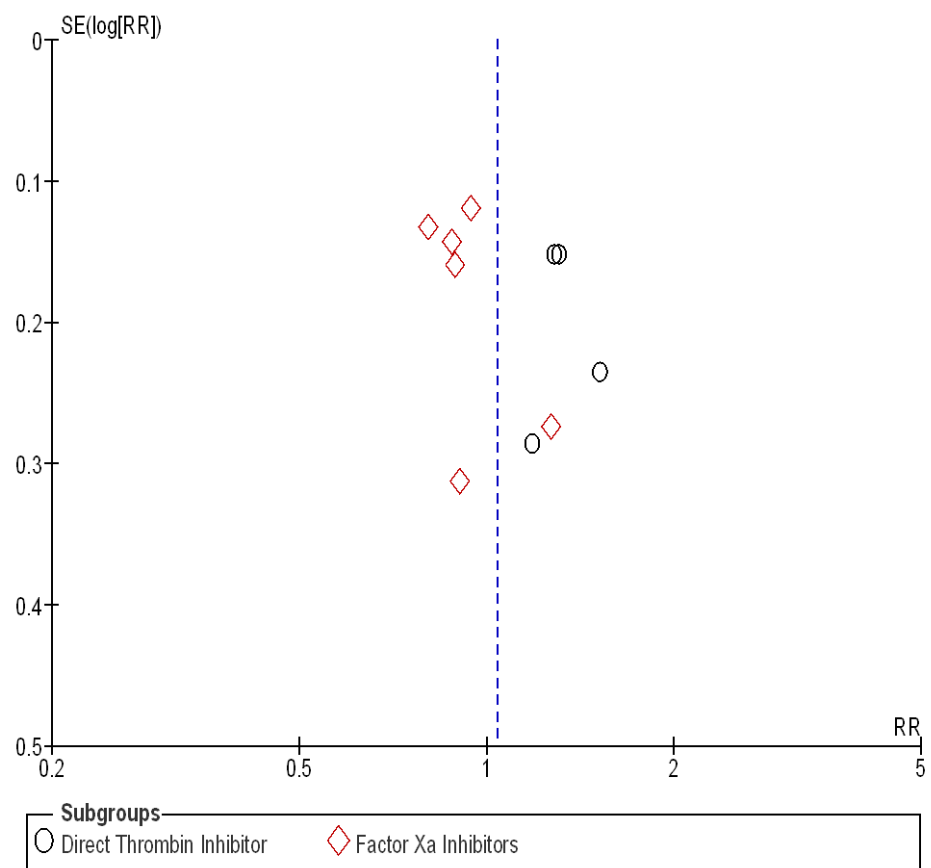
\*\* - results from reanalysis of RE-LY study [27]

**Figure S24A. The meta-analysis results for MI – reanalysis RE-LY [27] - intention to treat data after excluding ENGAGE AF-TIMI edoxaban 30 mg and combining study data with respect to doses.**

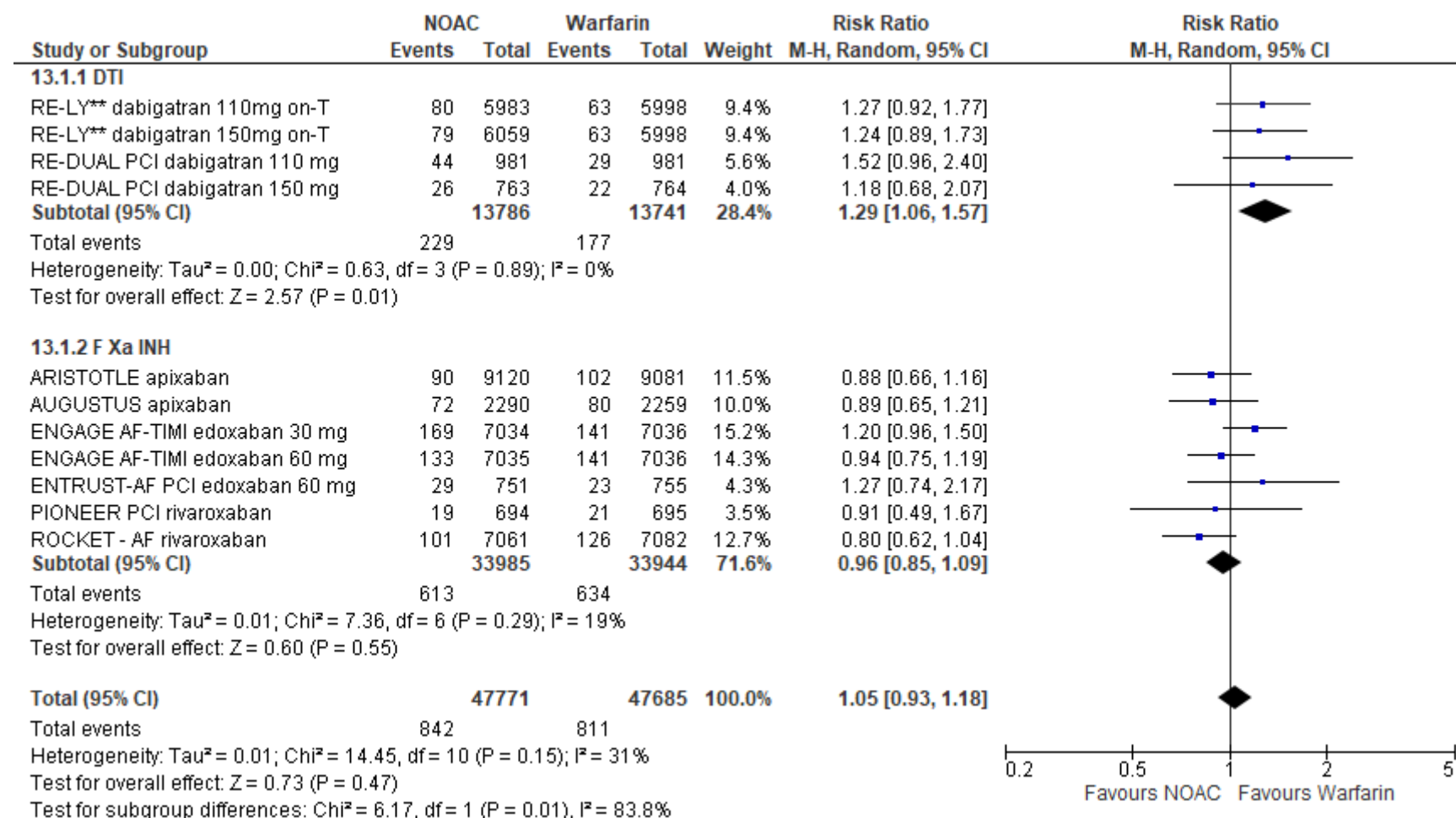




**Figure S25. The funnel plot for MI – reanalysis RE-LY [27] -intention to treat data after excluding ENGAGE AF-TIMI edoxaban 30 mg.**

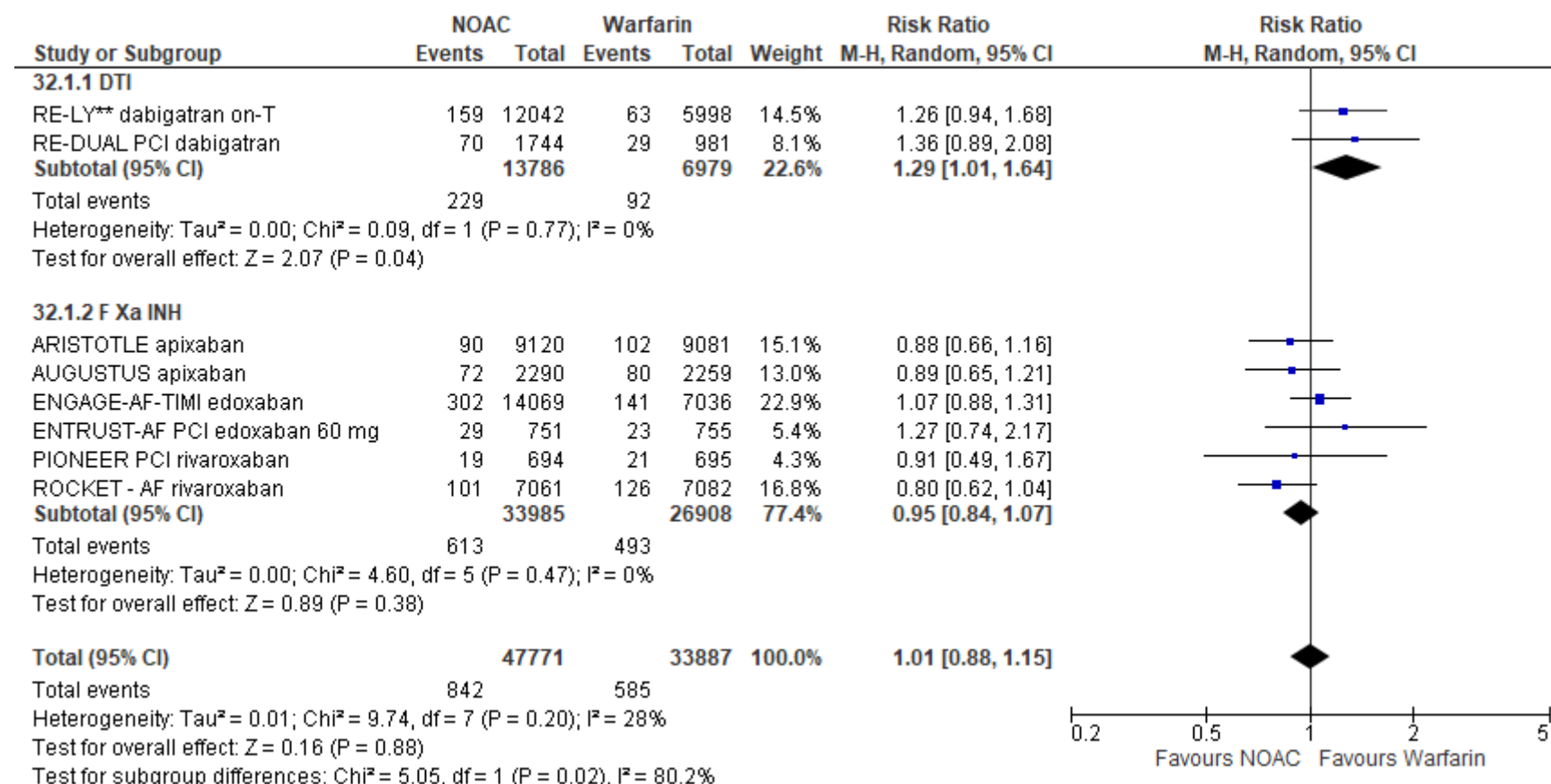


**Figure S26. The meta-analysis results for MI – reanalysis RE-LY [27] - on treatment data.**



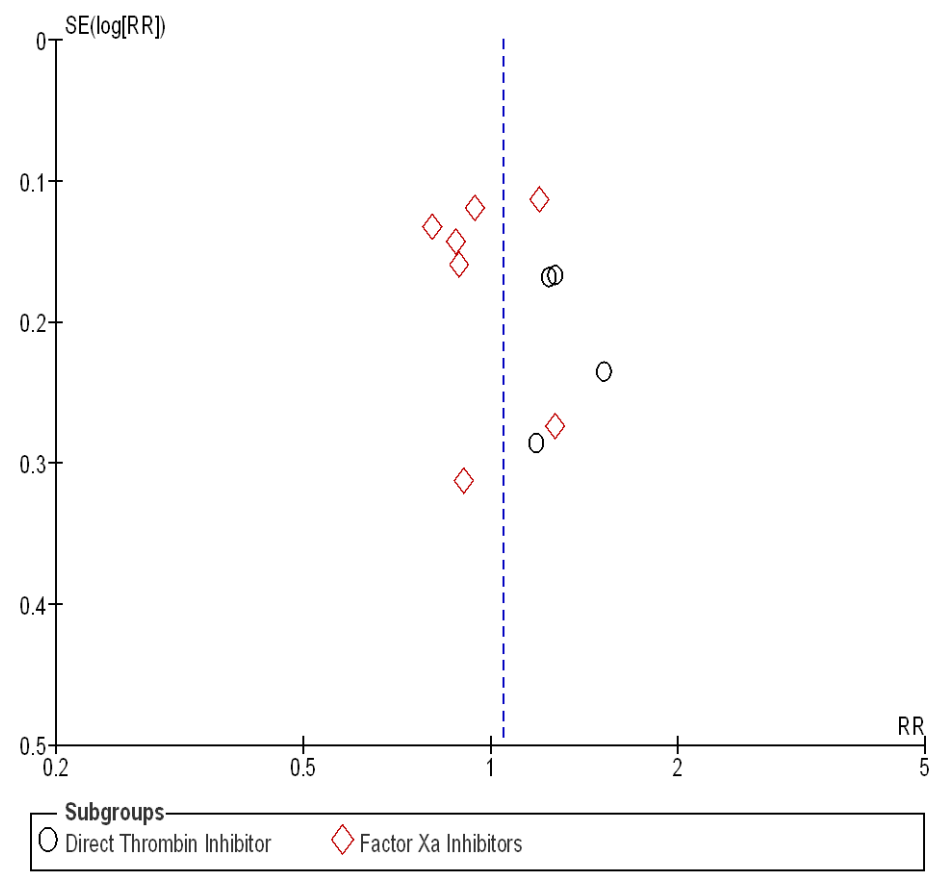
\*\* - results from reanalysis of RE-LY study [27]

**Figure S26A. The meta-analysis results for MI – reanalysis RE-LY [27] - on treatment data after combining study data with respect to doses.**

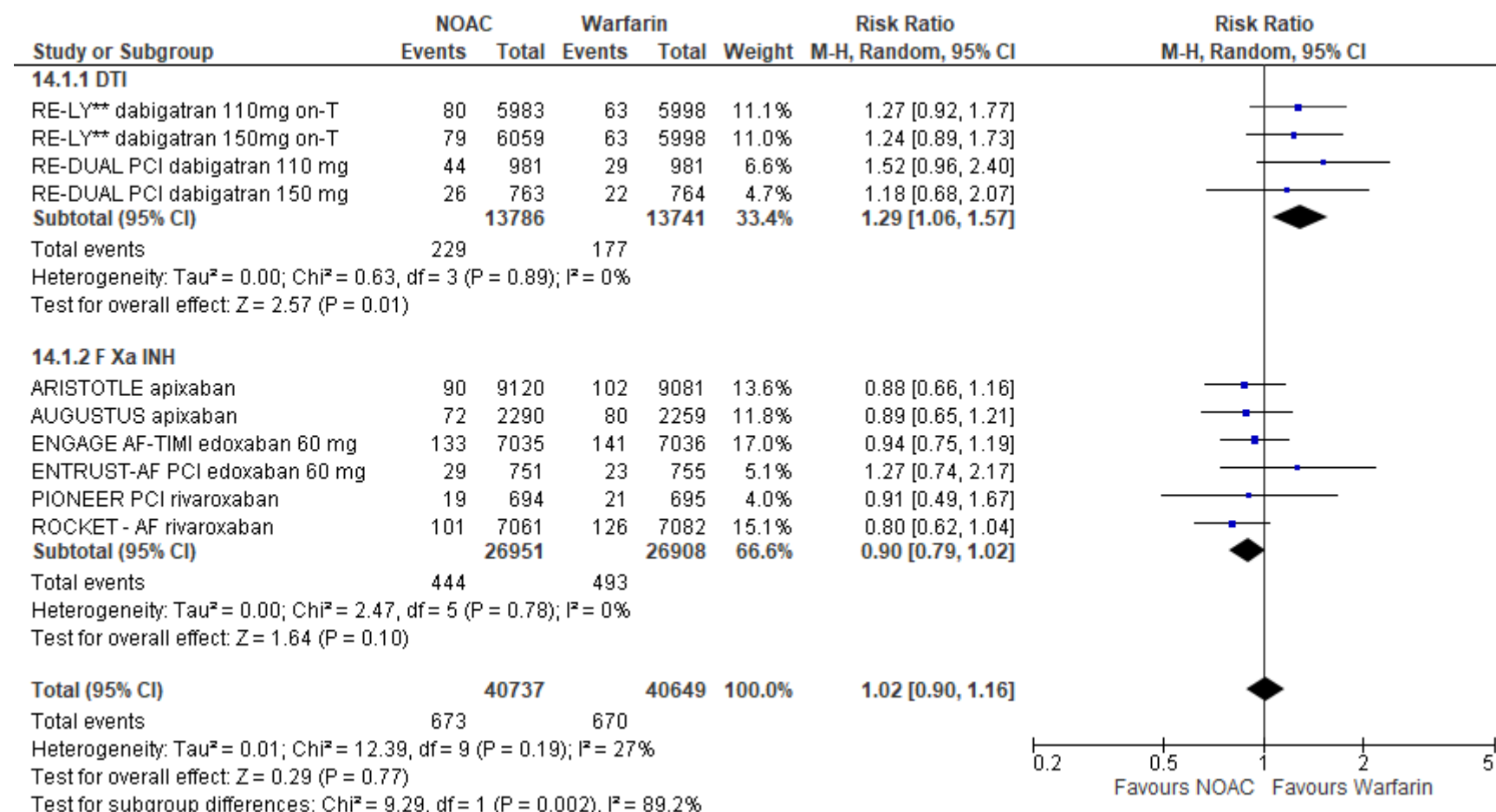


\*\* - results from reanalysis of RE-LY study [27]

**Figure S27. The funnel plot for MI – reanalysis RE-LY [27] - on treatment data.**

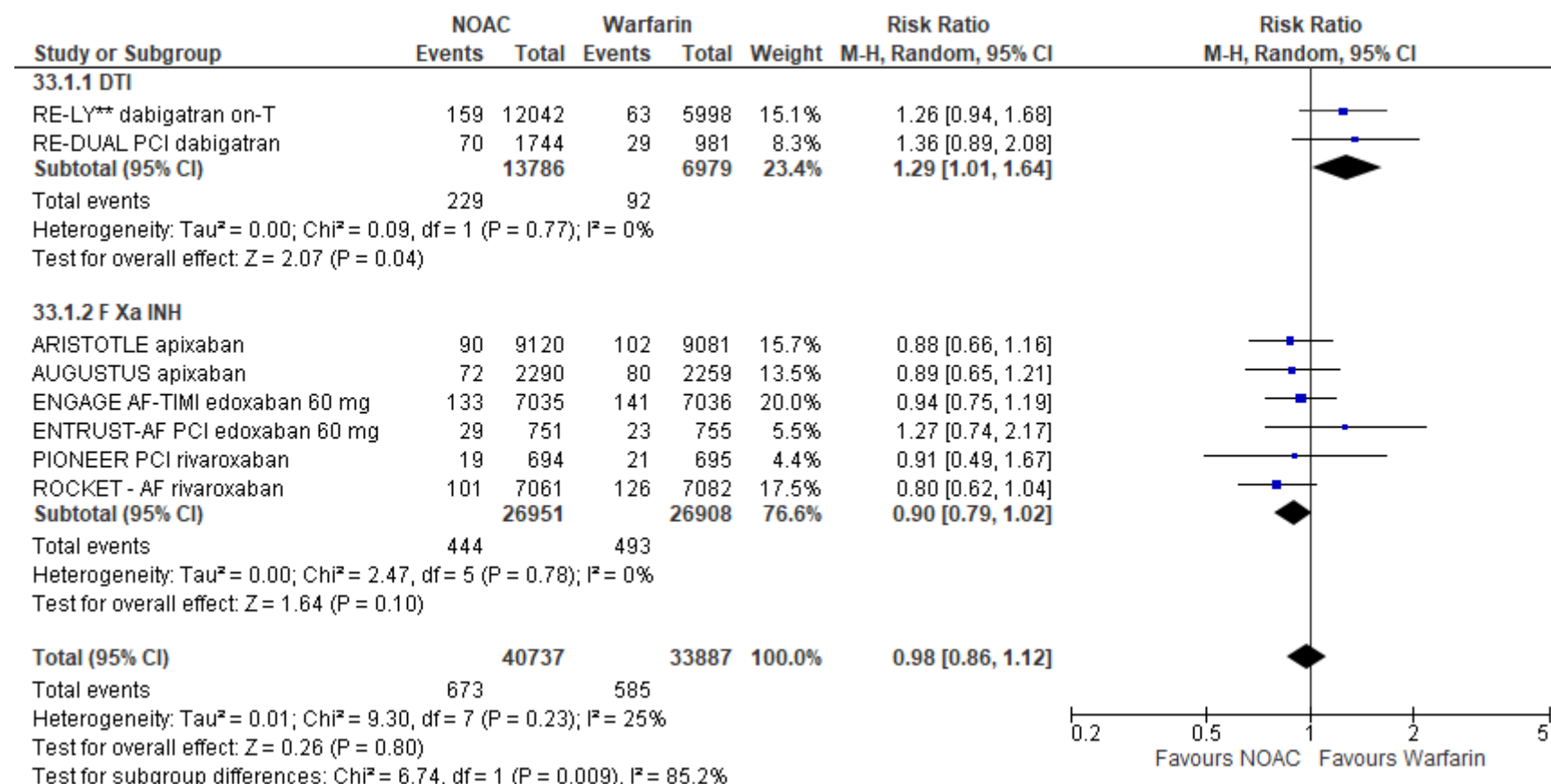


**Figure S28. The meta-analysis results for MI – reanalysis RE-LY [27] - on treatment data after excluding ENGAGE AF-TIMI edoxaban 30 mg.**



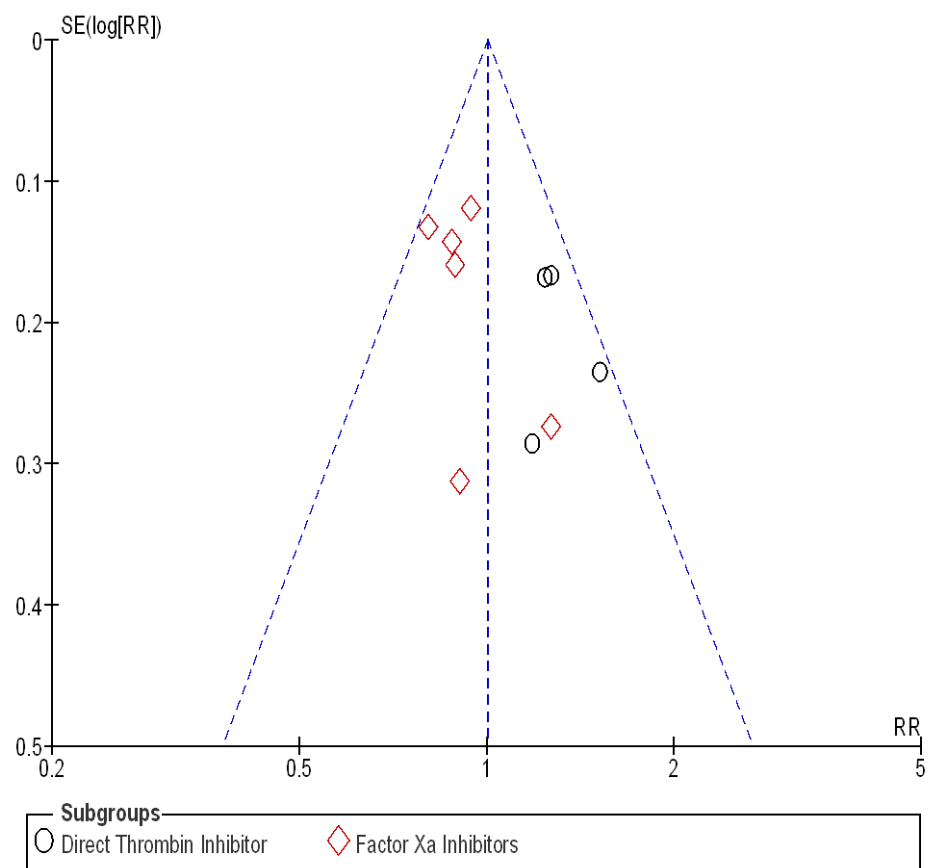
\*\* - results from reanalysis of RE-LY study [27]

**Figure S28A. The meta-analysis results for MI – reanalysis RE-LY [27] - on treatment data after excluding ENGAGE AF-TIMI edoxaban 30 mg and combining study data with respect to doses.**

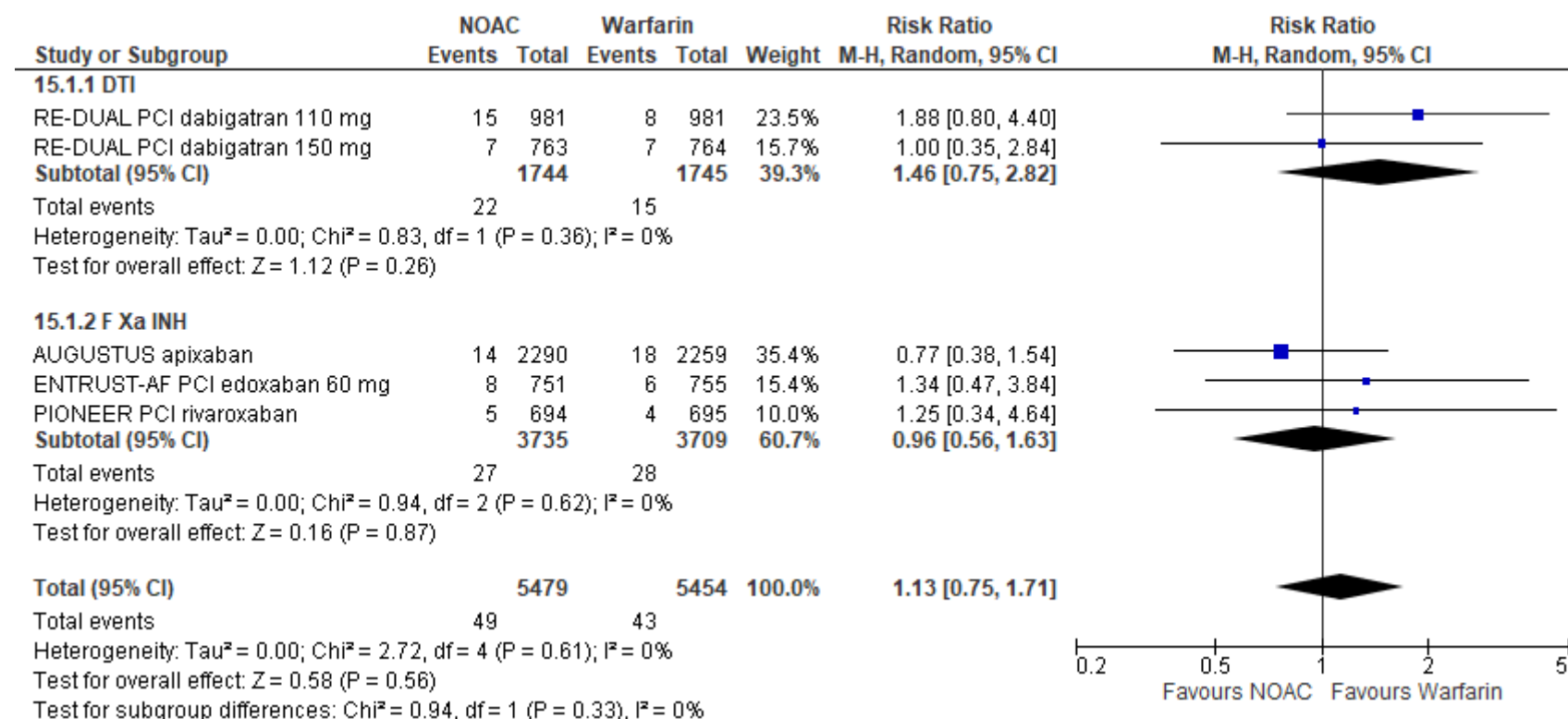


\*\* - results from reanalysis of RE-LY study [27]

**Figure S29. The funnel plot for MI – reanalysis RE-LY [27] - on treatment data after excluding ENGAGE AF-TIMI edoxaban 30 mg.**

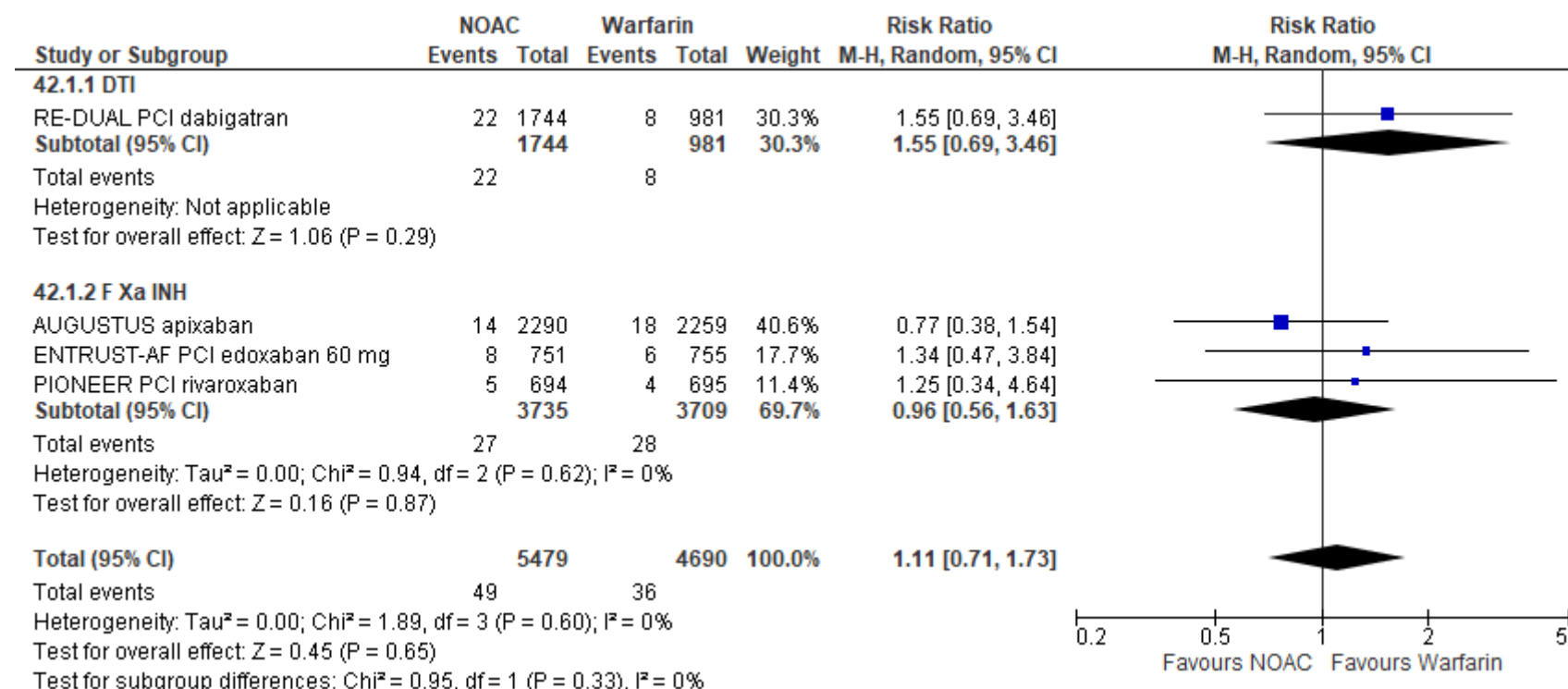


**Figure S30. The meta-analysis results for stent thrombosis.**

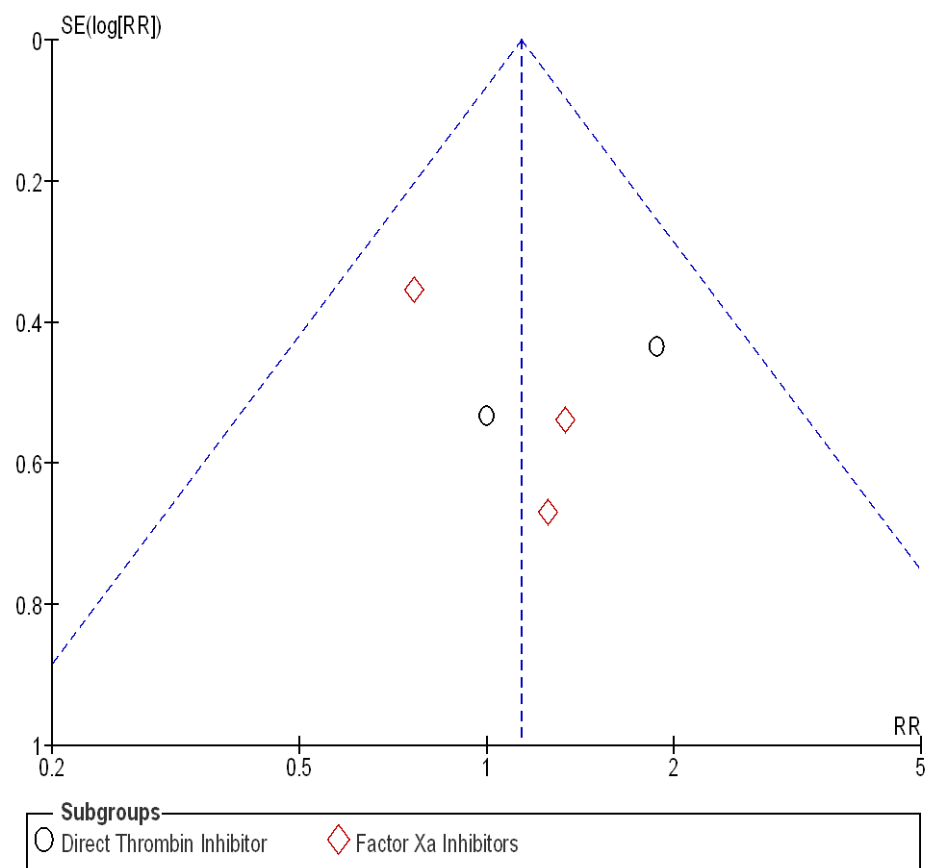




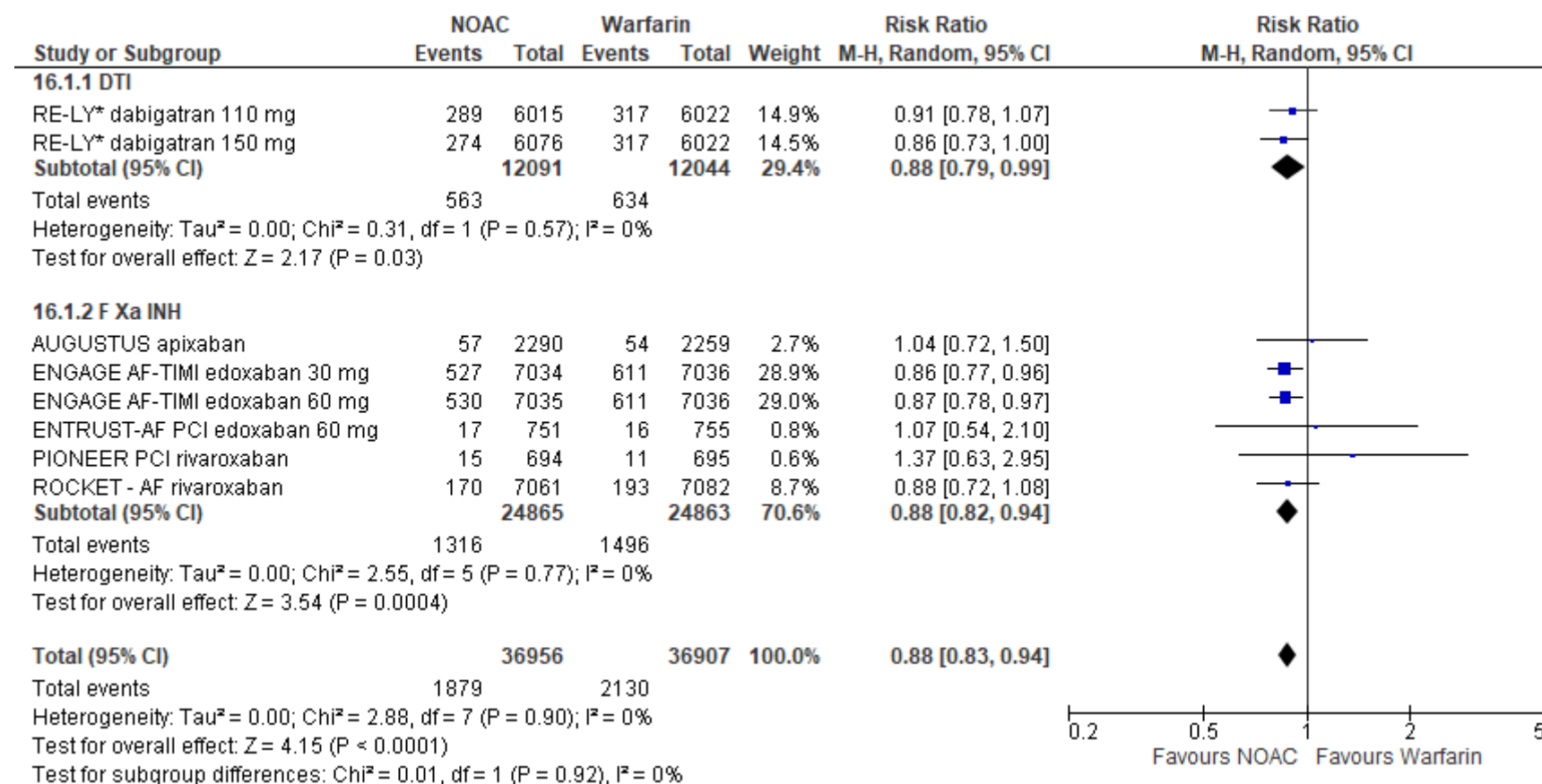
**Figure S30A. The meta-analysis results for stent thrombosis after combining study data with respect to doses.**



**Figure S31. The funnel plot for stent thrombosis.**

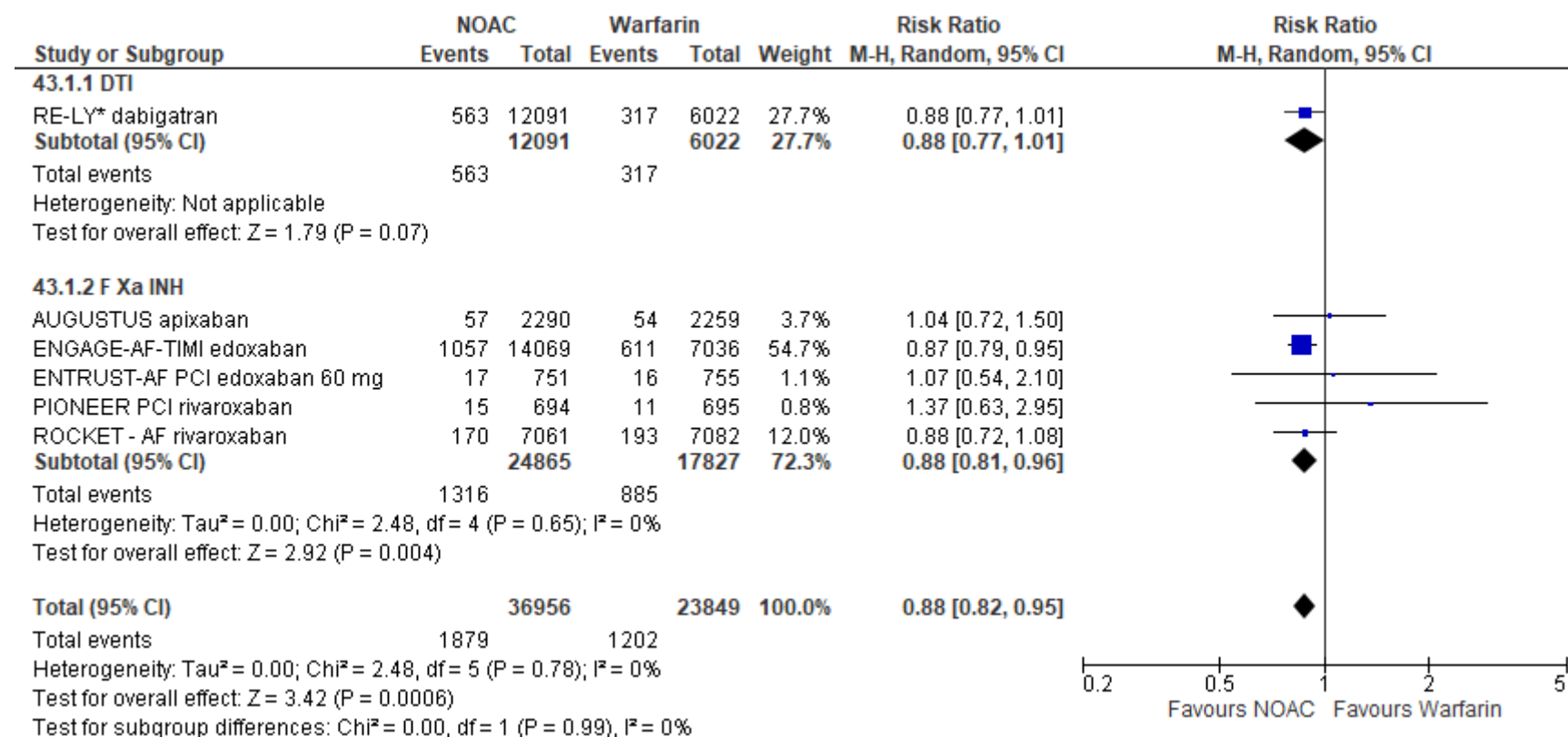


**Figure S32. The meta-analysis results for cardiovascular mortality.**



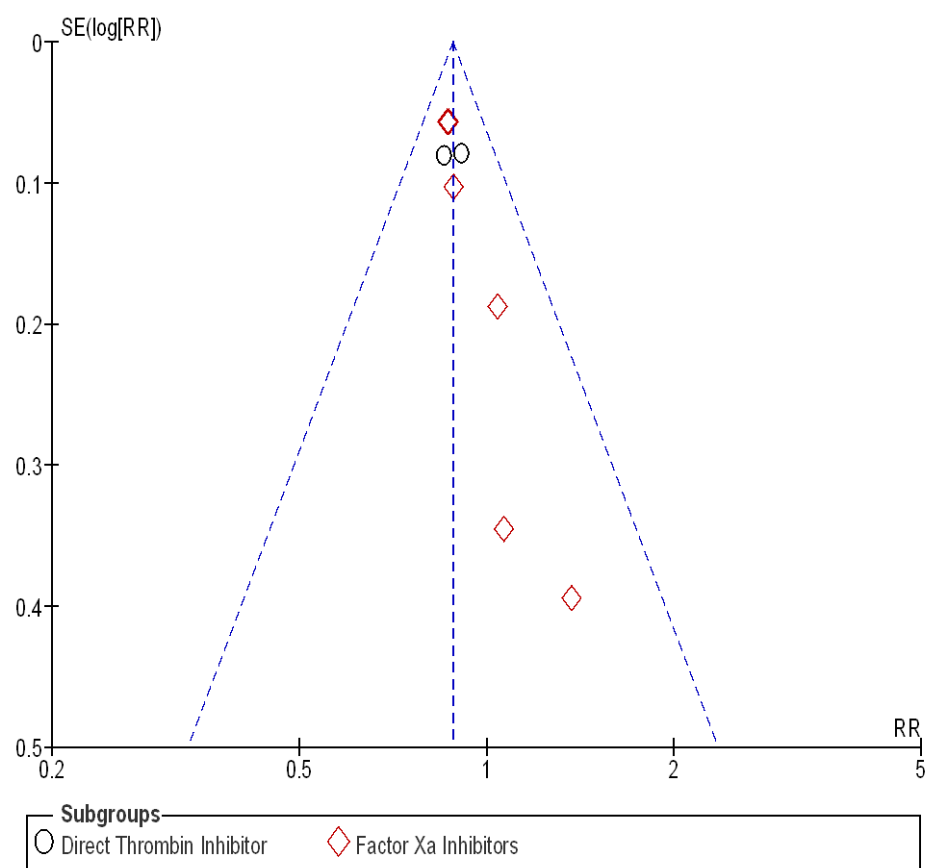
\* - Defined as death from vascular causes in RE-LY study [23]

**Figure S32A. The meta-analysis results for cardiovascular mortality after combining study data with respect to doses.**

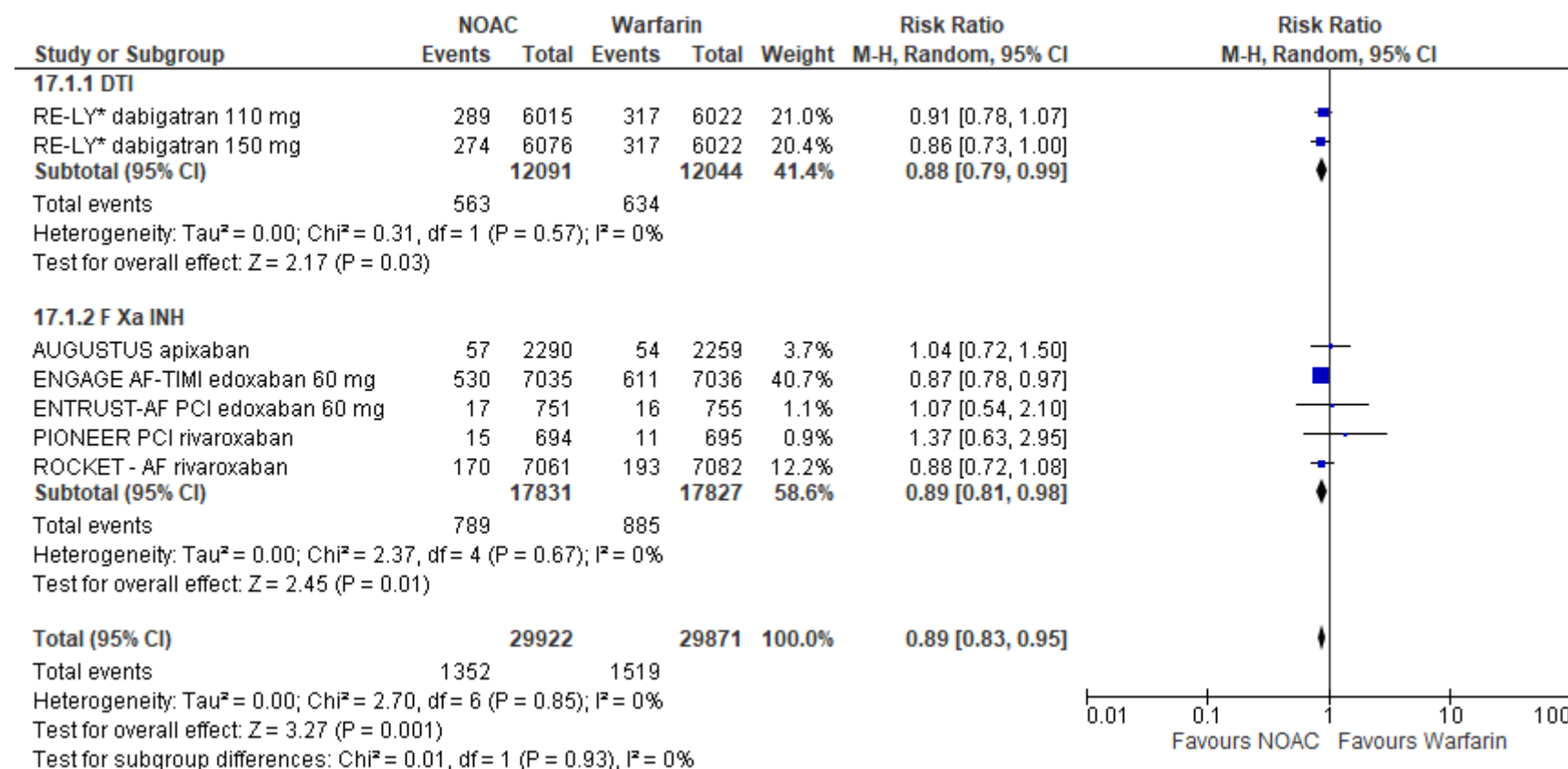


\* - Defined as death from vascular causes in RE-LY study [20]

**Figure S33. The funnel plot for cardiovascular mortality.**

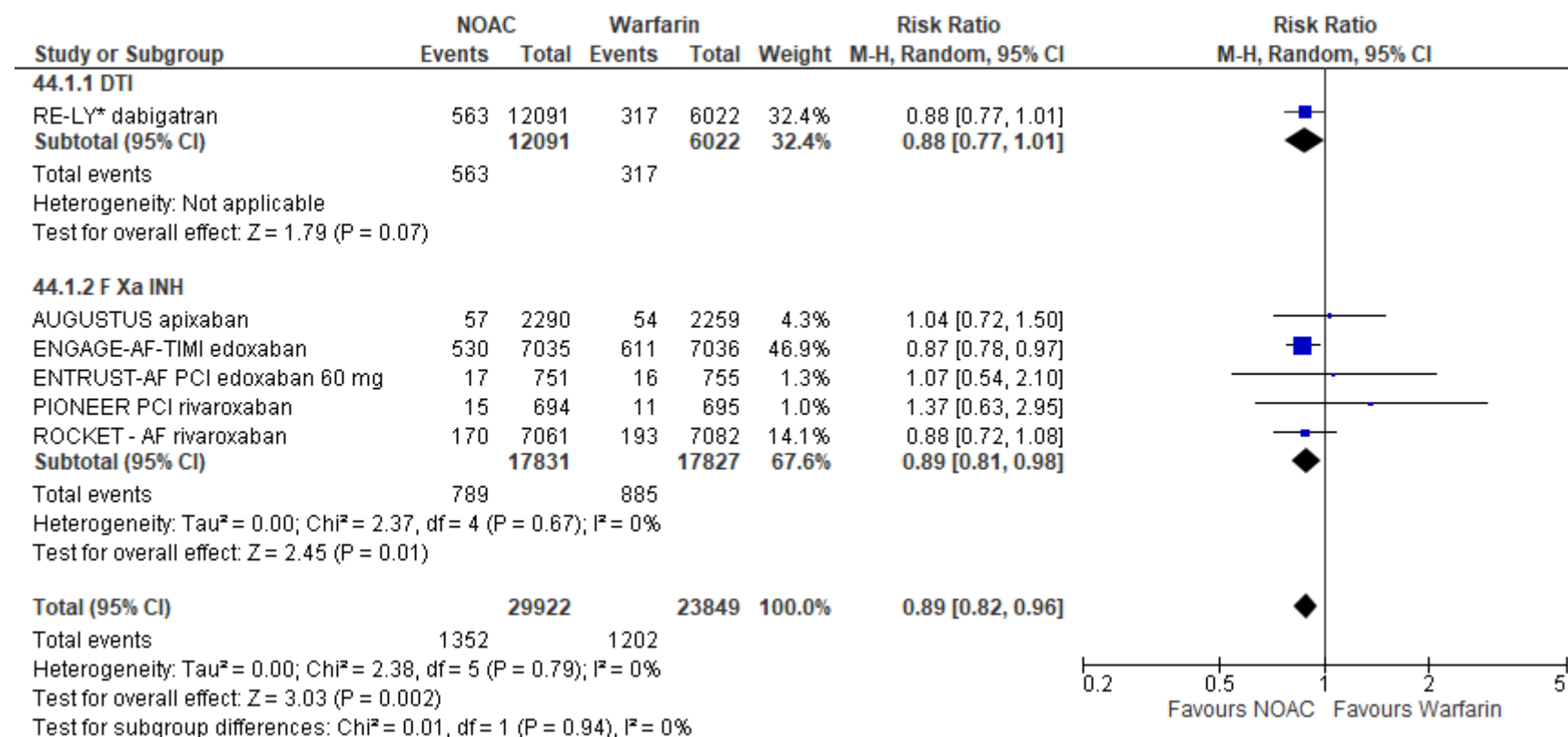


**Figure S34. The meta-analysis results for cardiovascular mortality after excluding ENGAGE AF-TIMI edoxaban 30 mg.**



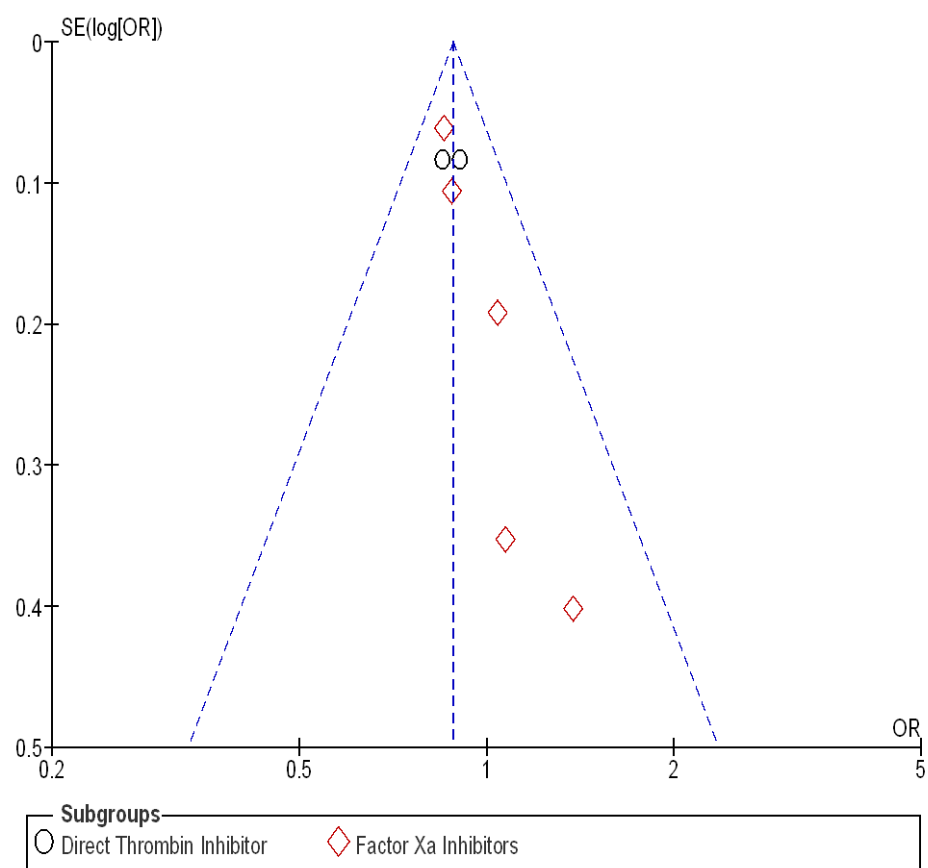
\*- Defined as death from vascular causes in RE-LY study [23]

**Figure S34A. The meta-analysis results for cardiovascular mortality after excluding ENGAGE AF-TIMI edoxaban 30 mg and combining study data with respect to doses.**



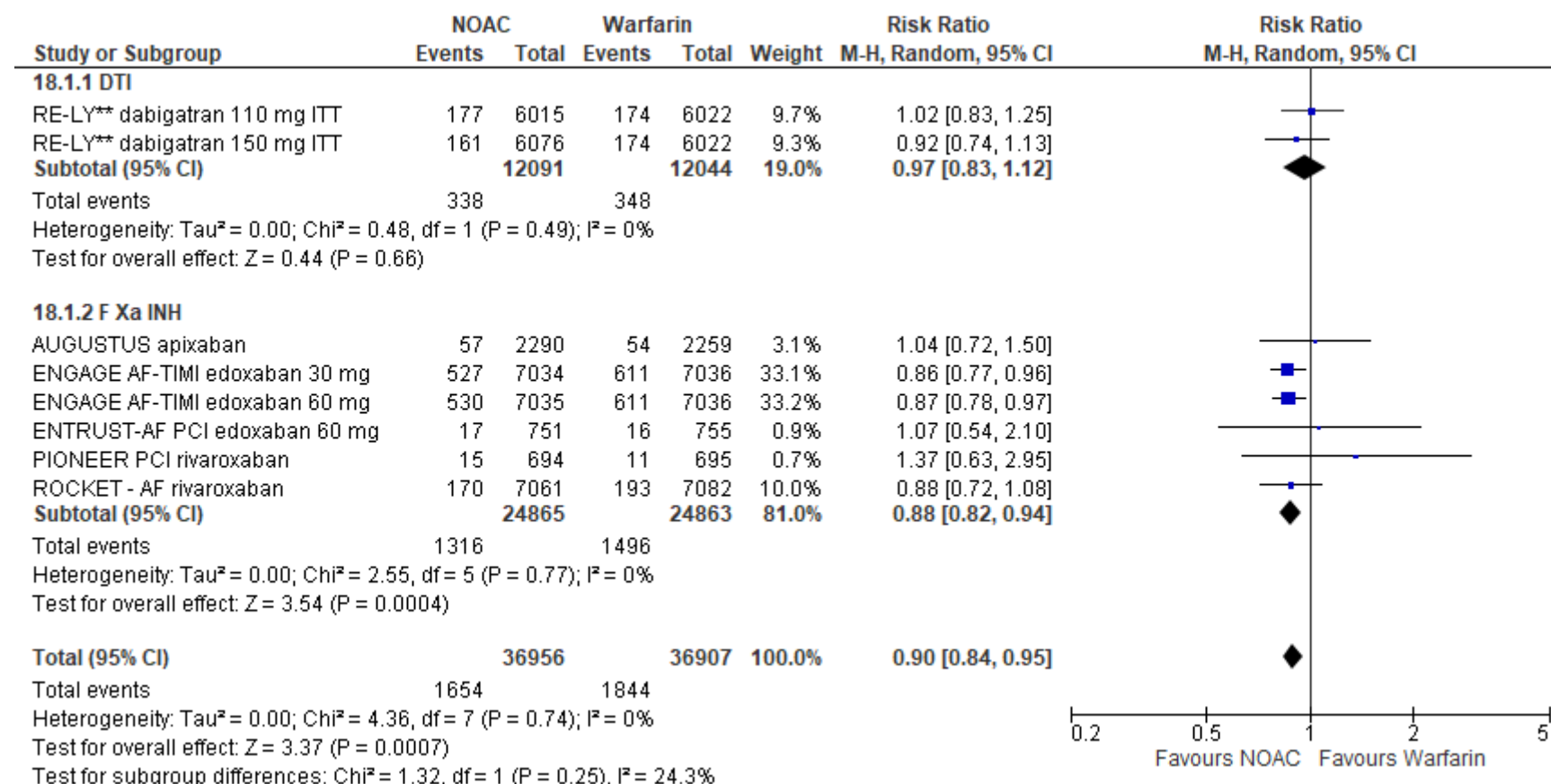
\*- Defined as death from vascular causes in RE-LY study [23]

**Figure S35. The funnel plot for cardiovascular mortality after excluding ENGAGE AF-TIMI edoxaban 30 mg.**



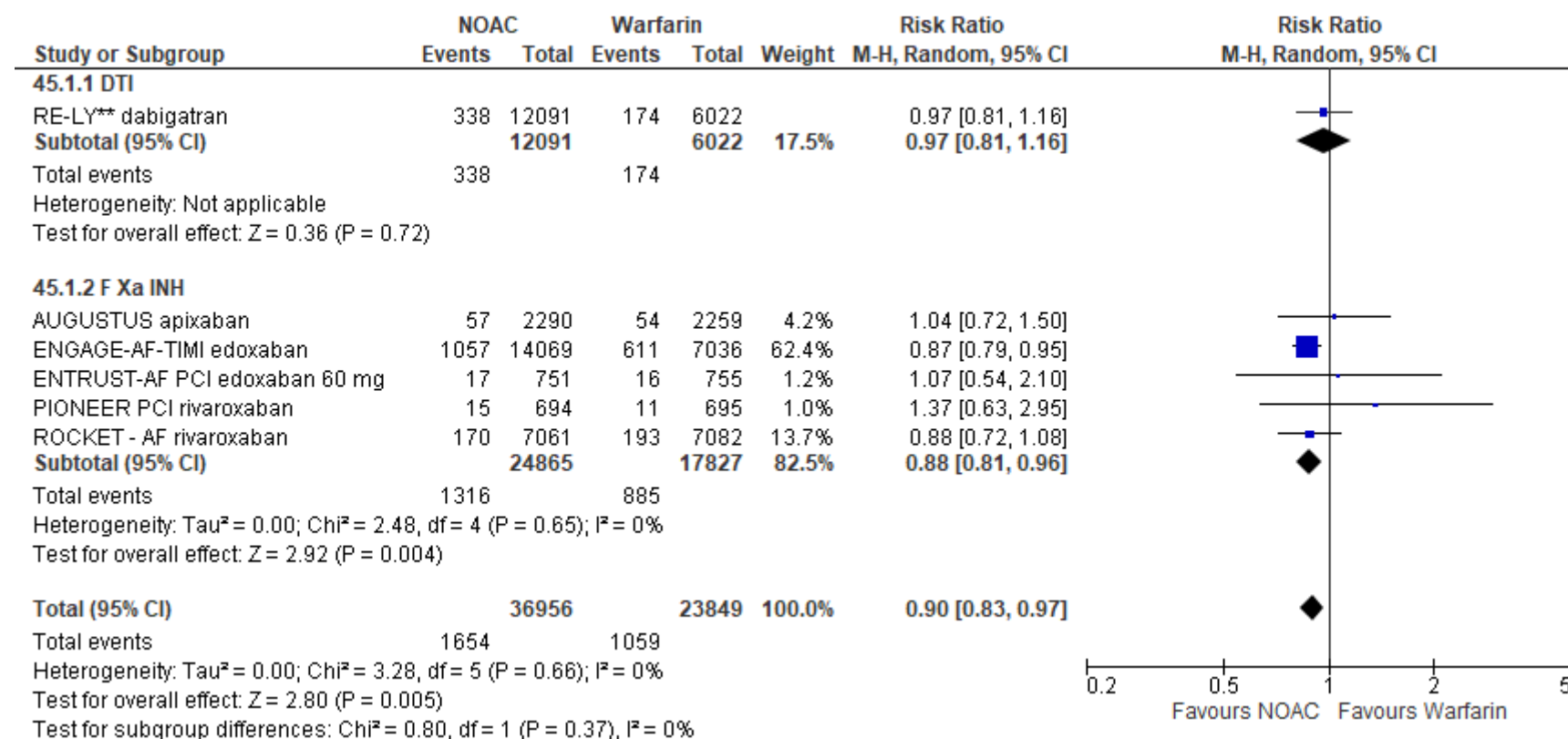


**Figure S36. The meta-analysis results for cardiovascular mortality reanalysis RE-LY [27]– intention to treat data.**



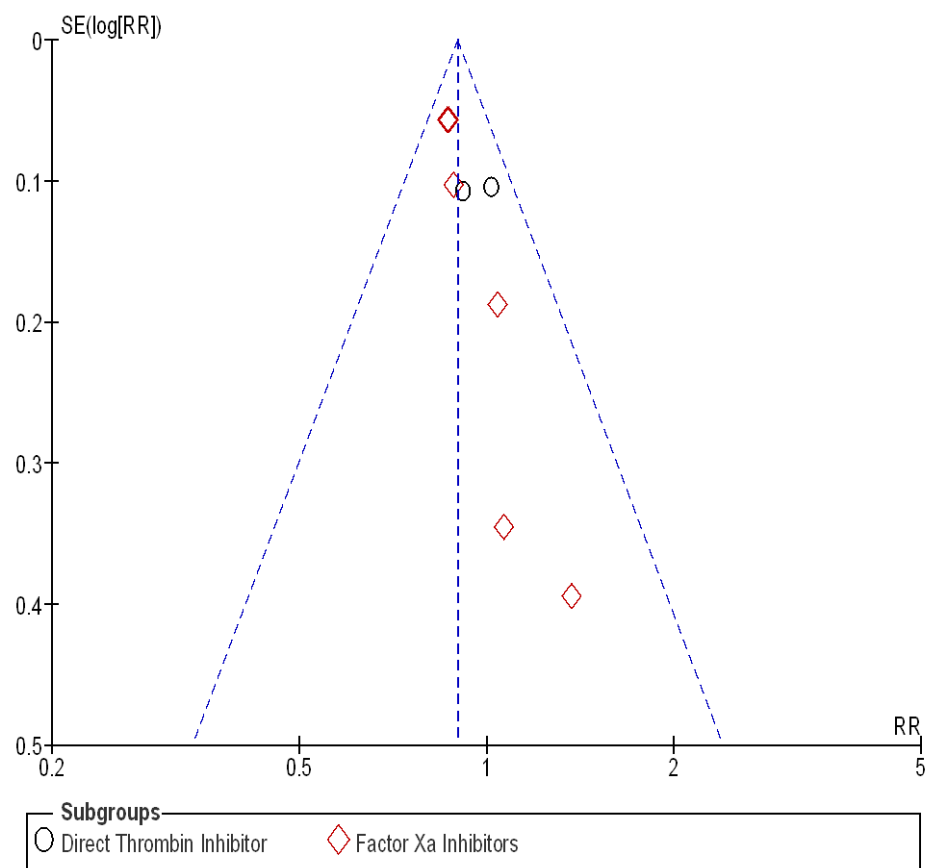
\*\* - Defined as cardiac death in reanalysis of RE-LY study [27]

**Figure S36A. The meta-analysis results for cardiovascular mortality reanalysis RE-LY [27]- intention to treat data after combining study data with respect to doses.**

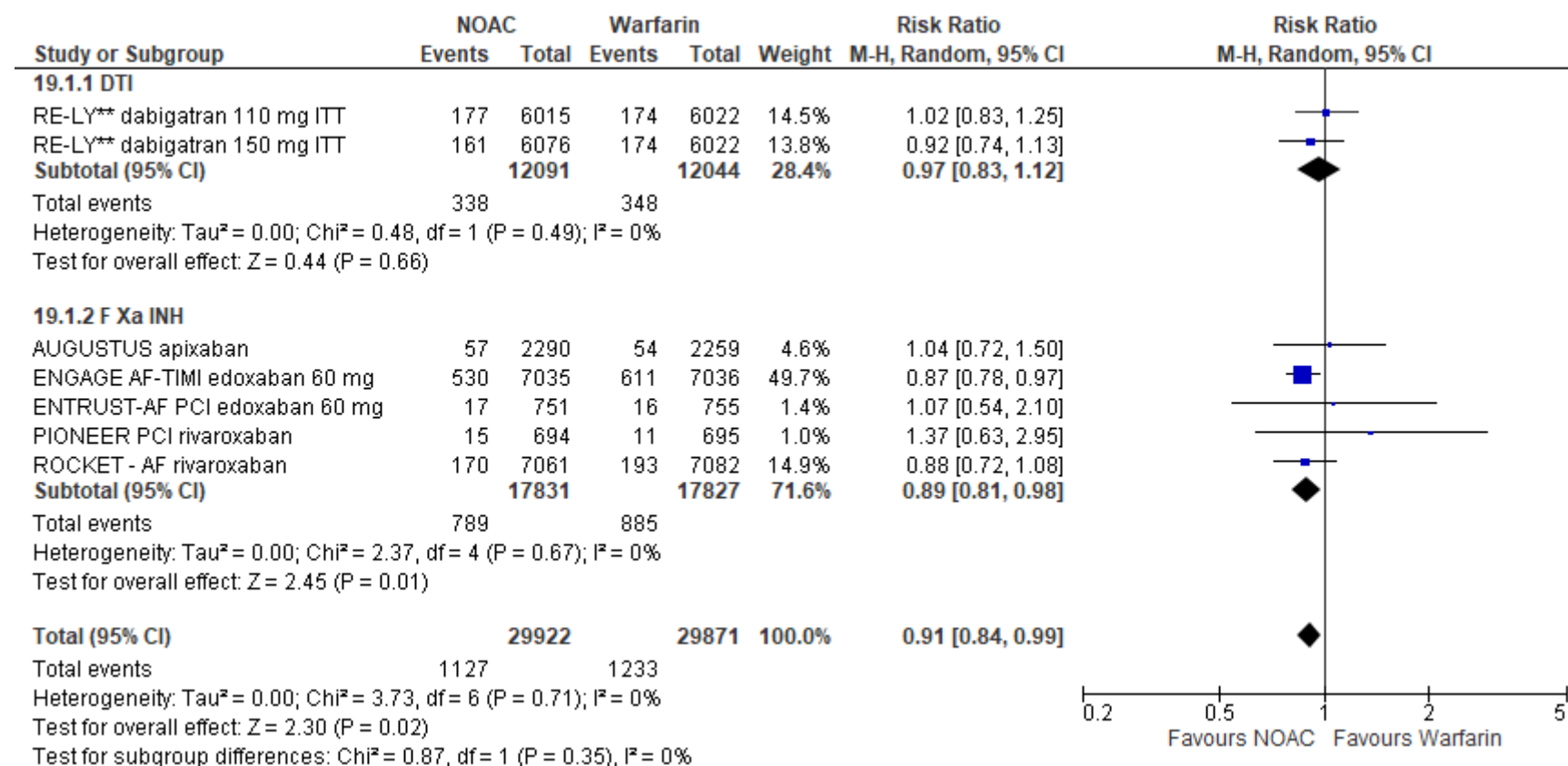


\*\* - Defined as cardiac death in reanalysis of RE-LY study [27]

**Figure S37. The funnel plot for cardiovascular mortality reanalysis RE-LY [27] – intention to treat data.**

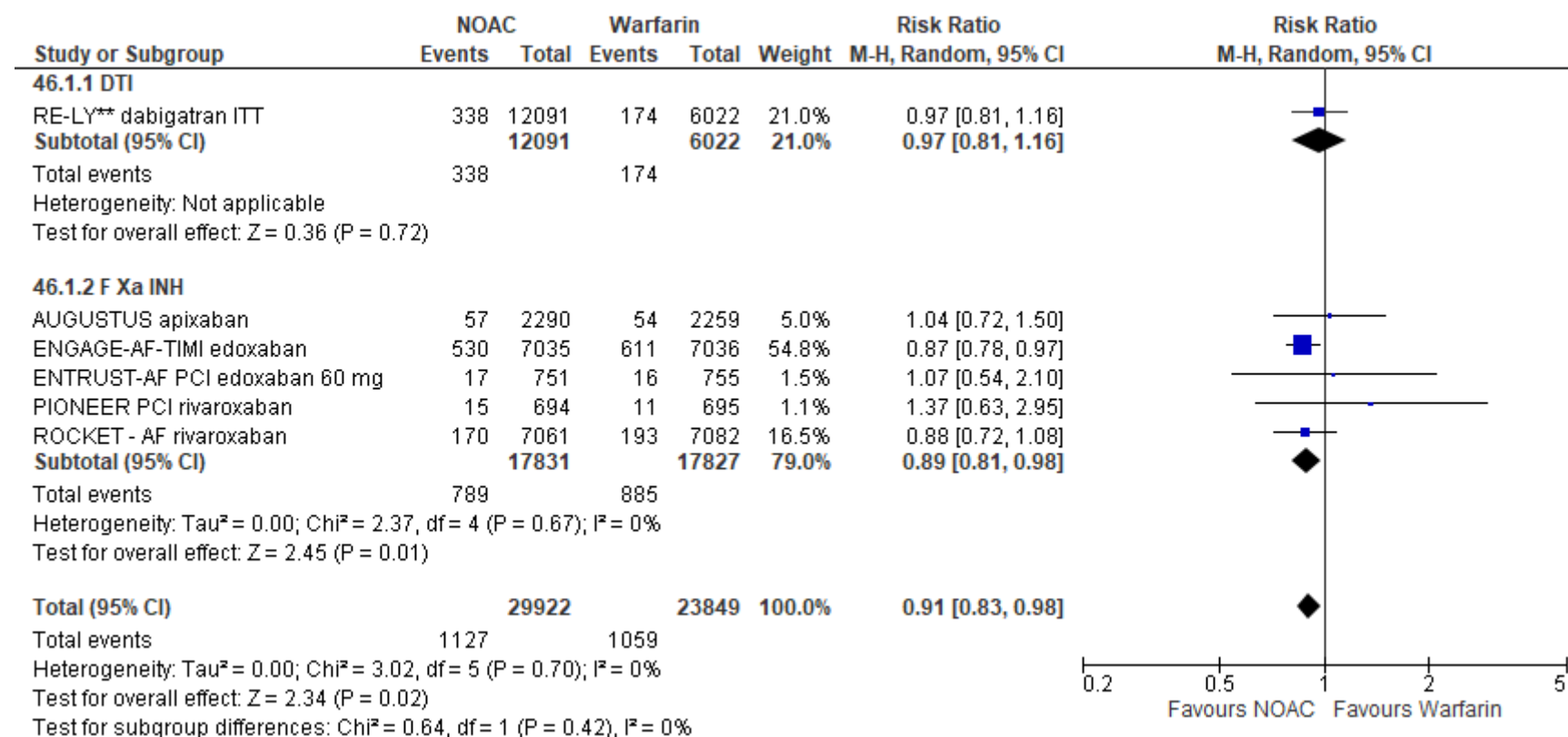


**Figure S38. The meta-analysis results for cardiovascular mortality reanalysis RE-LY [27]– intention to treat data after excluding ENGAGE AF-TIMI edoxaban 30 mg.**



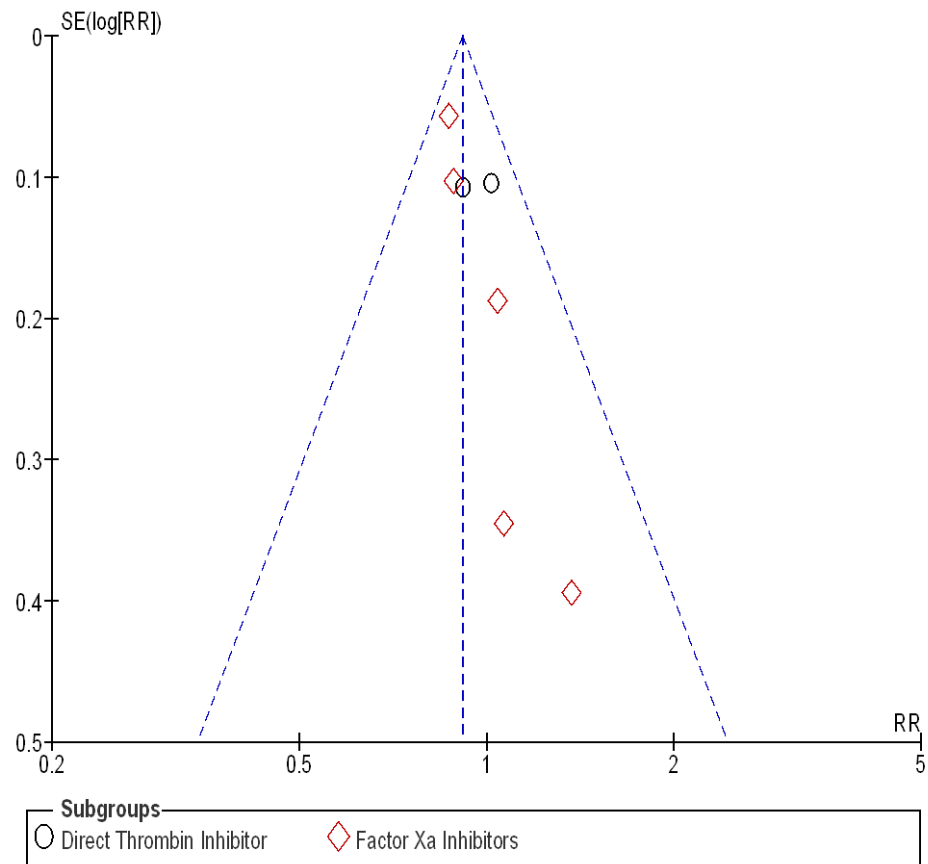
\*\* - Defined as cardiac death in reanalysis of RE-LY study [27]

**Figure S38A. The meta-analysis results for cardiovascular mortality reanalysis RE-LY [27]– intention to treat data after excluding ENGAGE AF-TIMI edoxaban 30 mg and combining study data with respect to doses.**

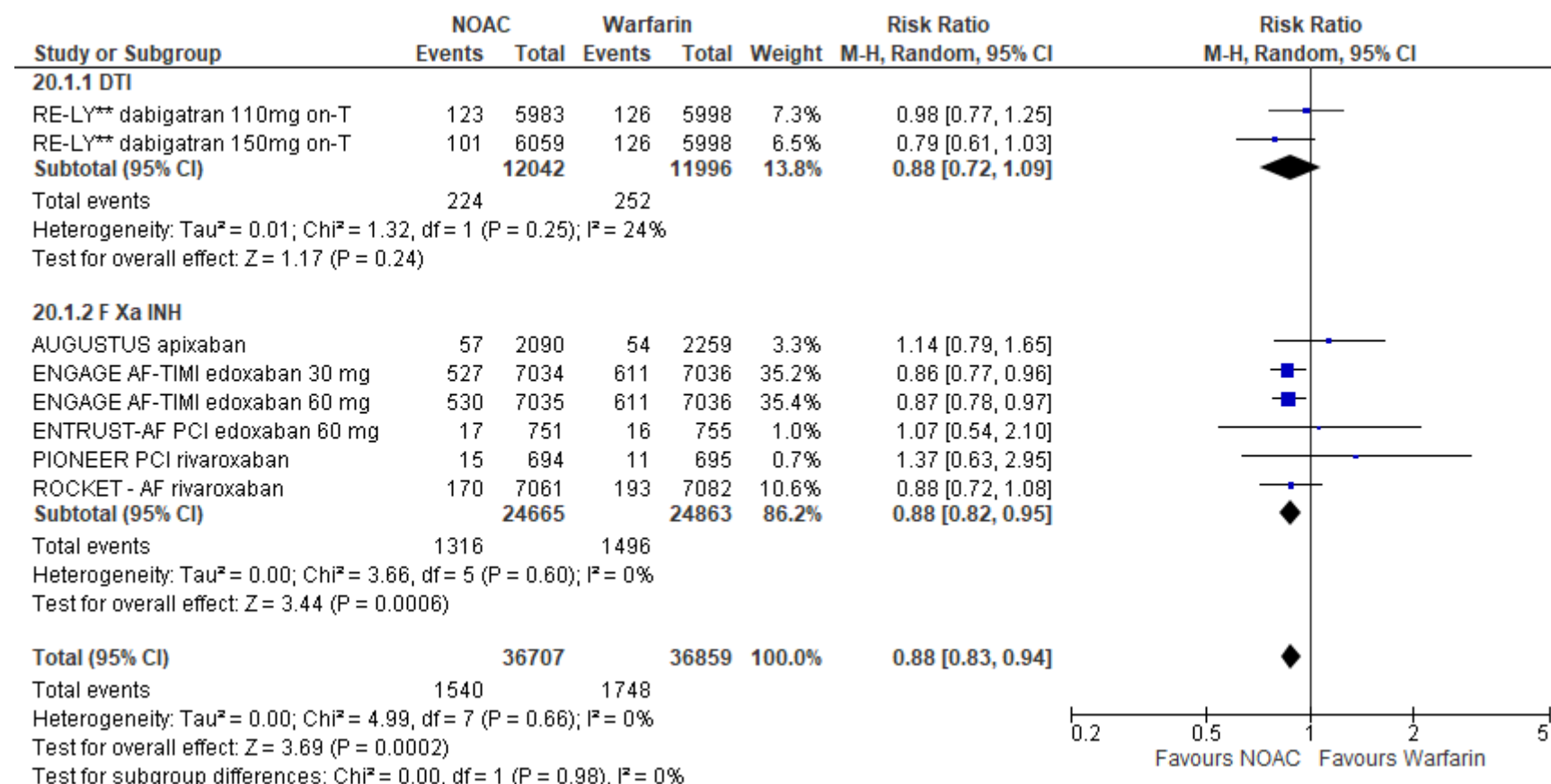


\*\* - Defined as cardiac death in reanalysis of RE-LY study [27]

**Figure S39. The funnel plot for cardiovascular mortality reanalysis RE-LY [27] – intention to treat data after excluding ENGAGE AF-TIMI edoxaban 30 mg.**

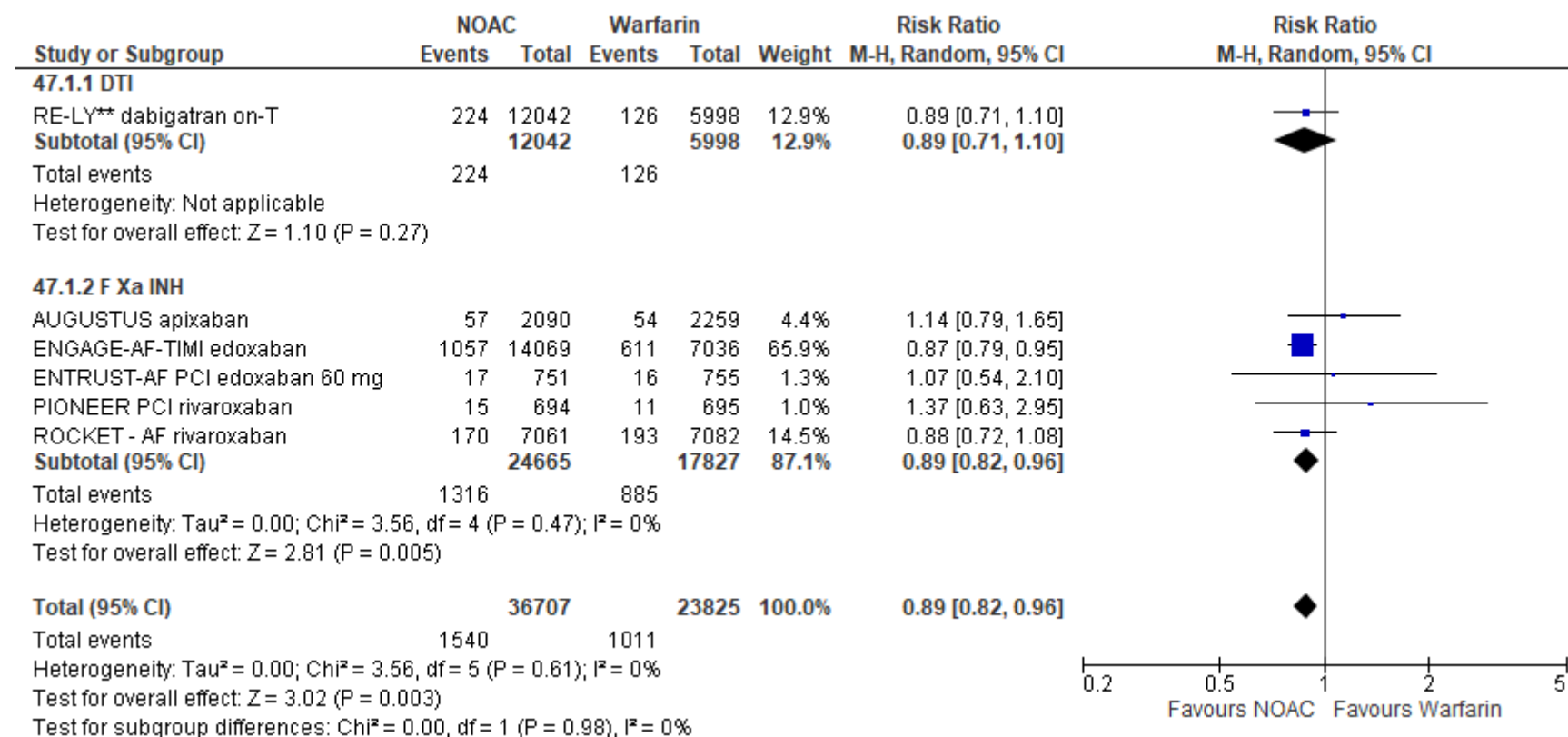


**Figure S40. The meta-analysis results for cardiovascular mortality reanalysis RE-LY [27] – on treatment data.**



\*\* - Defined as cardiac death in reanalysis of RE-LY study [27]

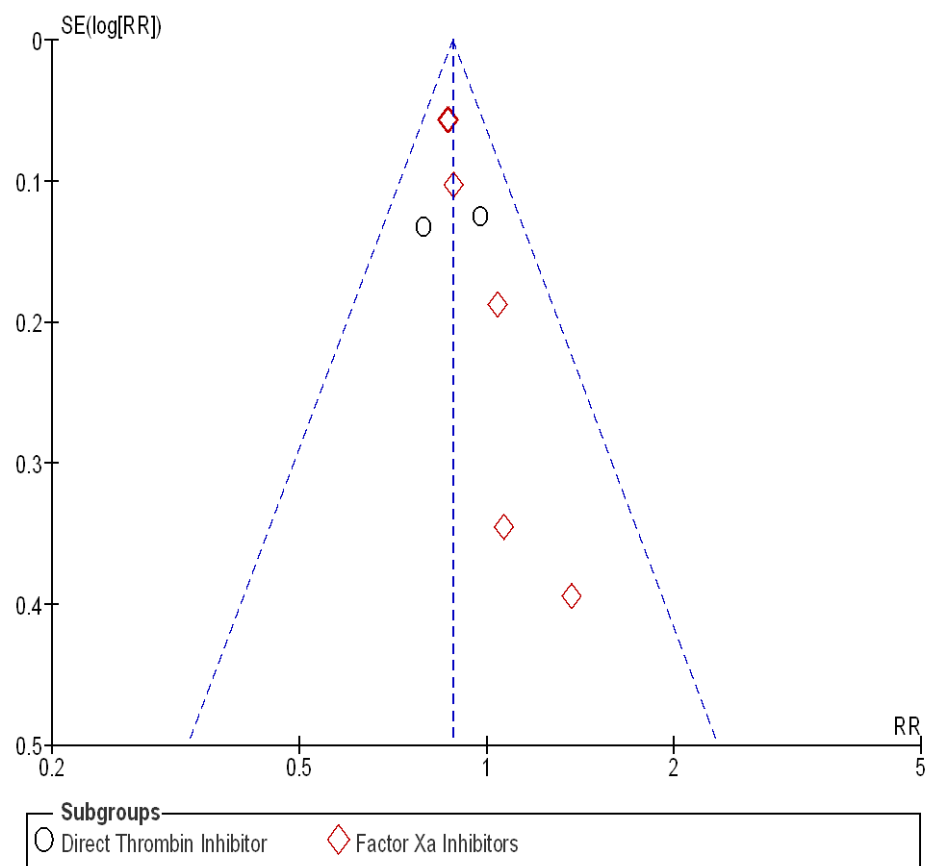
**Figure S40A. The meta-analysis results for cardiovascular mortality reanalysis RE-LY [27] – on treatment data after combining study data with respect to doses.**



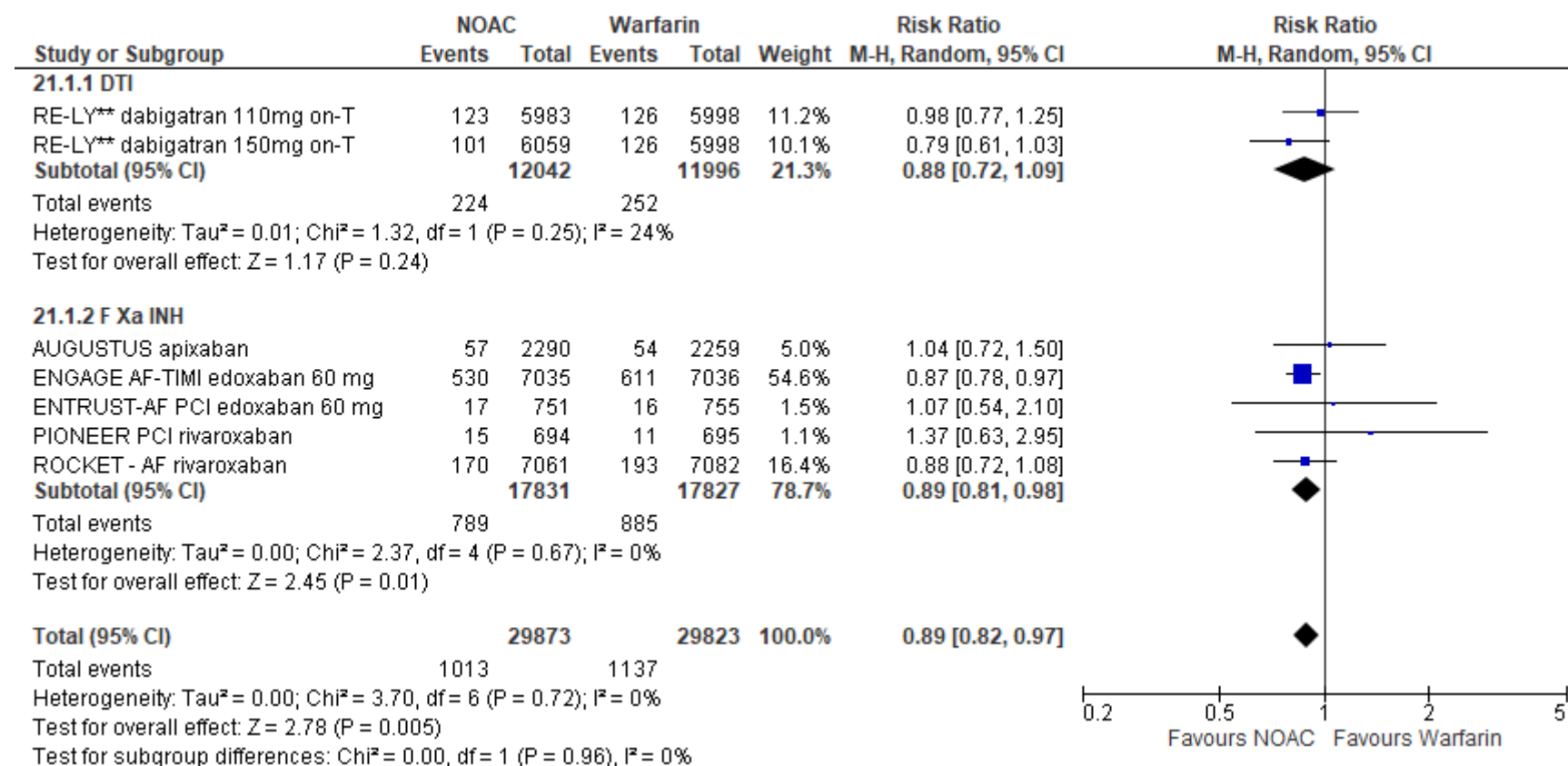
\*\* - Defined as cardiac death in reanalysis of RE-LY study [27]



**Figure S41. The funnel plot for cardiovascular mortality - re-analysis RE-LY [27] – on treatment data.**

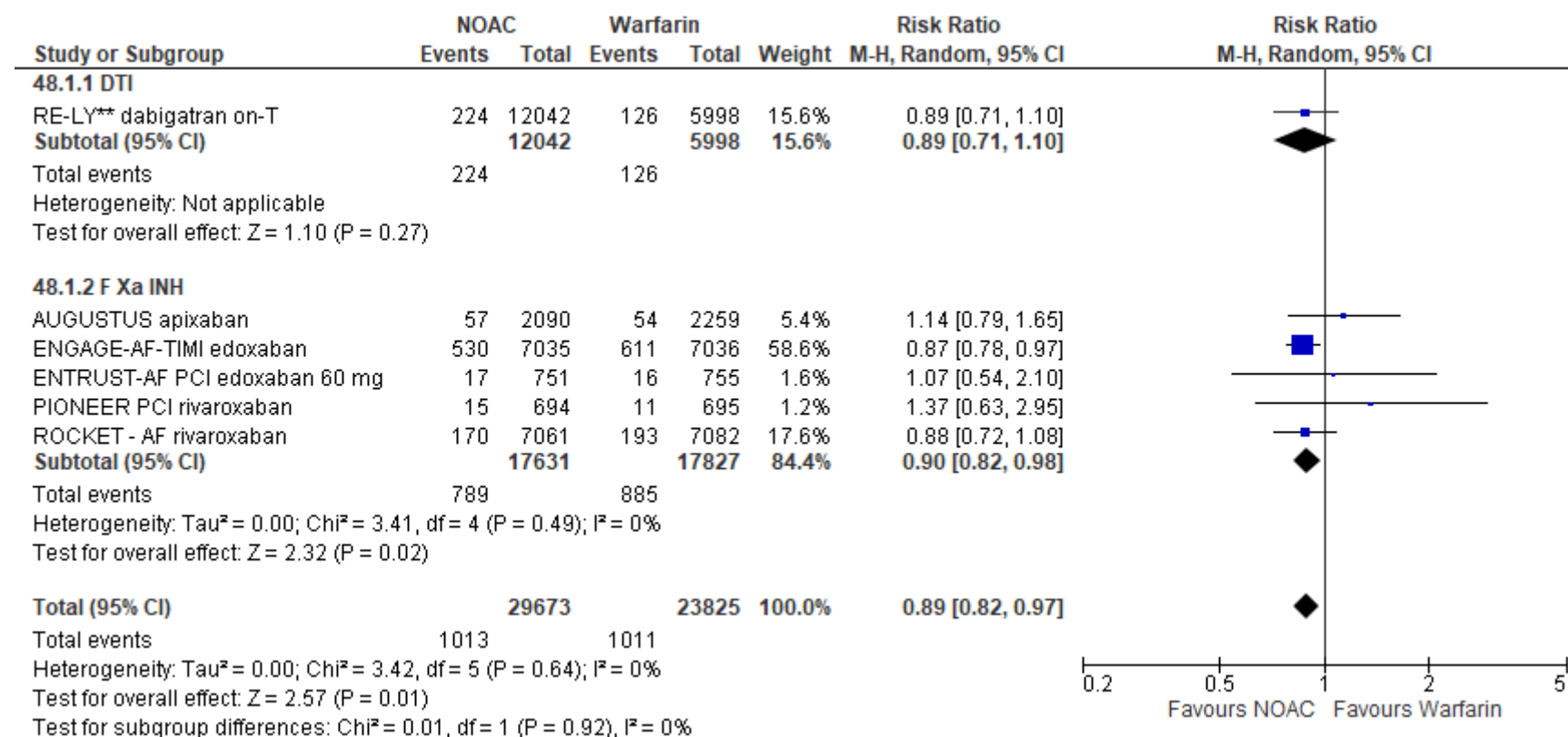


**Figure S42. The meta-analysis results for cardiovascular mortality reanalysis RE-LY [27] – on treatment data after excluding ENGAGE AF-TIMI edoxaban 30 mg.**



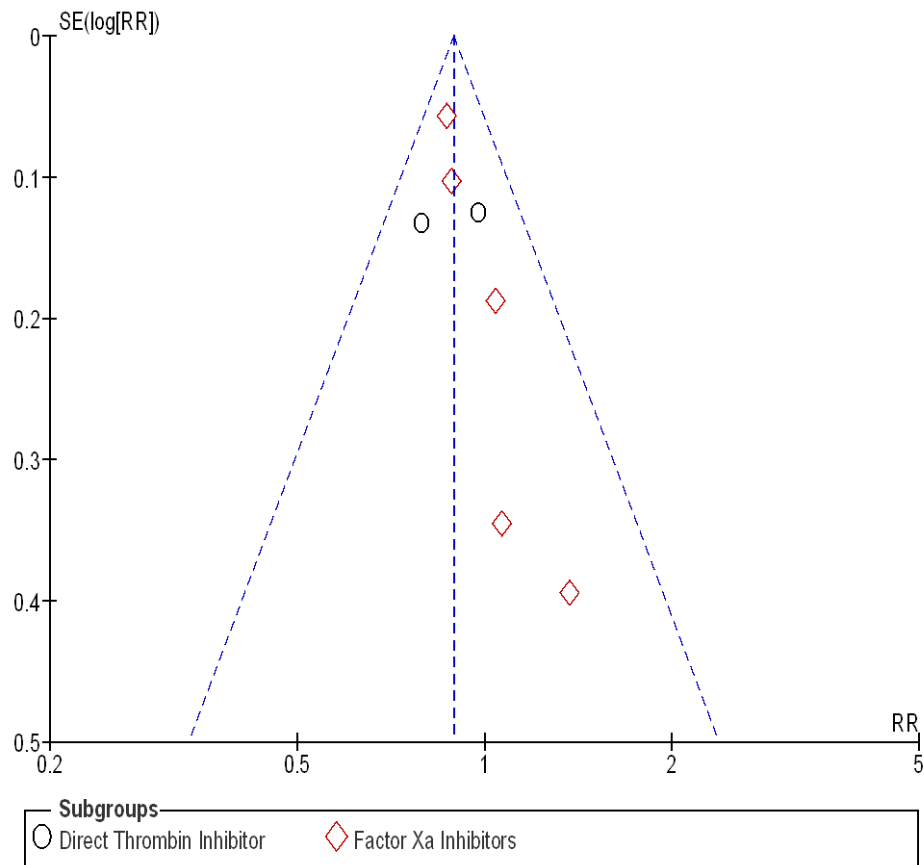
\*\* - Defined as cardiac death in reanalysis of RE-LY study [27]

**Figure S42A. The meta-analysis results for cardiovascular mortality reanalysis RE-LY [27] – on treatment data after excluding ENGAGE AF-TIMI edoxaban 30 mg and combining study data with respect to doses.**

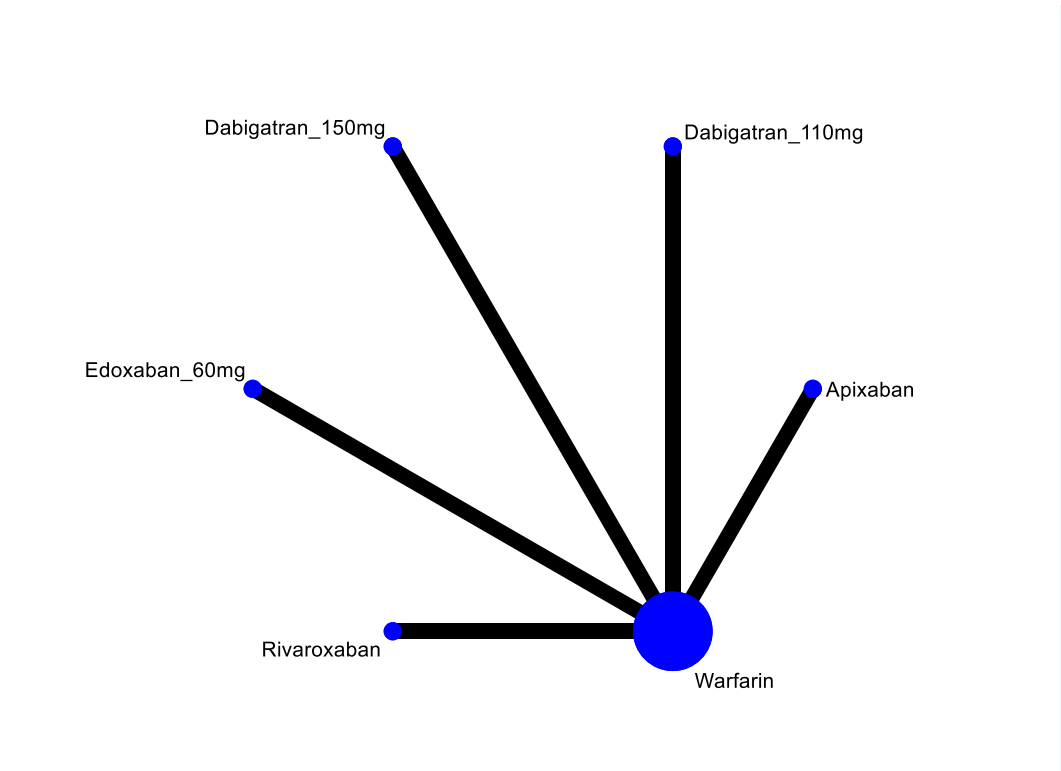


\*\* - Defined as cardiac death in reanalysis of RE-LY study [27]

**Figure S43. The funnel plot for cardiovascular mortality reanalysis RE-LY [27] – on treatment data after excluding ENGAGE AF-TIMI edoxaban 30 mg.**



**Figure S44. The network plot of compared NOAC's and warfarin.**



**Table S3. Direct and indirect comparison between warfarin and NOAC's – MACE\*\*– intention to treat data.**

Dabigatran_110mg RR (95%CI)				Treatment 1	
1,13 (0,93 - 1,39)	Dabigatran_150mg RR (95%CI)			RR (95%CI)	Treatment 2
1,13 (0,93 - 1,37)	0,99 (0,87 - 1,13)	Apixaban RR (95%CI)			
1,12 (0,92 - 1,36)	0,99 (0,87 - 1,13)	1 (0,88 - 1,12)	Edoxaban_60mg RR (95%CI)		
1,11 (0,84 - 1,48)	0,98 (0,74 - 1,31)	0,99 (0,75 - 1,31)	1 (0,88 - 1,12)	Rivaroxaban RR (95%CI)	
1,01 (0,85 - 1,21)	<b>0,89</b> <b>(0,81 - 0,99)</b>	<b>0,9</b> <b>(0,83 - 0,98)</b>	<b>0,9</b> <b>(0,83 - 0,98)</b>	0,91 (0,7 - 1,19)	Warfarin RR (95%CI)

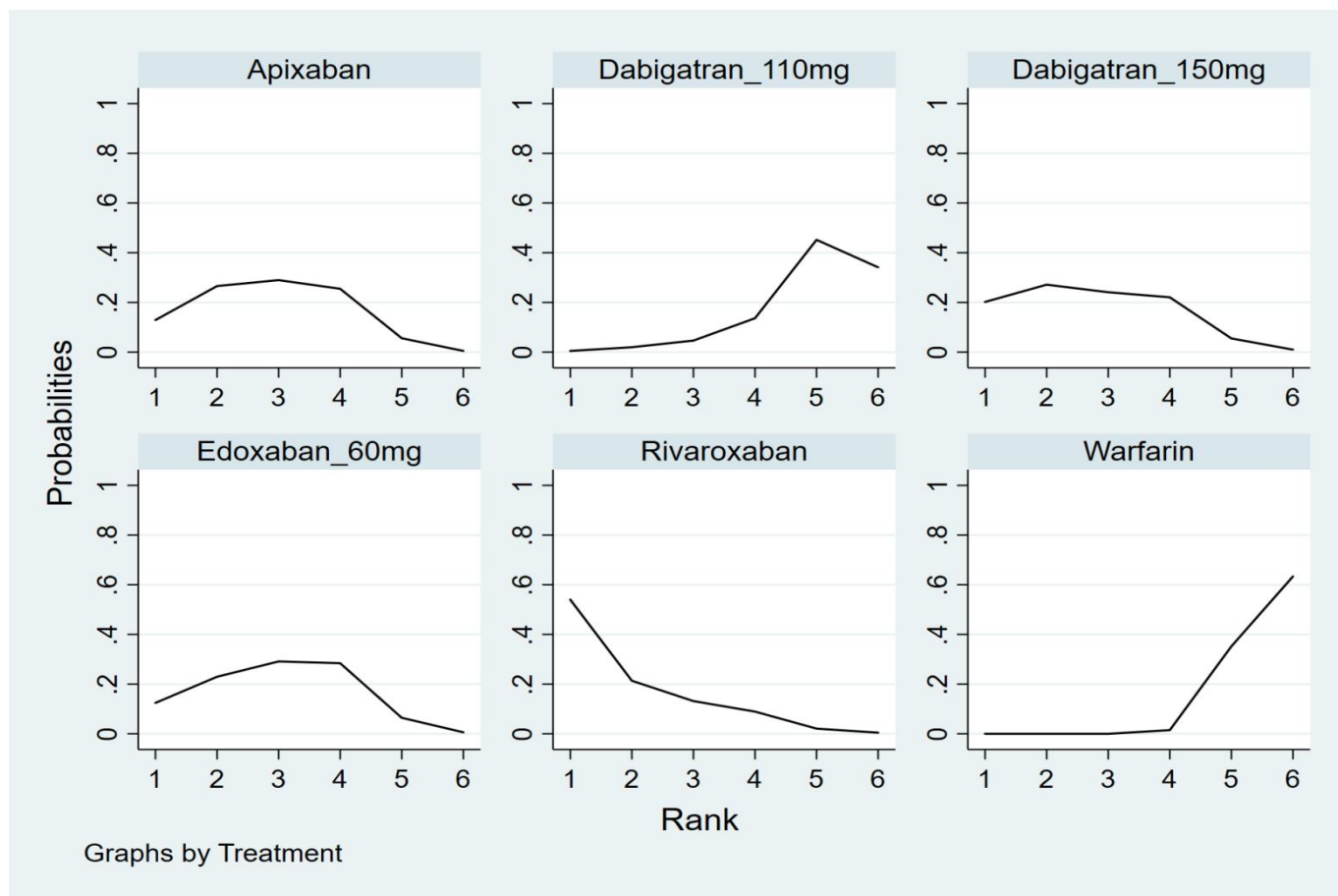
\*\* results from the reanalysis of RE-LY study [31]

**Table S4. Treatment hierarchy assessed by surface under the cumulative ranking (SUCRA) curves – MACE\*\***  
**– intention to treat data.**

Treatment	SUCRA
Warfarin	7,6
Apixaban	62,9
Dabigatran_110mg	19,3
Dabigatran_150mg	66,3
Edoxaban_60mg	60,9
Rivaroxaban	83,0

\*\* - results from the reanalysis of RE-LY study [31]

**Figure S45. Rankograms for the drugs network showing the probability every treatment being at particular order- MACE\*\* - intention to treat data.**



\*\* - results from the reanalysis of RE-LY study [31]



**Table S5. Direct and indirect comparison between warfarin and NOAC's – MACE\*\* – on treatment data.**

Dabigatran_110mg RR (95%CI)				Treatment 1	
1,18 (0,97 - 1,43)	Dabigatran_150mg RR (95%CI)			RR (95%CI)	Treatment 2
1,13 (0,94 - 1,36)	0,96 (0,84 - 1,1)	Apixaban RR (95%CI)			
1,13 (0,94 - 1,36)	0,96 (0,83 - 1,1)	1 (0,88 - 1,12)	Edoxaban_60mg RR (95%CI)		
1,12 (0,84 - 1,49)	0,95 (0,71 - 1,27)	0,99 (0,75 - 1,31)	1 (0,88 - 1,12)	Rivaroxaban RR (95%CI)	
1,02 (0,86 - 1,2)	<b>0,86</b> <b>(0,77 - 0,96)</b>	<b>0,9</b> <b>(0,83 - 0,98)</b>	<b>0,9</b> <b>(0,83 - 0,98)</b>	0,91 (0,7 - 1,19)	Warfarin RR (95%CI)

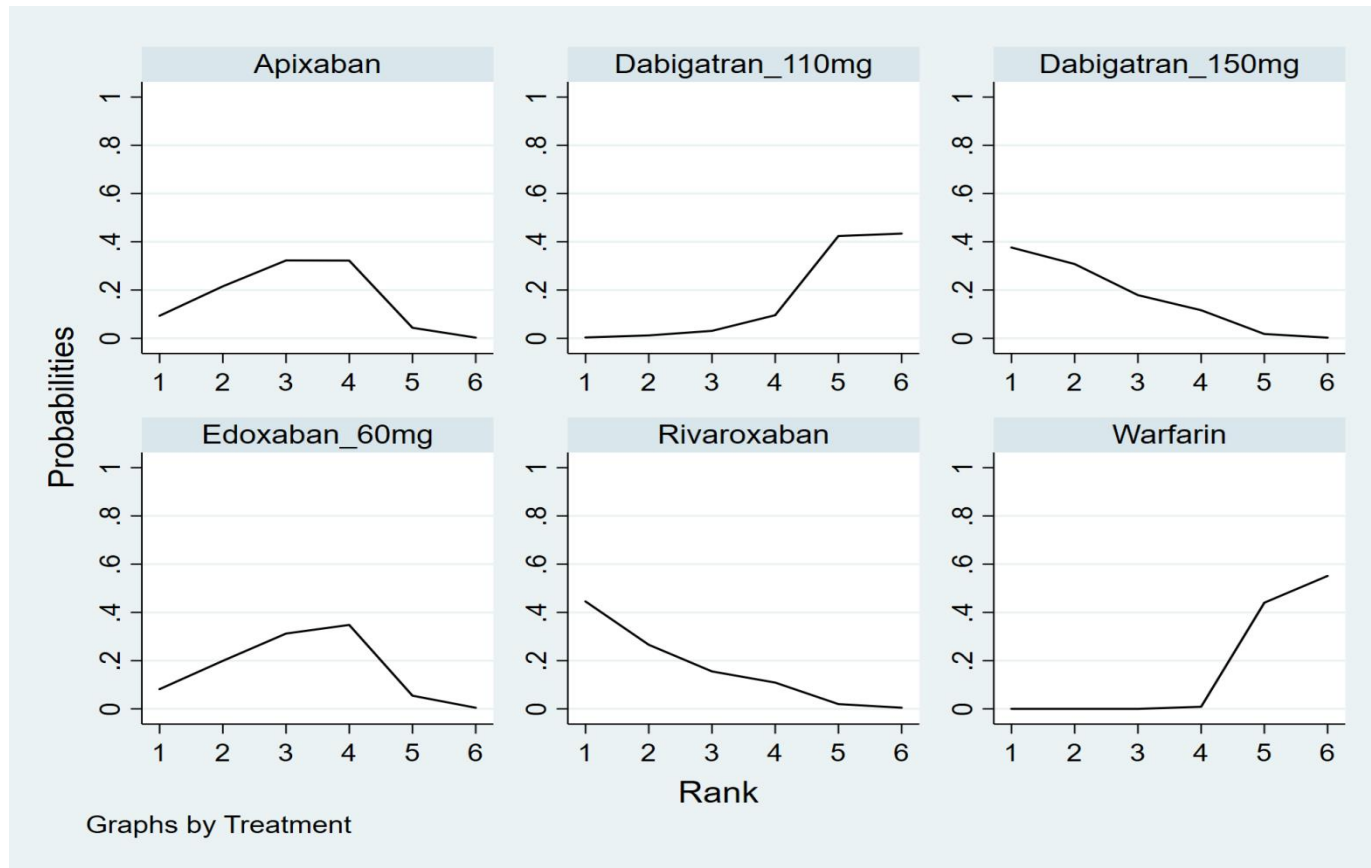
\*\* - results from the reanalysis of RE-LY study [31]

**Table S6. Treatment hierarchy assessed by surface under the cumulative ranking (SUCRA) curves – MACE\*\* on treatment data.**

Treatment	SUCRA
Warfarin	9,1
Apixaban	59,7
Dabigatran_110mg	15,5
Dabigatran_150mg	78,0
Edoxaban_60mg	57,8
Rivaroxaban	79,9

\*\* - results from the reanalysis of RE-LY study [31]

**Figure S46. Rankograms for the drugs network showing the probability every treatment being at particular order- MACE\*\* - on treatment data.**



\*\* - results from the reanalysis of RE-LY study [31]

**Table S7. Direct and indirect comparison between warfarin and NOAC's – MI\* data.**

Dabigatran_110mg RR (95%CI)				Treatment 1	
1,05 (0,72 - 1,55)	Dabigatran_150mg RR (95%CI)			RR (95%CI)	Treatment 2
<b>1,6</b> <b>(1,14 - 2,24)</b>	<b>1,52</b> <b>(1,07 - 2,15)</b>	Apixaban RR (95%CI)			
<b>1,43</b> <b>(1,02 - 2,01)</b>	1,36 (0,96 - 1,93)	0,89 (0,66 - 1,2)	Edoxaban_60mg RR (95%CI)		
<b>1,73</b> <b>(1,2 - 2,49)</b>	<b>1,64</b> <b>(1,14 - 2,37)</b>	1,08 (0,79 - 1,48)	0,89 (0,66 - 1,2)	Rivaroxaban RR (95%CI)	
<b>1,42</b> <b>(1,09 - 1,84)</b>	<b>1,34</b> <b>(1,02 - 1,77)</b>	0,88 (0,72 - 1,09)	0,99 (0,79 - 1,23)	0,82 (0,65 - 1,04)	Warfarin RR (95%CI)

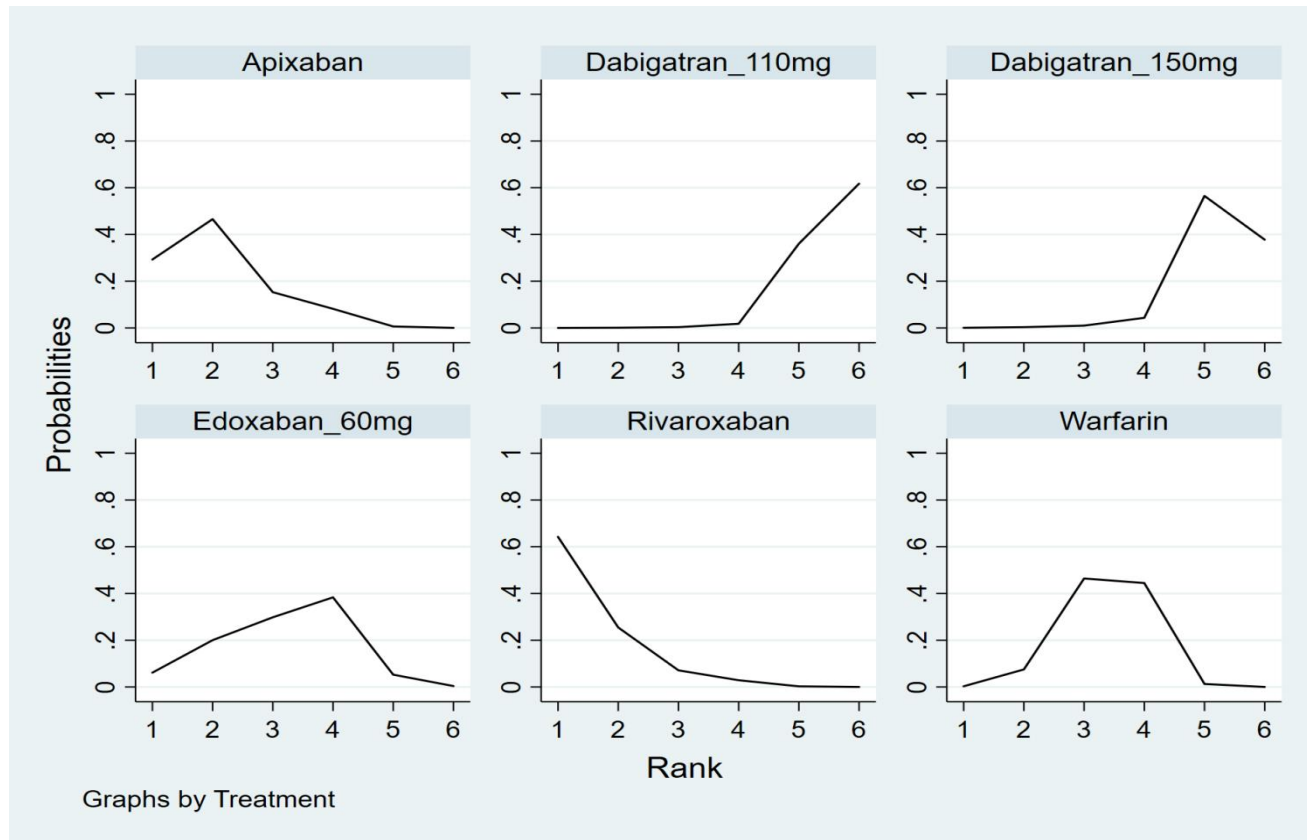
\* - results from the original RE-LY study [20]

**Table S8. Treatment hierarchy assessed by surface under the cumulative ranking (SUCRA) curves – MI\* data.**

Treatment	SUCRA
Warfarin	52,2
Apixaban	79,1
Dabigatran_110mg	8,2
Dabigatran_150mg	14,0
Edoxaban_60mg	56,4
Rivaroxaban	90,1

\* - results from the original RE-LY study [20]

**Figure S47. Rankograms for the drugs network showing the probability every treatment being at particular order– MI\* data.**



\* - results from the original RE-LY study [20]

**Table S9. Direct and indirect comparison between warfarin and NOAC's – MI\*\* - intention to treat data.**

Dabigatran_110mg RR (95%CI)				Treatment 1	
1,09 (0,75 - 1,56)	Dabigatran_150mg RR (95%CI)			RR (95%CI)	Treatment 2
<b>1,55</b> <b>(1,12 - 2,14)</b>	<b>1,43</b> <b>(1,02 - 2)</b>	Apixaban RR (95%CI)			
<b>1,38</b> <b>(0,99 - 1,92)</b>	1,27 (0,91 - 1,79)	0,89 (0,66 - 1,2)	Edoxaban_60mg RR (95%CI)		
<b>1,67</b> <b>(1,17 - 2,38)</b>	<b>1,54</b> <b>(1,08 - 2,19)</b>	1,08 (0,79 - 1,48)	0,89 (0,66 - 1,2)	Rivaroxaban RR (95%CI)	
<b>1,37</b> <b>(1,06 - 1,76)</b>	1,26 (0,97 - 1,64)	0,88 (0,72 - 1,09)	0,99 (0,79 - 1,23)	0,82 (0,65 - 1,04)	Warfarin RR (95%CI)

\*\* - results from the reanalysis of RE-LY study [31]

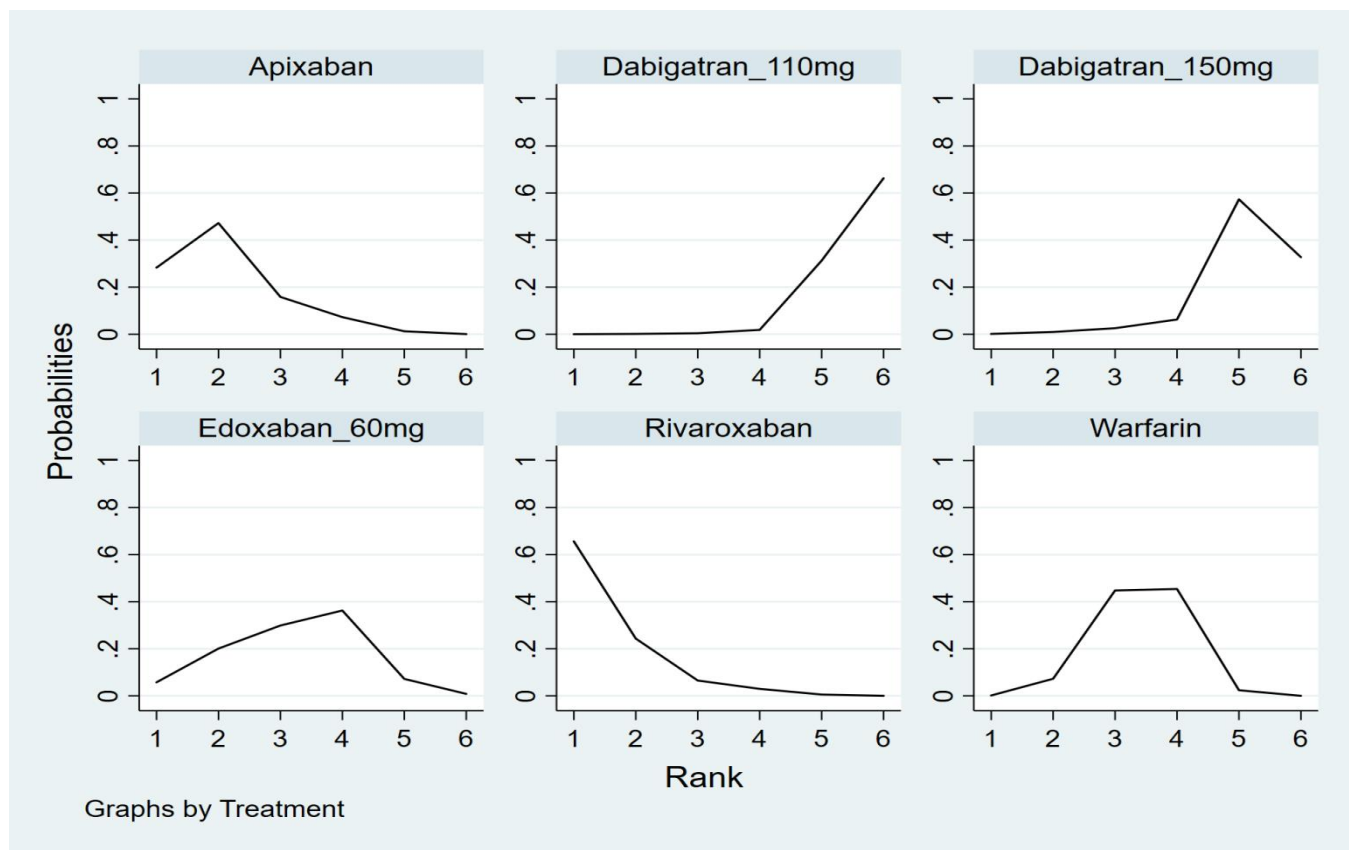
**Table S10. Treatment hierarchy assessed by surface under the cumulative ranking (SUCRA) curves – MI\*\* - intention to treat data.**

Treatment	SUCRA
Warfarin	51,5
Apixaban	78,8
Dabigatran_110mg	7,4
Dabigatran_150mg	16,4
Edoxaban_60mg	55,7
Rivaroxaban	90,3

\*\* - results from the reanalysis of RE-LY study [31]



**Figure S48. Rankograms for the drugs network showing the probability every treatment being at particular order- MI\*\* - intention to treat data.**



\*\* - results from the reanalysis of RE-LY study [31]

**Table S11. Direct and indirect comparison between warfarin and NOAC's – MI\*\* – on treatment data.**

Dabigatran_110mg RR (95%CI)				Treatment 1	
1,1 (0,75 - 1,63)	Dabigatran_150mg RR (95%CI)			RR (95%CI)	Treatment 2
<b>1,53</b> <b>(1,09 - 2,15)</b>	1,39 (0,98 - 1,97)	Apixaban RR (95%CI)			
1,37 (0,97 - 1,92)	1,24 (0,87 - 1,77)	0,89 (0,66 - 1,2)	Edoxaban_60mg RR (95%CI)		
<b>1,65</b> <b>(1,14 - 2,39)</b>	<b>1,5</b> <b>(1,03 - 2,17)</b>	1,08 (0,79 - 1,48)	0,89 (0,66 - 1,2)	Rivaroxaban RR (95%CI)	
<b>1,35</b> <b>(1,03 - 1,76)</b>	1,23 (0,92 - 1,63)	0,88 (0,72 - 1,09)	0,99 (0,79 - 1,23)	0,82 (0,65 - 1,04)	Warfarin RR (95%CI)

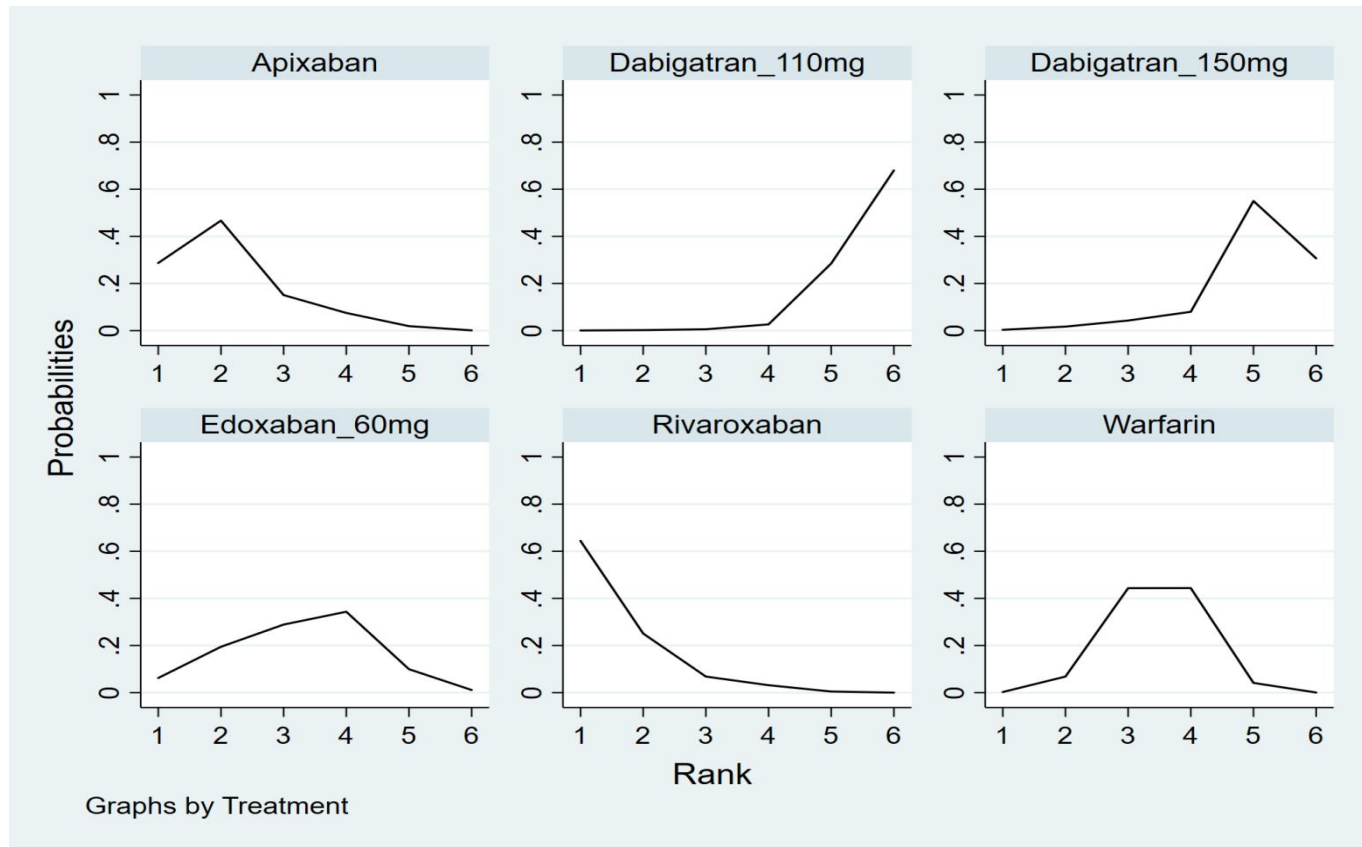
\*\* - results from the reanalysis of RE-LY study [31]

**Table S12. Treatment hierarchy assessed by surface under the cumulative ranking (SUCRA) curves – MI\*\***  
**– on treatment data.**

Treatment	SUCRA
Warfarin	50,9
Apixaban	78,5
Dabigatran_110mg	7,3
Dabigatran_150mg	18,5
Edoxaban_60mg	54,9
Rivaroxaban	90,0

\*\* - results from the reanalysis of RE-LY study [31]

**Figure S49. Rankograms for the drugs network showing the probability every treatment being at particular order- MI\*\* - on treatment data.**



\*\* - results from the reanalysis of RE-LY study [31]

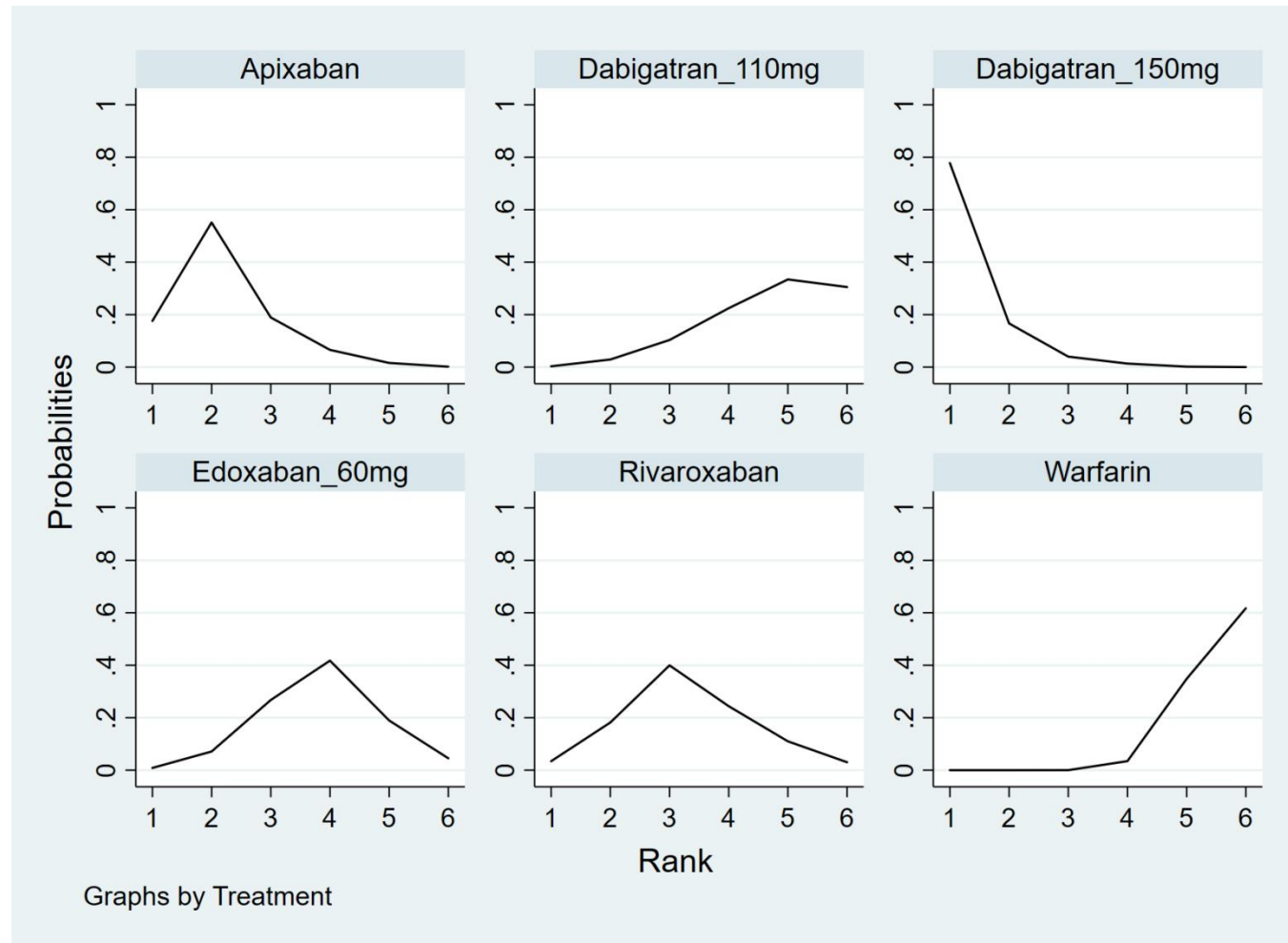
**Table S13. Direct and indirect comparison between warfarin and NOAC's – Stroke data.**

Dabigatran_110mg RR (95%CI)				Treatment 1	
1,36 (0,9 - 2,04)	Dabigatran_150mg RR (95%CI)			RR (95%CI)	Treatment 2
1,36 (0,86 - 2,14)	1 (0,58 - 1,73)	Apixaban RR (95%CI)			
1,07 (0,84 - 1,38)	0,79 (0,54 - 1,17)	0,79 (0,51 - 1,22)	Edoxaban_60mg RR (95%CI)		
1,13 (0,75 - 1,69)	0,83 (0,55 - 1,24)	0,83 (0,53 - 1,3)	0,79 (0,51 - 1,22)	Rivaroxaban RR (95%CI)	
0,95 (0,78 - 1,16)	0,7 (0,49 - 1)	0,7 (0,46 - 1,05)	0,89 (0,76 - 1,03)	0,84 (0,7 - 1,02)	Warfarin RR (95%CI)

**Table S14. Treatment hierarchy assessed by surface under the cumulative ranking (SUCRA) curves – Stroke data.**

Treatment	SUCRA
Warfarin	8,4
Apixaban	76,0
Dabigatran_110mg	24,5
Dabigatran_150mg	94,1
Edoxaban_60mg	43,1
Rivaroxaban	53,9

**Figure S50. Rankograms for the drugs network showing the probability every treatment being at particular order - Stroke data.**



**Table S15. Direct and indirect comparison between warfarin and NOAC's – overall mortality data.**

Dabigatran_110mg RR (95%CI)				Treatment 1	
1,07 (0,87 - 1,31)	Dabigatran_150mg RR (95%CI)			RR (95%CI)	Treatment 2
1,06 (0,87 - 1,28)	0,99 (0,84 - 1,16)	Apixaban RR (95%CI)			
0,95 (0,7 - 1,3)	0,89 (0,67 - 1,19)	0,9 (0,68 - 1,2)	Edoxaban_60mg RR (95%CI)		
1,13 (0,92 - 1,4)	1,06 (0,86 - 1,31)	1,07 (0,88 - 1,31)	0,9 (0,68 - 1,2)	Rivaroxaban RR (95%CI)	
0,95 (0,81 - 1,12)	0,89 (0,79 - 1)	0,9 (0,81 - 1)	1 (0,77 - 1,3)	0,84 (0,71 - 1)	Warfin RR (95%CI)



**Table S16. Treatment hierarchy assessed by surface under the cumulative ranking (SUCRA) curves – overall mortality data.**

Treatment	SUCRA
Warfarin	6,1
Apixaban	55,6
Dabigatran_110mg	42,9
Dabigatran_150mg	67,7
Edoxaban_60mg	44,4
Rivaroxaban	83,5

**Figure S51. Rankograms for the drugs network showing the probability every treatment being at particular order – overall mortality data.**

