SUPPLEMENTAL MATERIAL

Safety and Efficacy of Double Antithrombotic Therapy with Non–vitamin K Antagonist Oral Anticoagulants in Patients with Atrial Fibrillation Undergoing Percutaneous Coronary Intervention: A Systematic Review and Meta-Analysis

- **Figure S7**: Subgroup analysis for both MACE and clinically significant bleeding in different thromboembolic risk groups.
- **Figure S8**: Subgroup analysis for both MACE and clinically significant bleeding in different bleeding risk groups.
- **Figure S9**: Subgroup analysis for both MACE and clinically significant bleeding in different $P2Y_{12}$ inhibitor risk groups.
- **Figure S10**: SUCRA values according to MACE and clinically significant bleeding endpoints with fixed-effects model analysis**.**
- **Figure S11**: Rankograms according to MACE (A) and clinically significant bleeding (B) endpoints with random-effects model analysis.
- **Figure S12**: SUCRA values according MACE and clinically significant bleeding endpoints with random-effects model analysis.
- **Figure S13**: Incidences of bleeding endpoints through included randomized controlled trials
- **Figure S14**: Kaplan-Meier curves with landmark analysis before and after 30 and 180 days for significant bleeding endpoint.
- **Figure S15**: Risk of bias summary.
- **Figure S16**: Risk of bias graph.
- **Figure S17:** Funnel plots for MACE (A) and clinically significant bleeding (B) endpoints.

Data S1. SUPPLEMENTAL METHODS

Statistical analysis

Fixed-effect and random-effects models with inverse variance weighting, using trial-level log hazard ratios (HRs) and corresponding standard errors were fitted. Trial-level and pooled estimates are reported as HR and 95% confidence intervals (CIs); risk distribution is presented by forest plots with weighting and showing both random- and fixed-effects models. For the endpoints in which HRs were not available in all trials, relative risks (RR) were used and it was properly specified. We assessed heterogeneity across trials using I^2 statistics and the significance of Cochran's Q test. I^2 values less than 25% defined low heterogeneity; 25% to 50%, moderate heterogeneity and greater than 50%, high heterogeneity.

When not explicitly reported in the article text, patient survival data, rates and hazard ratios were reconstructed from digitized graphs using the WebPlotDigitizer software (4.2 version). With this software, individual patient data were reconstructed from published Kaplan-Meier curves. Retrieved spatial information, numbers at risk, and events for each time interval were used to run a validated algorithm as proposed by Guyot et al.[54]

In order to describe the different distribution of events over time and define cumulative incidence at 2-years follow-up, reconstructed individual patient data were used for time-to-first-event Kaplan-Meier analyses. A shared frailty model, accounting for clustering of patients across the original trials with semiparametric penalized likelihood estimation of the hazard function, was fitted to obtain the combined HRs.

In order to detect the timing of the greatest divergence among the two strategies for the primary bleeding endpoint, two landmark analyses, at 30 and 180 days, were performed. In the landmark method, a fixed time after the initiation of therapy is selected as a landmark for conducting the analysis of survival by response. Only patients alive at the landmark times

were included in the analyses. Importantly, these analyses considered only the time to first event, not accounting for the occurrences of repeat events.

To investigate the consistency of the effect sizes across subsets of interest, several subgroups analyses were performed. In addition, a Bayesian Network Meta-Analysis (NMA) was fitted to simultaneously compare multiple regimens. Analyses with both fixed and random-effects models, with uniform priors, were performed. We extracted the sample size and total number of events for each of the pre-specified outcomes in each treatment group from eligible RCTs. The NMA model combines evidence about direct and indirect comparisons of regimens by accounting for the correlation among multi-arm trials. We estimated HRs of the effects of the 2 regimens and the associated 95% credible intervals using Markov chain Monte Carlo algorithms. We checked convergence of Markov chain Monte Carlo chains for all model parameter, using trace plots and Gelman-Rubin diagnostic statistics.[55] To evaluate and rank regimens for both primary endpoints, we calculated rank probabilities (i.e. probability of a regimen being the best, second best, or worst for an outcome) and the Surface Under the Cumulative Ranking (SUCRA). The SUCRA is a numerical summary that accounts for both magnitude and uncertainty of the estimated effect for each regimen.[56] A larger SUCRA value indicates better performance for the outcome. All analyses were performed with R, version 3.3.1 (R Foundation).

Trial sequential analysis

The methodology of trial sequential analysis (TSA) has been previously described.[57-63] In brief, the aim of a TSA is to assess the openness of the effect size of the present meta-analysis to change according to potential future data and thereby the risk of type I error and the need for future data. TSA combines an estimation of required information size (combined

sample size of the included trials) with an adjusted threshold for statistical significance in the cumulative meta-analyses. A model variance-adjusted information size was used for the TSA based on α=0.05, β=0.20 (power of 80%), an incidence in control arm of 22.6% for clinically significant bleeding and 7% for MACE (as derived from the pooled analysis), a relative risk reduction (RRR) of 35% for clinically significant bleeding and a relative risk increase of 20% for MACE. The conservative trial sequential monitoring boundaries were set by O'Brien–Fleming as the α spending function. The cumulative Z-curve of each cumulative meta-analysis was calculated and plotted against the above monitoring boundaries. The crossing of the cumulative Z-curve into the trial sequential monitoring boundary for benefit indicates that a sufficient level of evidence has been reached, and no further trials may be needed to demonstrate the superiority of the intervention. If the cumulative Z-curve does not cross any of the trial sequential monitoring boundaries, there is probably insufficient evidence to reach a conclusion and additional trials may be required. If the cumulative Z-score curve crosses into the futility area boundary, future trials are unlikely to alter the trend of evidence.

SUPPLEMENTAL TABLES

Table S1: PRISMA Checklist

Section/topic	#	Checklist item	Reported on page #
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	1
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	3-4
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	5-6
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	6
METHODS			

Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	6-7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	7
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	7
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	7
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	7
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	7
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources) and any assumptions and simplifications made.	6-8
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	8
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	9
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., $I^{2)}$ for each meta-analysis.	9

Risk of bias across studies	15	Specify any assessment of risk of bias that may affect the cumulative evidence (e.g., publication bias, selective reporting within studies).	8
Additional analyses	16	Describe methods of additional analyses (e.g., sensitivity or subgroup analyses, meta-regression), if done, indicating which were pre-specified.	9-10
RESULTS			
Study selection	17	Give numbers of studies screened, assessed for eligibility, and included in the review, with reasons for exclusions at each stage, ideally with a flow diagram.	11
Study characteristics	18	For each study, present characteristics for which data were extracted (e.g., study size, PICOS, follow-up period) and provide the citations.	11-12
Risk of bias within studies	19	Present data on risk of bias of each study and, if available, any outcome level assessment (see item 12).	16-17
Results of individual studies	20	For all outcomes considered (benefits or harms), present, for each study: (a) simple summary data for each intervention group (b) effect estimates and confidence intervals, ideally with a forest plot.	13-16
Synthesis of results	21	Present results of each meta-analysis done, including confidence intervals and measures of consistency.	13-16
Risk of bias across studies	22	Present results of any assessment of risk of bias across studies (see Item 15).	16-17
Additional analysis	23	Give results of additional analyses, if done (e.g., sensitivity or subgroup analyses, meta-regression [see Item 16]).	13-16
DISCUSSION			

Summary of evidence	24	Summarize the main findings including the strength of evidence for each main outcome; consider their relevance to key groups (e.g., healthcare providers, users, and policy makers).	17-21
Limitations	25	Discuss limitations at study and outcome level (e.g., risk of bias), and at review-level (e.g., incomplete retrieval of identified research, reporting bias).	21
Conclusions	26	Provide a general interpretation of the results in the context of other evidence, and implications for future research.	22
FUNDING			
Funding	27	Describe sources of funding for the systematic review and other support (e.g., supply of data); role of funders for the systematic review.	1-2

Abbreviations: PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Table S2: Included randomized controlled trials feature

Trial	Year	Country	Trial design	Sample size	Population	Intervention	Control	Safety endpoint	Bleeding definition	Efficacy endpoint	Follow-up
AUGUSTUS (NCT02415400)	2019	Worldwide	Non-inferiority and superiority	4,614	AF patients who had an ACS or had undergone urgent or elective PCI	Apixaban 5 mg twice daily + $P2Y_{12}$ inhibitor (any) ± ASA	VKA + $P2Y_{12}$ inhibitor (any) ± ASA	Major or clinically relevant non-major bleeding	ISTH for primary analysis; GUSTO, TIMI	Composite of death and hospitalization; composite of death, stroke, MI, stent thrombosis or urgent revascularization	6 months
						ASA + $P2Y_{12}$ inhibitor (any) + OAC (either apixaban or VKA)	$P2Y_{12}$ inhibitor (any) + OAC (apixaban or VKA)				
ENTRUST-AF PCI (NCT02866175)	2019	Asia and Europe	Non-inferiority and superiority	1,506	AF patients who had undergone urgent or elective PCI with stenting	Edoxaban 60 mg + $P2Y_{12}$ inhibitor (clopidogrel or ticagrelor or prasugrel)	VKA + ASA + $P2Y_{12}$ inhibitor (clopidogrel or ticagrelor or prasugrel)	Major or clinically relevant non-major bleeding	ISTH	Composite of cardiovascular death, stroke, systemic embolic events, spontaneous myocardial infarction, or	12 months

										definite stent thrombosis	
PIONEER AF-PCI (NCT01830543)	2016	Worldwide	Superiority	2,124	AF patients who had undergone urgent or elective PCI with stenting	Rivaroxaban 15 mg + $P2Y_{12}$ inhibitor (clopidogrel or ticagrelor or prasugrel) Rivaroxaban 2.5 mg twice daily + DAPT (ASA and clopidogrel or ticagrelor or prasugrel) for 1, 6 or 12 months	VKA + ASA + $P2Y_{12}$ inhibitor (clopidogrel or ticagrelor or prasugrel)	Clinically significant bleeding	TIMI for primary endpoint; ISTH and GUSTO for exploratory endpoints	Composite of cardiovascular death, MI or stroke; stent thrombosis	12 months
RE-DUAL PCI (NCT02164864)	2017	Worldwide	Non-inferiority	2,725	AF patients who had undergone urgent or elective	Dabigatran (150 or 110 mg) + $P2Y_{12}$ inhibitor (clopidogrel or ticagrelor)	VKA + ASA + $P2Y_{12}$ inhibitor (clopidogrel or ticagrelor)	Major or clinically relevant non-major bleeding	ISTH	Composite of death, MI, stroke, systemic embolism or unplanned revascularization	Minimum 6 months, mean 14 months, maximum

					PCI with stenting						up to 30 months

Abbreviations: ACS = Acute Coronary Syndrome; AF = Atrial Fibrillation; ASA = Acetylsalicylic Acid; AUGUSTUS = A Study of Apixaban in Patients With Atrial Fibrillation, Not Caused by a Heart Valve Problem, Who Are at Risk for Thrombosis (Blood Clots) Due to Having Had a Recent Coronary Event, Such as a Heart Attack or a Procedure to Open the Vessels of the Heart; DAPT = Dual Antiplatelet Therapy; ENTRUST-AF PCI = Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention; GUSTO = Global Use of Strategies to Open Occluded Arteries; ISTH = International Society on Thrombosis and Hemostasis; MI = Myocardial Infarction; OAC = Oral Anticoagulant; PIONEER AF-PCI = A Study Exploring Two Strategies of Rivaroxaban and One of Oral Vitamin K Antagonist in Patients With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention; PCI = Percutaneous Coronary Intervention; RE-DUAL PCI = Evaluation of Dual Therapy With Dabigatran versus Triple Therapy With Warfarin in Patients With AF That Undergo a PCI With Stenting; TIMI = Thrombolysis In Myocardial Infarction; VKA = Vitamin K Antagonist.

Table S3: Bleeding definitions across included randomized controlled trials

	AUGUSTUS (NCT02415400)	**ENTRUST-AF PCI (NCT02866175)**	**PIONEER AF-PCI (NCT01830543)**	**RE-DUAL PCI (NCT02164864)**
Bleeding Criteria	ISTH major bleeding or clinically relevant non-major bleeding	ISTH major bleeding or clinically relevant non-major bleeding	TIMI major bleeding, minor bleeding, and bleeding requiring medical attention	ISTH major bleeding or clinically relevant non-major bleeding
Bleeding Definition	**Major bleeding:** ▪ Fatal bleeding; ▪ Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome; ▪ Bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells.	**Major bleeding:** ▪ Fatal bleeding; ▪ Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome; ▪ Bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells.	**Major bleeding:** ▪ Any intracranial bleeding (excluding microhemorrhages <10 mm evident only on gradient-echo MRI); ▪ Clinically overt signs of hemorrhage associated with a drop in hemoglobin of ≥5 g/dL or a ≥15% absolute decrease in haematocrit; ▪ Fatal bleeding (bleeding that directly results in death within 7 days).	**Major bleeding:** ▪ Fatal bleeding; ▪ Symptomatic bleeding in a critical area or organ, such as intracranial, intraspinal, intraocular, retroperitoneal, intra-articular or pericardial, or intramuscular with compartment syndrome; ▪ Bleeding causing a fall in hemoglobin level of 20 g/L (1.24 mmol/L) or more, or leading to transfusion of two or more units of whole blood or red cells.

	Clinically relevant non-major bleeding: any sign or symptom of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for the ISTH definition of major bleeding but does meet at least one of the following criteria: ▪ requiring medical intervention by a healthcare professional; ▪ leading to hospitalization or increased level of care; ▪ prompting a face to face (i.e., not just a telephone or electronic communication) evaluation.	**Clinically relevant non-major bleeding:** any sign or symptom of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for the ISTH definition of major bleeding but does meet at least one of the following criteria: ▪ requiring medical intervention by a healthcare professional; ▪ leading to hospitalization or increased level of care; ▪ prompting a face to face (i.e., not just a telephone or electronic communication) evaluation.	**Minor bleeding:** clinically overt bleeding (including imaging), resulting in hemoglobin drop of 3 to <5 g/dL.	**Clinically relevant non-major bleeding:** any sign or symptom of hemorrhage (e.g., more bleeding than would be expected for a clinical circumstance, including bleeding found by imaging alone) that does not fit the criteria for the ISTH definition of major bleeding but does meet at least one of the following criteria: ▪ requiring medical intervention by a healthcare professional; ▪ leading to hospitalization or increased level of care; ▪ prompting a face to face (i.e., not just a telephone or electronic communication) evaluation.

			Bleeding requiring medical attention: any overt sign of hemorrhage that meets one of the following criteria and does not meet criteria for a major or minor bleeding event, as defined above: ▪ Requiring intervention (medical practitioner-guided medical or surgical treatment to stop or treat bleeding, including temporarily or permanently discontinuing or changing the dose of a medication or study drug); ▪ Leading to or prolonging hospitalization; ▪ Prompting evaluation (leading to an unscheduled visit to a healthcare professional and diagnostic testing, either laboratory or imaging).	

Abbreviations: AUGUSTUS = A Study of Apixaban in Patients With Atrial Fibrillation, Not Caused by a Heart Valve Problem, Who Are at Risk for Thrombosis (Blood Clots) Due to Having Had a Recent Coronary Event, Such as a Heart Attack or a Procedure to Open the Vessels of the Heart; ENTRUST-AF PCI = Edoxaban Treatment

Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention; ISTH = International Society on Thrombosis and Hemostasis; MRI = Magnetic Resonance Imaging; PIONEER AF-PCI = A Study Exploring Two Strategies of Rivaroxaban and One of Oral Vitamin K Antagonist in Patients With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention; RE-DUAL PCI = Evaluation of Dual Therapy With Dabigatran versus Triple Therapy With Warfarin in Patients With AF That Undergo a PCI With Stenting; TIMI = Thrombolysis In Myocardial Infarction.

Table S4: Randomized controlled trials inclusion and exclusion criteria

	AUGUSTUS (NCT02415400)	**ENTRUST-AF PCI (NCT02866175)**	**PIONEER AF-PCI (NCT01830543)**	**RE-DUAL PCI (NCT02164864)**
Inclusion Criteria	Adults with either active or a history of AF or atrial flutter with the planned or existing use of an oral anticoagulant for prophylaxis of thromboembolism. In addition, subjects must have had an ACS or PCI with a stent within the prior 14 days	OAC indication for AF for a period of at least 12 months following successful PCI with stenting	Have a documented medical history of paroxysmal, persistent, or permanent atrial fibrillation	Male or female patients aged ≥18 years
	Planned use of antiplatelet agents for at least 1 to 6 months		Have undergone PCI procedure with stent placement for primary atherosclerotic disease	Patients with AF
	Males and Females ≥18 years of age		INR of 2.5 or below	Patient presenting with an ACS that was successfully treated by PCI and stenting (either bare metal stent or drug-eluting stent) or with stable coronary artery disease with at least one lesion eligible for PCI that was successfully treated by elective PCI and

				stenting (either bare metal stent or drug-eluting stent)
	Women of childbearing potential must have a negative serum or urine pregnancy test within 24 hours prior to the start of study drug		Women must be postmenopausal before entry or practicing a highly effective method of birth control when heterosexually active	Patients able to give informed consent in accordance with International Conference on Harmonisation Good Clinical Practice guidelines and local legislation and/or regulations
			Be willing and able to adhere to the prohibitions and restrictions specified in the study protocol	
Exclusion Criteria	Conditions other than AF that require chronic anticoagulation (e.g. prosthetic mechanical heart valve)	Known bleeding diathesis including but not limited to uncontrolled active bleeding	Any condition that contraindicates anticoagulant or antiplatelet therapy or an unacceptable risk of bleeding, such as, but not limited to: platelet count <90,000/microliter at screening, history of intracranial hemorrhage, 12-month history of clinically significant gastrointestinal bleeding, non-VKA induced elevated prothrombin time at screening	Patients with a mechanical or biological heart valve prosthesis

	Severe renal insufficiency (serum creatinine >2.5 mg/dL or a calculated creatinine clearance <30 mL/min)	INR >2.5 (the subject can be reconsidered at a later time, but within 5 days of sheath removal)	Anemia of unknown cause with a hemoglobin level <10 g/dL (<6.21 mmol/L)	Cardiogenic shock during current hospitalization
	Patients with a history of intracranial hemorrhage	Contraindication to edoxaban, VKA, ASA and/or $P2Y_{12}$ antagonists	History of stroke or transient ischemic attack	Stroke within 1 month prior to screening visit
	Patients have had or will undergo CABG for their index ACS event	Concomitant treatment with other antithrombotic agents, fibrinolytic therapy and chronic nonsteroidal anti-inflammatory drugs	Calculated creatinine clearance <30 mL/min at screening	Patients who have had major surgery within the month prior to screening
	Patients with known ongoing bleeding and patients with known coagulopathies	Critically ill or hemodynamically unstable subjects	known significant liver disease or liver function test abnormalities	Gastrointestinal hemorrhage within one month prior to screening, unless, in the opinion of the Investigator, the cause has been permanently eliminated
	Any contraindications or allergies to VKA, apixaban, or to intended $P2Y_{12}$ antagonists or to aspirin	Any prior mechanical valvular prosthesis	Any severe condition that would limit life expectancy to less than 12 months	Major bleeding episode including life-threatening bleeding episode in one month prior to screening visit
		Planned coronary or vascular intervention or major surgery within 12 months		Anemia (hemoglobin <10g/dL) or thrombocytopenia including heparin-induced

				thrombocytopenia (platelet count <100 x 109/L) at screening
		Moderate or severe mitral stenosis		Severe renal impairment (estimated creatinine clearance calculated by Cockcroft-Gault equation <30mL/min at screening
		Ischemic stroke within 2 weeks prior to randomization		Active liver disease
		Uncontrolled severe hypertension with a systolic blood pressure ≥180 mmHg and/or diastolic blood pressure ≥ 120 mmHg		
		End-stage renal disease (creatinine clearance < 15 mL/min or on dialysis)		
		Known abnormal liver function prior to randomization		
		Platelet count < 50 x109/L or hemoglobin < 8 mg/dL		
		Unable to provide written informed consent		

		Female subjects of childbearing potential without using highly effective contraception in the last 3 months		
		Pregnant or breast-feeding subjects		
		Assessment that the subject is not likely to comply with the study procedures or have complete follow-up		
		Participating in another clinical trial that potentially interferes with the current study		
		Previous randomization in this study		
		Active on prescription drug abuse and addiction; abuse of illicit substances (i.e. marijuana, cocaine, methamphetamine, heroin) and alcohol abuses during the last 12 months according to the judgement of the investigator		

		Life expectancy < 12 months		

Abbreviations: ACS = Acute Coronary Syndrome; AF = Atrial Fibrillation; ASA = Acetylsalicylic Acid; AUGUSTUS = A Study of Apixaban in Patients With Atrial Fibrillation, Not Caused by a Heart Valve Problem, Who Are at Risk for Thrombosis (Blood Clots) Due to Having Had a Recent Coronary Event, Such as a Heart Attack or a Procedure to Open the Vessels of the Heart; CABG = Coronary Artery Bypass Grafting; ENTRUST-AF PCI = Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention; INR = International Normalized Ratio; OAC = Oral Anticoagulant; PCI = Percutaneous Coronary Intervention; PIONEER AF-PCI = A Study Exploring Two Strategies of Rivaroxaban and One of Oral Vitamin K Antagonist in Patients With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention; RE-DUAL PCI = Evaluation of Dual Therapy With Dabigatran versus Triple Therapy With Warfarin in Patients With AF That Undergo a PCI With Stenting; VKA = Vitamin K Antagonist.

Table S5: Patients' characteristics across included RCTs

	AUGUSTUS (NCT02415400)			**ENTRUST-AF PCI (NCT02866175)**			**PIONEER AF-PCI (NCT01830543)**			**RE-DUAL PCI (NCT02164864)**			
	Overall (4,614)	TAT (2,307)	DAT (2,307)	Overall (1506)	VKA + DAPT (755)	NOAC + SAPT (751)	Overall (1,415)	VKA + DAPT (706)	NOAC + SAPT (709)	Overall (2,725)	VKA + DAPT (981)	NOAC + SAPT 150 mg (763)	NOAC + SAPT 110 mg (981)
Mean age (years)	70.7 (64.2-77.2)	70.8 (64.4-77.3)	70.6 (63.8-77.2)	70 (63-77)	70 (64-77)	69 (63-77)	NR	69.9 ± 8.7	70.4 ± 9.1	70.8 ± NA	71.7 ± 8.9	68.6 ± 7.7	71.5 ± 8.9
Gender (male)	3277 (71.0%)	1,611 (69.8%)	1,666 (72.2%)	1120 (74.4%)	563 (74.6%)	557 (74.2%)	1,046 (73.9%)	518 (73.4%)	528 (74.5%)	2,070 (76.0%)	750 (76.5%)	592 (77.6%)	728 (74.2%)
Race or Country													
Asian	140 (3.0%)	74 (3.2%)	66 (2.9%)	169 (11.2%)	87 (11.5%)	82 (10.9%)	58 (4.1%)	33 (4.7%)	25 (3.5%)	NR	NR	NR	NR
Black	59 (1.3%)	29 (1.3%)	30 (1.3%)	NR	NR	NR	8 (0.6%)	1 (0.1%)	7 (1.0%)	NR	NR	NR	NR
White	4,184 (90.7%)	2,082 (90.2%)	2,102 (91.1%)	1,337 (88.8%)	668 (88.5%)	669 (89.1%)	1,326 (93.7%)	664 (94.1%)	662 (93.4%)	NR	NR	NR	NR

Other	231 (5.0%)	122 (5.3%)	109 (4.7%)	NR	NR	NR	23 (1.6%)	8 (1.1%)	15 (2.1%)	NR	NR	NR	NR
Diabetes mellitus	1678 (36.4%)	842 (36.5%)	836 (36.2%)	517 (34.3%)	258 (34.2%)	259 (34.5%)	425 (30.0%)	221 (31.3%)	204 (28.8%)	993 (36.4%)	371 (37.8%)	260 (34.1%)	362 (36.9%)
Hypertension	4,073 (88.3%)	2,031 (88.0%)	2,042 (88.5%)	1361 (90.4%)	687 (91.0%)	674 (89.7%)	1,052 (74.3%)	532 (75.4%)	520 (73.3%)	NR	NR	NR	NR
Hypercholesterolemia	NR	NR	NR	981 (65.1%)	484 (64.1%)	497 (66.2%)	618 (43.7%)	316 (44.8%)	302 (42.6%)	NR	NR	NR	NR
Prior MI	NR	NR	NR	365 (24.2%)	177 (23.4%)	188 (25%)	297 (21.0%)	157 (22.2%)	140 (19.8%)	699 (25.6%)	268 (7.3%)	194 (25.4%)	237 (24.2%)
Prior PCI	NR	NR	NR	394 (26.2%)	195 (25.8%)	199 (26.5%)	NR	NR	NR	912 (33.5%)	347 (35.4%)	239 (31.3%)	326 (33.2%)
Prior CABG	NR	NR	NR	95 (6.3%)	49 (6.5%)	46 (6.1%)	NR	NR	NR	287 (10.5%)	111 (11.3%)	79 (10.4%)	97 (9.9%)
Prior stroke	633 (13.7%)	297 (12.9%)	336 (14.6%)	189 (12.5%)	92 (12.2%)	97 (12.9%)	NR	NR	NR	226 (8.3%)	100 (10.2%)	52 (6.8%)	74 (7.5%)
PAD	NR	NR	NR	158 (10.5%)	82 (10.9%)	76 (10.1%)	65 (4.3%)	35 (5.0%)	30 (4.2%)	NR	NR	NR	NR

Heart failure	1,973 (42.8%)	982 (42.6%)	991 (43.0%)	826 (54.8%)	408 (54.0%)	418 (55.7%)	355 (23.4%)	175 (24.8%)	180 (25.4%)	NR	NR	NR	NR
CHA_2DS_2-VASc	3.9 ± 1.6	3.9 ± 1.6	3.9 ± 1.6	4.0 (3.0-5.0)	4.0 (3.0-5.0)	4.0 (3.0-5.0)	3.8 ± 1.6	3.8 ± 1.5	3.7 ± 1.7	NR	3.8 ± 1.5	3.3 ± 1.5	3.7 ± 1.6
HAS-BLED	2.9 ± 0.9	2.8 ± 0.9	2.9 ± 1.0	3.0 (2.0-3.0)	3.0 (2.0-3.0)	3.0 (2.0-3.0)	3.0 ± 0.9	3.0 ± 0.9	3.0 ± 0.9	NR	2.8 ± 0.8	2.6 ± 0.7	2.7 ± 0.7
ACS	2,811 (60.9%)	1,391 (60.3%)	1,420 (61.5%)	777 (51.6%)	389 (51.5%)	388 (51.7%)	722 (51.0%)	361 (51.1%)	361 (50.9%)	1,375 (50.5%)	475 (48.4%)	391 (51.2%)	509 (51.9%)
$P2Y_{12}$ inhibitor (any)	4,496 (97.5%)	2,253 (97.7%)	2,243 (97.3%)	1505 (99.9%)	755 (100%)	750 (99.9%)	1,415 (100.0%)	706 (100.0%)	709 (100.0%)	2690 (98.7%)	963 (98.1%)	755 (99.0%)	972 (99.0%)
Clopidogrel	4,165 (90.3%)	2,075 (90.0%)	2,090 (90.6%)	1391 (92.4%)	695 (92%)	696 (92.7%)	1,340 (94.7%)	680 (96.3%)	660 (93.1%)	2397 (88.0%)	886 (90.3%)	663 (86.9%)	848 (86.4%)
Prasugrel	51 (1.1%)	31 (1.3%)	20 (0.9%)	8 (0.5%)	3 (0.4%)	5 (0.7%)	17 (1.2%)	5 (0.7%)	12 (1.7%)	NR	NR	NR	NR
Ticagrelor	280 (6.1%)	147 (6.4%)	133 (5.8%)	106 (7.0%)	57 (7.5%)	49 (6.5%)	58 (4.1%)	21 (3.0%)	37 (5.2%)	293 (10.7%)	77 (7.8%)	92 (12.1%)	124 (12.6%)
DES	NR	NR	NR	NR	NR	NR	958 (67.7%)	480 (68.0%)	478 (67.4%)	2,292 (84.1%)	838 (85.4%)	631 (82.7%)	823 (83.9%)

Time from index event to randomization (days)	6.6 ± 4.2	6.7 ± 4.3	6.5 ± 4.1	1.9 (0.9-3.2)	1.9 (0.9-3.2)	1.9 (0.9-3.2)	<3	<3	<3	≤5	≤5	≤5	≤5
Time in therapeutic range in VKA group (%)	58.6 (33.3-81.0)	NR	NR	NA	63.1 (46.3-75.6)	NA	NA	65 ± NR	NA	NA	64 ± NR	NA	NA

Data are expressed as number (percentages). Age, CHA_2DS_2-VASc and HAS-BLED risk scores were reported differently among the included RCTs. Data with ± are reported as mean ± standard deviation; data with numbers into brackets are reported as median with interquartile range. In PIONEER-AF overall and VKA+DAPT column, group 2 patients (very-low dose rivaroxaban + $P2Y_{12}$) have been excluded.

CHA_2DS_2-VASc score includes congestive heart failure/left ventricular dysfunction, hypertension, age, diabetes mellitus, cerebrovascular events, vascular disease and gender as variables.

HAS-BLED includes hypertension, abnormal renal/liver function, stroke, bleeding, labile INR, age and drugs or alcohol as variables.

In AUGUSTUS, both double and triple therapy subgroups included 2306 patients in Apixaban and 2308 patients in VKA, equally distributed between the two subgroups, because of its factorial randomization, whereas all other trial included exclusively patients on NOAC+SAPT or VKA+DAPT. Baseline characteristics of patients on NOAC+SAPT and VKA+DAPT in AUGUSTUS trial were not available. Abbreviations: ACS = Acute Coronary Syndrome; AF = Atrial Fibrillation; AUGUSTUS = A Study of Apixaban in Patients With Atrial Fibrillation, Not Caused by a Heart Valve Problem, Who Are at Risk for Thrombosis (Blood Clots) Due to Having Had a Recent Coronary Event, Such as a Heart Attack or a Procedure to Open the Vessels of the Heart; CABG = Coronary Artery Bypass Grafting; CAD = Coronary Artery Disease; CVEs = Cardiovascular Events; DAPT = Dual Antiplatelet Therapy; DAT = Dual Antithrombotic Therapy; DES = Drug-eluting stent; ENTRUST-AF PCI = Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention; MI = Myocardial Infarction; NA = Not Applicable; NOAC= Non-vitamin K antagonist Oral Anticoagulant; NR = Not Reported; PAD = Peripheral Artery Disease; PCI = Percutaneous Coronary Intervention; PIONEER AF-PCI = A Study Exploring Two Strategies of Rivaroxaban and One of Oral Vitamin K Antagonist in Patients With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention; RE-DUAL PCI = Evaluation of

Dual Therapy With Dabigatran versus Triple Therapy With Warfarin in Patients With AF That Undergo a PCI With Stenting; SAPT= Single Antiplatelet Therapy; SD = Standard Deviation; TAT = Triple Antithrombotic Therapy; VKA=Vitamin K Antagonist.

Table S6: Leave-one-out sensitivity analysis for MACE and clinically significant bleedings

	Trial removed	HR	CI	P value for difference	I^2	P value for Heterogeneity
MACE	**PIONEER AF-PCI**	1.05	0.89-1.24	0.547	0	0.982
	RE-DUAL PCI	1.07	0.86-1.35	0.538	0	0.997
	AUGUSTUS	1.05	0.88-1.25	0.592	0	0.988
	ENTRUST AF-PCI	1.06	0.89-1.25	0.528	0	0.977
Clinically significant bleeding	**PIONEER AF-PCI**	0.54	0.33-0.91	0.02	91.69	0
	RE-DUAL PCI	0.55	0.33-0.92	0.022	92.51	0
	AUGUSTUS	0.66	0.52-0.83	0.001	62.26	0.069
	ENTRUST AF-PCI	0.48	0.34-0.69	0	82.51	0.003

Abbreviations: AUGUSTUS = A Study of Apixaban in Patients With Atrial Fibrillation, Not Caused by a Heart Valve Problem, Who Are at Risk for Thrombosis (Blood Clots) Due to Having Had a Recent Coronary Event, Such as a Heart Attack or a Procedure to Open the Vessels of the Heart; CI = Confidence Interval; HR = Hazard Ratio; ENTRUST-AF PCI = Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention; MACE = Major Adverse Cardiovascular Event; PIONEER AF-PCI = A Study Exploring Two Strategies of Rivaroxaban and One of Oral Vitamin K Antagonist in Patients With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention; RE-DUAL PCI = Evaluation of Dual Therapy With Dabigatran versus Triple Therapy With Warfarin in Patients With AF That Undergo a PCI With Stenting.

Table S7: Relative-effects table according to random-effects model analysis

		Apixaban + SAPT	**Dabigatran 110 mg + SAPT**	**Dabigatran 150 mg + SAPT**	**Edoxaban + SAPT**	**Rivaroxaban + SAPT**	**VKA + DAPT**
MACE	**Apixaban + SAPT**		1.05 (0.58, 1.88)	0.81 (0.44, 1.47)	0.98 (0.5, 1.91)	0.93 (0.47, 1.83)	0.93 (0.59, 1.44)
	Dabigatran 110 mg + SAPT	0.95 (0.53, 1.71)		0.77 (0.52, 1.15)	0.94 0.5, 1.74)	0.89 (0.48, 1.67)	0.88 (0.6, 1.29)
	Dabigatran 150 mg + SAPT	1.23 (0.68, 2.27)	1.3 (0.87, 1.93)		1.21 (0.64, 2.3)	1.16 (0.61, 2.2)	1.14 (0.77, 1.71)
	Edoxaban + SAPT	1.02 (0.52, 2.01)	1.07 (0.58, 2.01)	0.83 (0.43, 1.56)		0.96 (0.47, 1.94)	0.94 (0.57, 1.56)
	Rivaroxaban + SAPT	1.07 (0.55, 2.11)	1.12 (0.6, 2.1)	0.86 (0.46, 1.63)	1.05 (0.52, 2.15)		0.99 (0.6, 1.63)
	VKA + DAPT	1.08 (0.7, 1.7)	1.13 (0.78, 1.66)	0.87 (0.59, 1.3)	1.06 (0.64, 1.76)	1.01 (0.61, 1.67)	
Clinically significant bleeding	**Apixaban + SAPT**		1.68 (0.25, 11.31)	2.19 (0.32, 14.65)	2.38 (0.35, 16.16)	1.85 (0.27, 12.57)	2.92 (0.76, 11.51)
	Dabigatran 110 mg + SAPT	0.6 (0.09, 4.01)		1.31 (0.34, 5.08)	1.42 (0.21, 9.34)	1.1 (0.16, 7.45)	1.75 (0.46, 6.62)
	Dabigatran 150 mg + SAPT	0.46 (0.07, 3.09)	0.76 (0.2, 2.95)		1.08 (0.16, 7.23)	0.84 (0.12, 5.73)	1.34 (0.35, 5.11)
	Edoxaban + SAPT	0.42 (0.06, 2.86)	0.71 0.11, 4.77)	0.93 (0.14, 6.27)		0.78 (0.11, 5.28)	1.23 (0.32, 4.83)
	Rivaroxaban + SAPT	0.54 (0.08, 3.75)	0.91 (0.13, 6.13)	1.19 (0.17, 8.11)	1.29 (0.19, 8.79)		1.59 (0.41, 6.11)
	VKA + DAPT	0.34 (0.09, 1.31)	0.57 (0.15, 2.18)	0.75 (0.2, 2.89)	0.81 (0.21, 3.11)	0.63 (0.16, 2.43)	

Data are expressed in RR (CI). Abbreviations: CI = Confidence Interval; DAPT = Dual Antiplatelet Therapy; MACE = Major Adverse Cardiovascular Event; RR = Relative Risk; SAPT = Single Antiplatelet Therapy; VKA = Vitamin K Antagonist.

Table S8: Leave-one-out sensitivity analysis for secondary endpoints

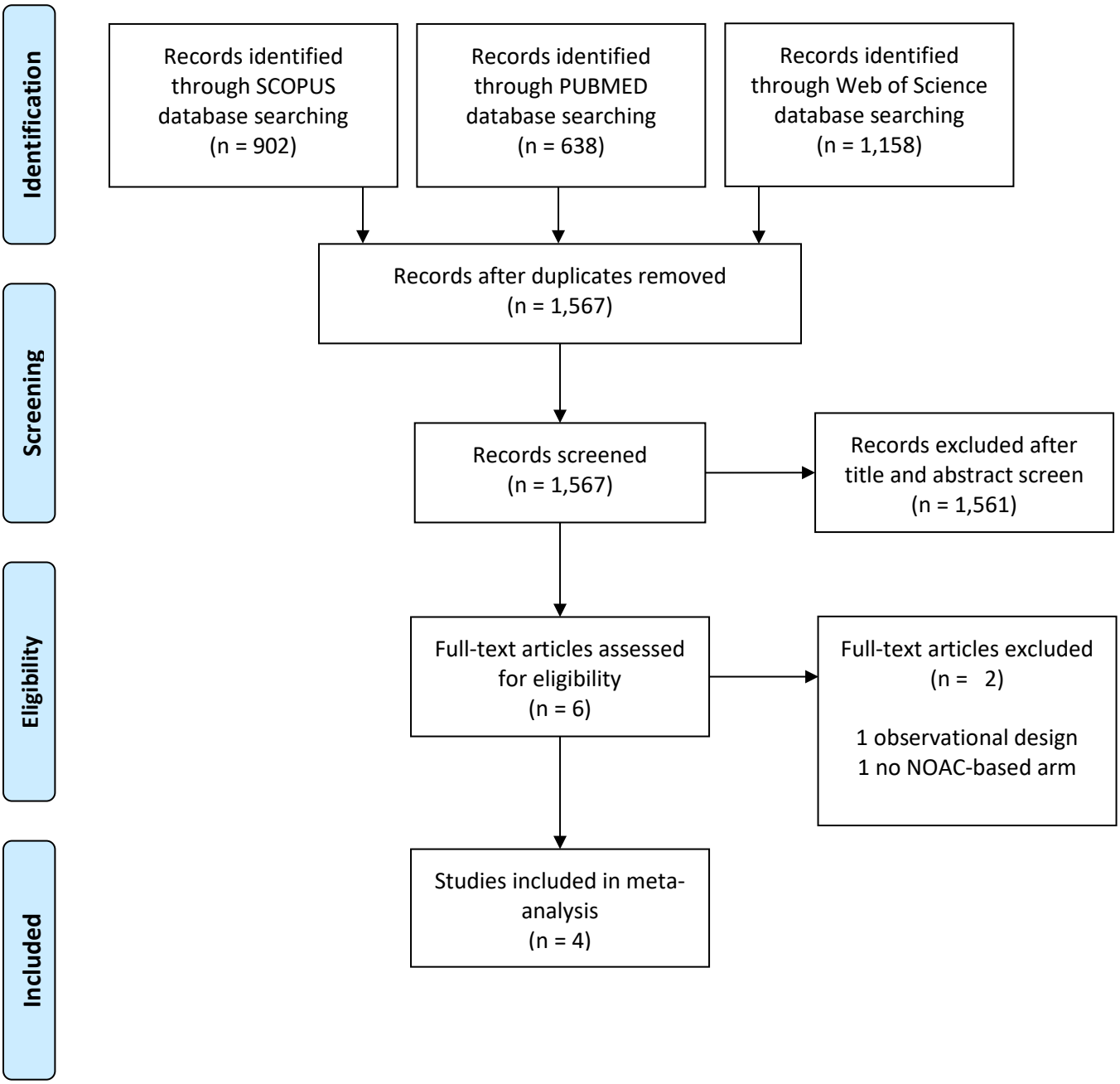
	Trial removed	HR	CI	P value for difference	I^2	P value for heterogeneity
Death	PIONEER AF-PCI	1.1	0.87-1.39	0.414	0	0.728
	RE-DUAL PCI tot	1.13	0.86-1.48	0.394	0	0.717
	AUGUSTUS	1.06	0.83-1.35	0.666	0	0.647
	ENTRUST-AF PCI	1.02	0.8-1.31	0.858	0	0.821
Stroke	PIONEER AF-PCI	0.83	0.5-1.37	0.468	12.06	0.293
	RE-DUAL PCI tot	0.76	0.44-1.31	0.323	0	0.38
	AUGUSTUS	1.03	0.65-1.64	0.895	0	0.845
	ENTRUST-AF PCI	0.88	0.5-1.56	0.67	20.98	0.257
Myocardial	PIONEER AF-PCI	1.24	0.95-1.62	0.12	0	0.84
infarction	RE-DUAL PCI tot	1.1	0.81-1.49	0.53	0	0.735
	AUGUSTUS	1.2	0.9-1.61	0.214	0	0.579
	ENTRUST-AF PCI	1.16	0.88-1.53	0.302	0	0.577
Stent thrombosis	PIONEER AF-PCI	1.38	0.87-2.19	0.174	0	0.871
	RE-DUAL PCI (tot)	1.30	0.73-2.32	0378	0	0.836
	AUGUSTUS	1.37	0.85-2.21	0.196	0	0.945
	ENTRUST-AF PCI	1.39	0.83-2.32	0.212	0	0.906
	RE-DUAL PCI (Dabigatran 110 mg arm)	1.22	0.74-2.03	0.440	0	0.846
Intracranial	PIONEER AF-PCI	0.31	0.14-0.67	0.003	0	0.702
haemorrhage	RE-DUAL PCI tot	0.41	0.18-0.92	0.032	0	0.888
	AUGUSTUS	0.35	0.17-0.7	0.003	0	0.668
	ENTRUST-AF PCI	0.29	0.13-0.66	0.003	0	0.768
Clinically relevant	PIONEER AF-PCI	0.64	0.42-0.98	0.042	89.37	0
non-major bleeding	RE-DUAL PCI tot	0.63	0.42-0.97	0.035	87.72	0.001

	AUGUSTUS	0.75	0.66-0.85	0	0	0.381
	ENTRUST-AF PCI	0.6	0.43-0.84	0.003	84.09	0.004
Major bleeding	PIONEER AF-PCI	0.71	0.48-1.05	0.087	62.94	0.075
	RE-DUAL PCI tot	0.83	0.64-1.06	0.136	0	0.672
	AUGUSTUS	0.69	0.44-1.08	0.102	58.91	0.08
	ENTRUST-AF PCI	0.64	0.45-0.9	0.01	33.35	0.249

Abbreviations: AUGUSTUS = A Study of Apixaban in Patients With Atrial Fibrillation, Not Caused by a Heart Valve Problem, Who Are at Risk for Thrombosis (Blood Clots) Due to Having Had a Recent Coronary Event, Such as a Heart Attack or a Procedure to Open the Vessels of the Heart; CI = Confidence Interval; ENTRUST-AF PCI = Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention; Available; HR = Hazard Ratio; PIONEER AF-PCI = A Study Exploring Two Strategies of Rivaroxaban and One of Oral Vitamin K Antagonist in Patients With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention; RE-DUAL PCI = Evaluation of Dual Therapy With Dabigatran versus Triple Therapy With Warfarin in Patients With AF That Undergo a PCI With Stenting.

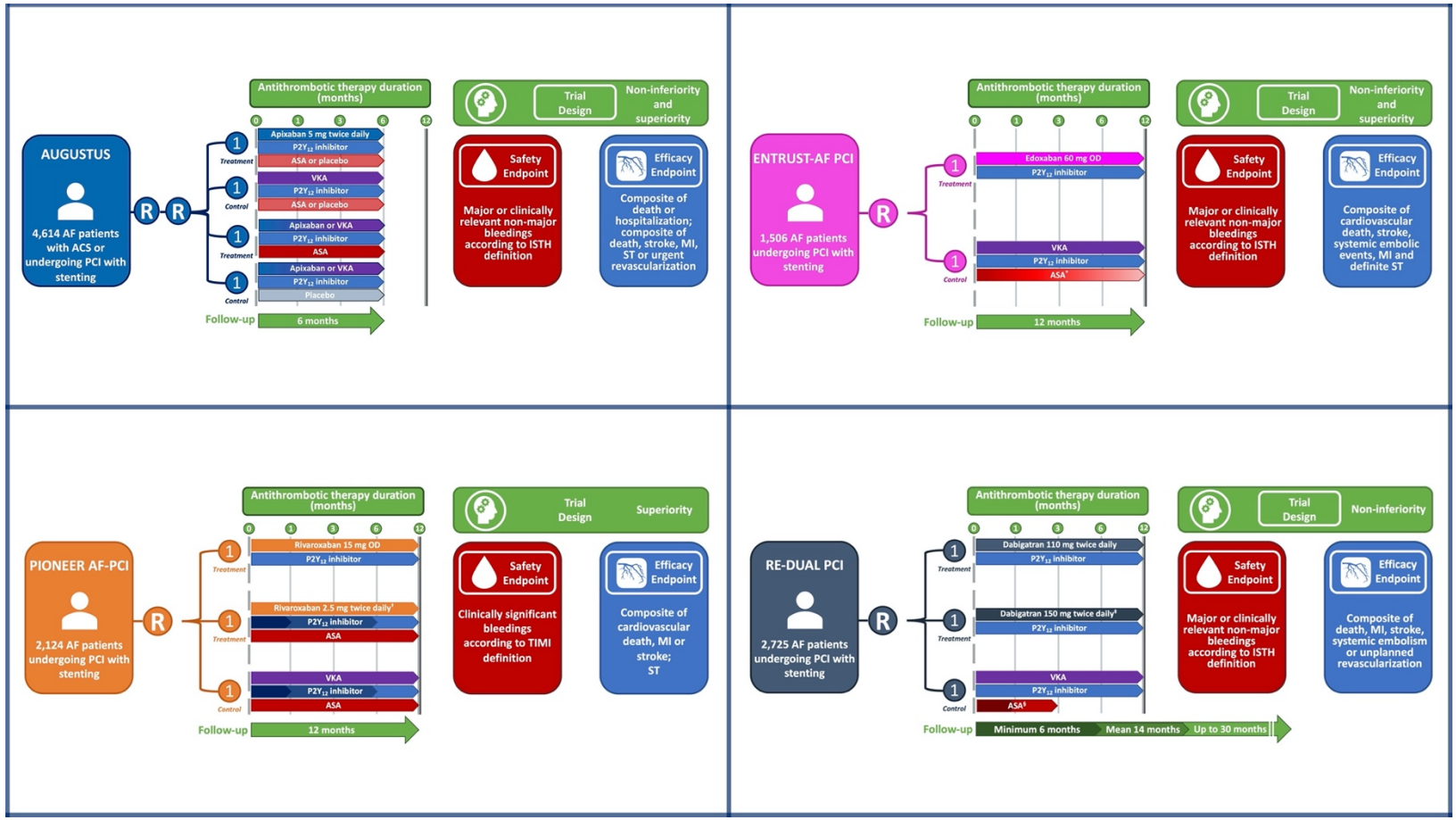
SUPPLEMENTAL FIGURES

Figure S1: PRISMA Diagram Flow



Abbreviations: NOAC = Non-Vitamin K Antagonist Oral Anticoagulant; PRISMA = Preferred Reporting Items for Systematic Reviews and Meta-Analyses.

Figure S2: Comparison of included randomized controlled trials' designs



*In the control arm of ENTRUST-AF PCI, ASA was administered for a minimum of 1 month and up to 12 months at the discretion of the investigator.

†PIONEER AF-PCI very-low dose rivaroxaban (2.5 mg twice daily) was escalated to low-dose rivaroxaban (15 mg OD) at the time of $P2Y_{12}$ inhibitor stop.

‡Elderly patients outside the US were not eligible to be assigned dabigatran 150 mg in accordance to country-specific drug labels.

§Aspirin was discontinued after 1 month in patients in whom a bare metal stent was implanted and after 3 months in patients in whom a drug-eluting stent was implanted.

Abbreviations: ACS = Acute Coronary Syndrome; AF = Atrial Fibrillation; ASA = Acetylsalicylic Acid; AUGUSTUS = A Study of Apixaban in Patients With Atrial Fibrillation, Not Caused by a Heart Valve Problem, Who Are at Risk for Thrombosis (Blood Clots) Due to Having Had a Recent Coronary Event, Such as a Heart Attack or a Procedure to Open the

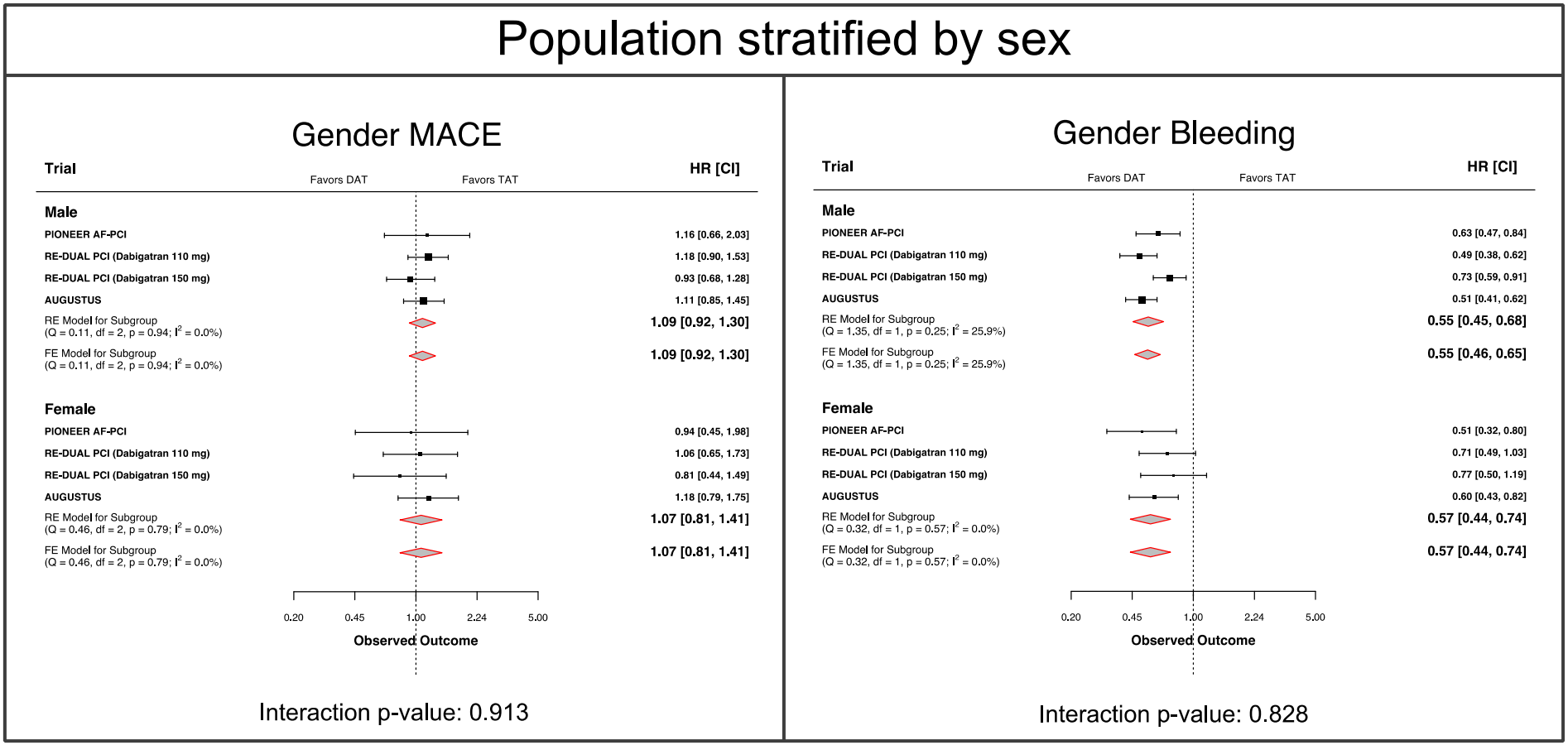
Vessels of the Heart; ENTRUST-AF PCI = Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention; ISTH = International Society on Thrombosis and Hemostasis; MI = Myocardial Infarction; OD = Once Daily; PIONEER AF-PCI = A Study Exploring Two Strategies of Rivaroxaban and One of Oral Vitamin K Antagonist in Patients With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention; PCI = Percutaneous Coronary Intervention; R = Randomization; RE-DUAL PCI = Evaluation of Dual Therapy With Dabigatran versus Triple Therapy With Warfarin in Patients With AF That Undergo a PCI With Stenting; ST = Stent Thrombosis; TIMI = Thrombolysis In Myocardial Infarction; VKA = Vitamin K Antagonist.

Figure S3: Incidences of MACE endpoint and individual components of MACE in included randomized controlled trials

The composite of death and ischemic events (stroke, myocardial infarction, ST, urgent revascularization) has been selected as primary efficacy outcome for AUGUSTUS trial since it is similar to other trials' primary efficacy outcomes. In AUGUSTUS trial, incidences of events for patients on NOAC+SAPT and VKA+DAPT were only available for MACEs and death, whereas incidences of stroke, myocardial infarction and ST concern the whole double and triple therapy subgroups.

Abbreviations: AUGUSTUS = A Study of Apixaban in Patients With Atrial Fibrillation, Not Caused by a Heart Valve Problem, Who Are at Risk for Thrombosis (Blood Clots) Due to Having Had a Recent Coronary Event, Such as a Heart Attack or a Procedure to Open the Vessels of the Heart; DAPT = Dual Antiplatelet Therapy; ENTRUST-AF PCI = Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention; MACE = Major Adverse Cardiovascular Event; NA = Not Available; NOAC = Non-Vitamin K antagonist Oral Anticoagulants; PIONEER AF-PCI = A Study Exploring Two Strategies of Rivaroxaban and One of Oral Vitamin K Antagonist in Patients With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention; RE-DUAL PCI = Evaluation of Dual Therapy With Dabigatran versus Triple Therapy With Warfarin in Patients With AF That Undergo a PCI With Stenting; SAPT= Single Antiplatelet Therapy; ST = Stent Thrombosis; VKA=Vitamin K Antagonist

Figure S4: Subgroup analysis for both MACE and clinically significant bleeding in different sex groups

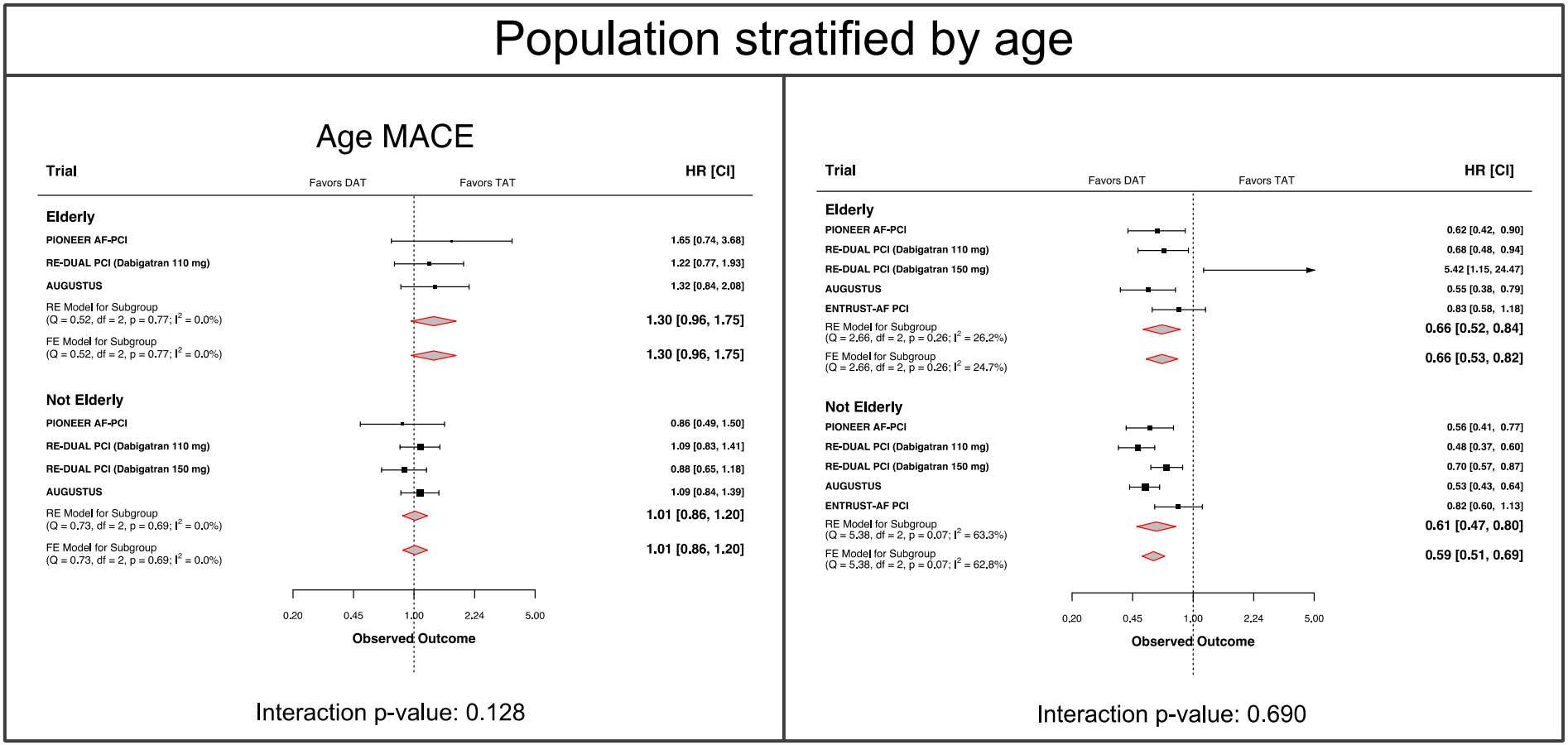


In AUGUSTUS, both double and triple therapy subgroups included patients on Apixaban or VKA, equally distributed between the two subgroups, because of its factorial randomization, whereas all other trials included exclusively patients on NOAC+SAPT and VKA+DAPT. Subgroup analyses of patients on NOAC+SAPT and VKA+DAPT were not available in AUGUSTUS trial.

Abbreviations: AUGUSTUS = A Study of Apixaban in Patients With Atrial Fibrillation, Not Caused by a Heart Valve Problem, Who Are at Risk for Thrombosis (Blood Clots) Due to Having Had a Recent Coronary Event, Such as a Heart Attack or a Procedure to Open the Vessels of the Heart; CI = Confidence Interval; DAT = Dual Antithrombotic Therapy; ENTRUST-AF PCI = Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention; FE = Fixed Effects; HR = Hazard Ratio; MACE = Major Adverse Cardiovascular Event; NOAC = Non-Vitamin K antagonist Oral Anticoagulant; PIONEER AF-PCI = A Study Exploring Two Strategies of Rivaroxaban and One of Oral Vitamin K

Antagonist in Patients With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention; RE = Random Effects; RE-DUAL PCI = Evaluation of Dual Therapy With Dabigatran versus Triple Therapy With Warfarin in Patients With AF That Undergo a PCI With Stenting; TAT = Triple Antithrombotic Therapy; VKA = Vitamin K Antagonist.

Figure S5: Subgroup analysis for both MACE and clinically significant bleeding in different age groups



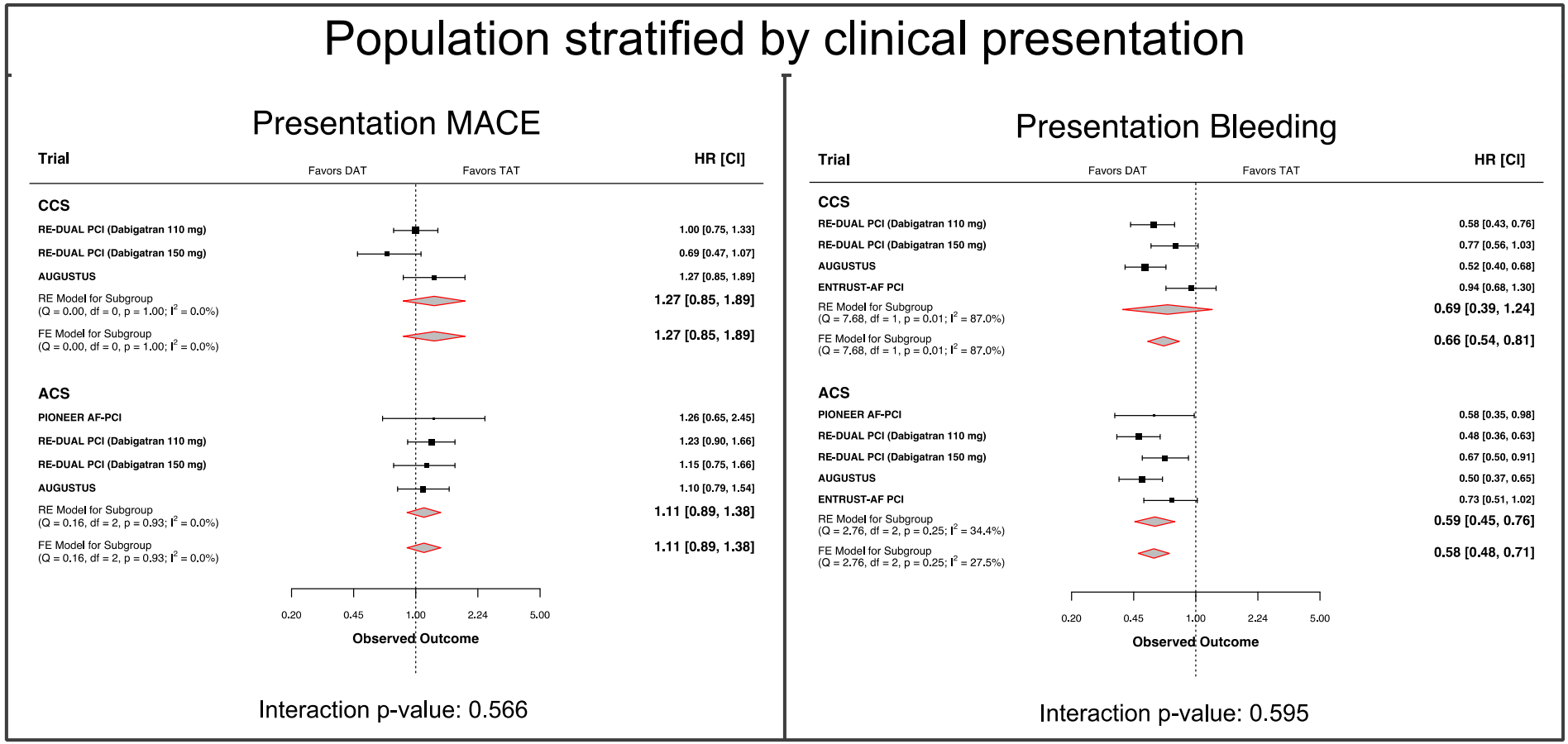
ENTRUST-AF PCI and PIONEER AF-PCI used as cutoff value for elderly vs not elderly people 75 years of age, whereas AUGUSTUS and RE-DUAL PCI used 80 years of age.

In AUGUSTUS, both double and triple therapy subgroups included patients on Apixaban or VKA, equally distributed between the two subgroups, because of its factorial randomization, whereas all other trials included exclusively patients on NOAC+SAPT and VKA+DAPT. Subgroup analyses of patients on NOAC+SAPT and VKA+DAPT were not available in AUGUSTUS trial.

Abbreviations: AUGUSTUS = A Study of Apixaban in Patients With Atrial Fibrillation, Not Caused by a Heart Valve Problem, Who Are at Risk for Thrombosis (Blood Clots) Due to Having Had a Recent Coronary Event, Such as a Heart Attack or a Procedure to Open the Vessels of the Heart; CI = Confidence Interval; DAT = Dual Antithrombotic Therapy; ENTRUST-AF PCI = Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention; FE = Fixed Effects; HR = Hazard Ratio; MACE = Major

Adverse Cardiovascular Event; NOAC = Non-Vitamin K antagonist Oral Anticoagulant; PIONEER AF-PCI = A Study Exploring Two Strategies of Rivaroxaban and One of Oral Vitamin K Antagonist in Patients With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention; RE = Random Effects; RE-DUAL PCI = Evaluation of Dual Therapy With Dabigatran versus Triple Therapy With Warfarin in Patients With AF That Undergo a PCI With Stenting; TAT = Triple Antithrombotic Therapy; VKA = Vitamin K Antagonist.

Figure S6: Subgroup analysis for both MACE and clinically significant bleeding in different clinical presentation groups

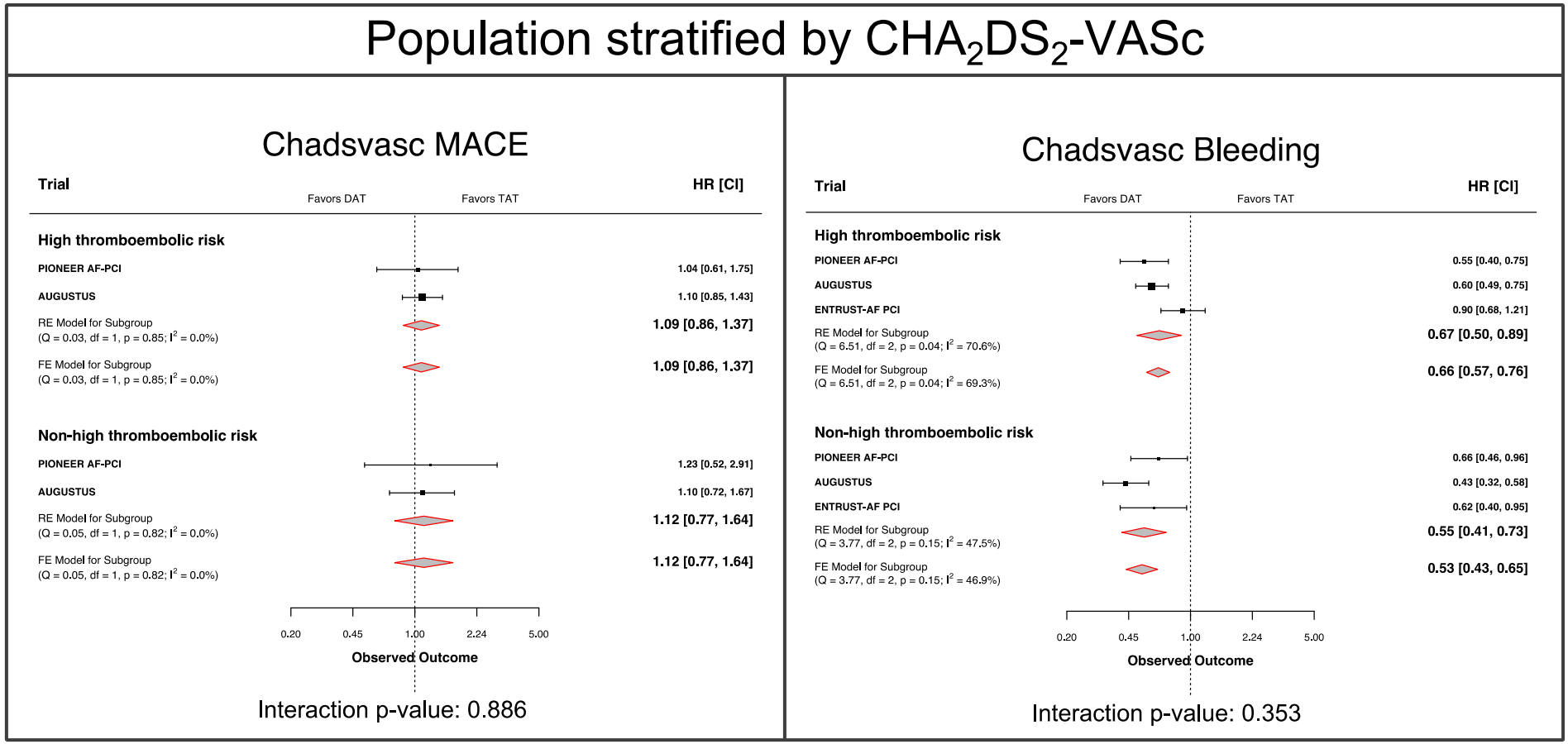


In AUGUSTUS, both double and triple therapy subgroups included patients on Apixaban or VKA, equally distributed between the two subgroups, because of its factorial randomization, whereas all other trials included exclusively patients on NOAC+SAPT and VKA+DAPT. Subgroup analyses of patients on NOAC+SAPT and VKA+DAPT were not available in AUGUSTUS trial.

Abbreviations: AUGUSTUS = A Study of Apixaban in Patients With Atrial Fibrillation, Not Caused by a Heart Valve Problem, Who Are at Risk for Thrombosis (Blood Clots) Due to Having Had a Recent Coronary Event, Such as a Heart Attack or a Procedure to Open the Vessels of the Heart; CI = Confidence Interval; DAT = Dual Antithrombotic Therapy; ENTRUST-AF PCI = Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention; FE = Fixed Effects; HR = Hazard Ratio; MACE = Major Adverse Cardiovascular Event; PIONEER AF-PCI = A Study Exploring Two Strategies of Rivaroxaban and One of Oral Vitamin K Antagonist in Patients With Atrial Fibrillation Who Undergo

Percutaneous Coronary Intervention; RE = Random Effects; RE-DUAL PCI = Evaluation of Dual Therapy With Dabigatran versus Triple Therapy With Warfarin in Patients With AF That Undergo a PCI With Stenting; TAT = Triple Antithrombotic Therapy; VKA = Vitamin K Antagonist.

Figure S7: Subgroup analysis for both MACE and clinically significant bleeding in different thromboembolic risk groups



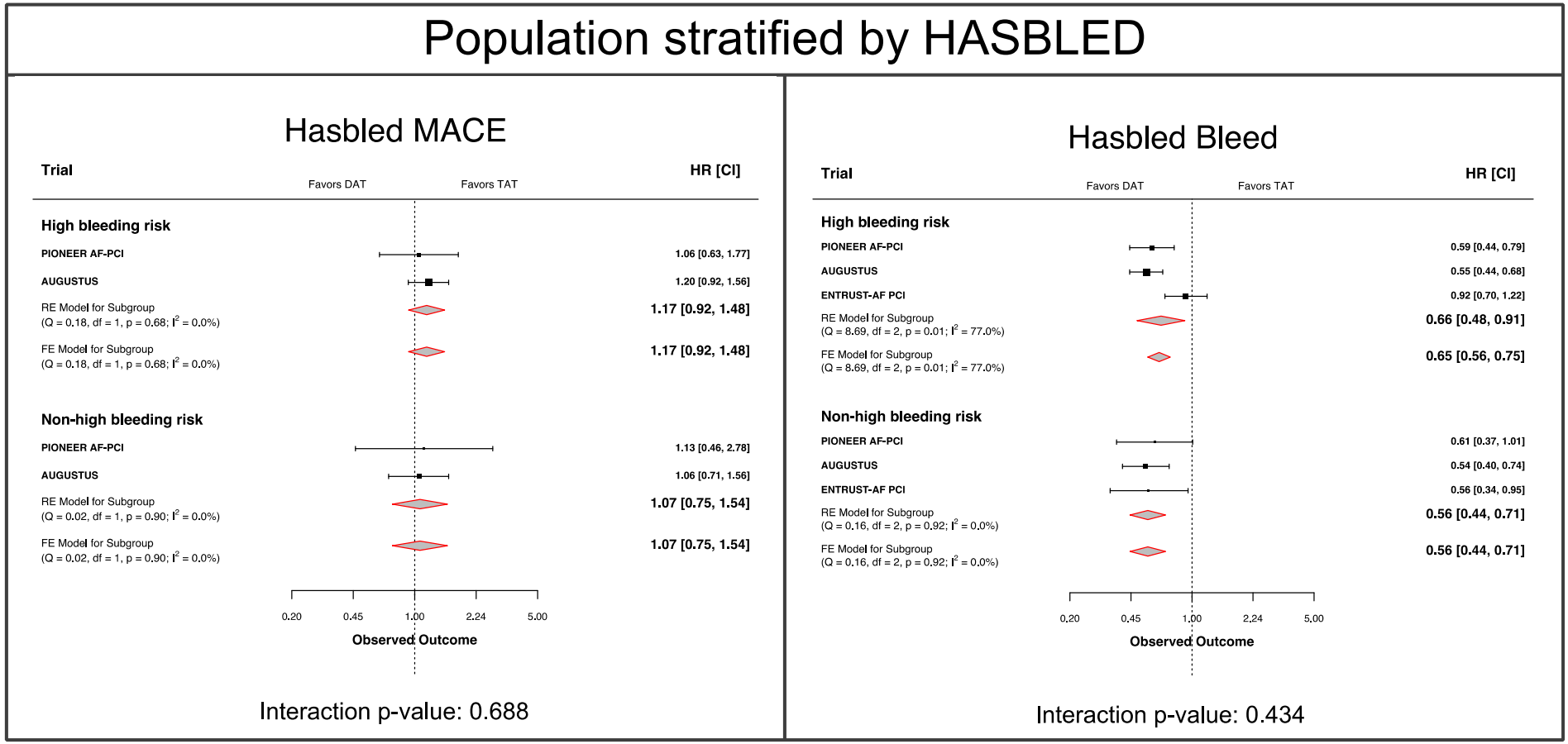
In ENTRUST-AF PCI trial a CHA_2DS_2-VAScl ≥ 3 was considered to define high thromboembolic risk, whereas in AUGUSTUS and PIONEER AF-PCI trial a value ≥ 4 was used.

In AUGUSTUS, both double and triple therapy subgroups included patients on Apixaban or VKA, equally distributed between the two subgroups, because of its factorial randomization, whereas all other trials included exclusively patients on NOAC+SAPT and VKA+DAPT. Subgroup analyses of patients on NOAC+SAPT and VKA+DAPT were not available in AUGUSTUS trial.

Abbreviations: AUGUSTUS = A Study of Apixaban in Patients With Atrial Fibrillation, Not Caused by a Heart Valve Problem, Who Are at Risk for Thrombosis (Blood Clots) Due to Having Had a Recent Coronary Event, Such as a Heart Attack or a Procedure to Open the Vessels of the Heart; CI = Confidence Interval; DAT = Dual Antithrombotic Therapy; ENTRUST-AF PCI = Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention; FE = Fixed Effects; HR = Hazard Ratio; MACE = Major Adverse Cardiovascular Event; NOAC = Non-vitamin K antagonist Oral Anticoagulant; PIONEER AF-PCI = A Study Exploring Two Strategies of Rivaroxaban and One of Oral Vitamin K

Antagonist in Patients With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention; RE = Random Effects; RE-DUAL PCI = Evaluation of Dual Therapy With Dabigatran versus Triple Therapy With Warfarin in Patients With AF That Undergo a PCI With Stenting; TAT = Triple Antithrombotic Therapy; VKA = Vitamin K Antagonist.

Figure S8: Subgroup analysis for both MACE and clinically significant bleeding in different bleeding risk groups



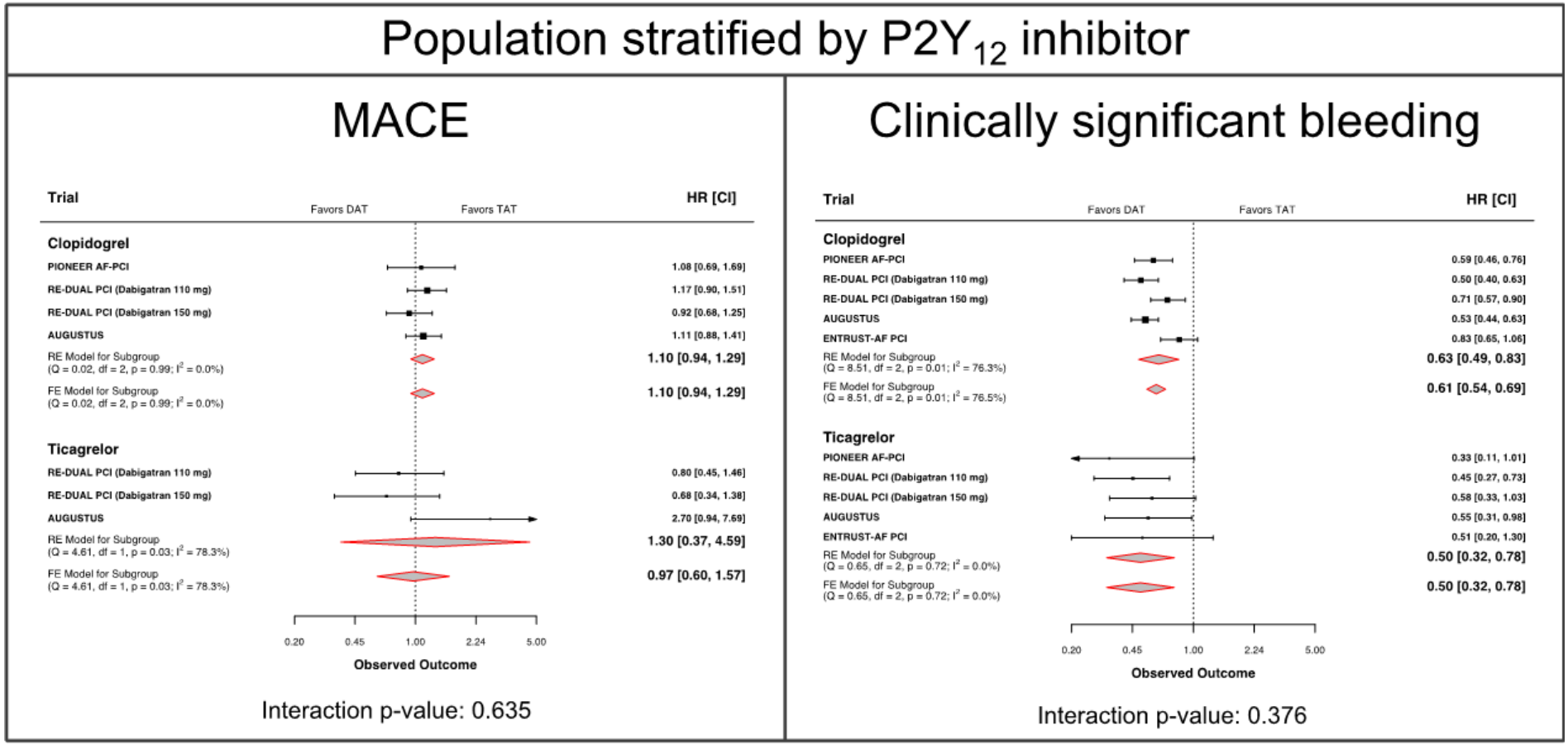
A HASBLED ≥ 3 was used to define high bleeding risk.

In AUGUSTUS, both double and triple therapy subgroups included patients on Apixaban or VKA, equally distributed between the two subgroups, because of its factorial randomization, whereas all other trials included exclusively patients on NOAC+SAPT and VKA+DAPT. Subgroup analyses of patients on NOAC+SAPT and VKA+DAPT were not available in AUGUSTUS trial.

Abbreviations: AUGUSTUS = A Study of Apixaban in Patients With Atrial Fibrillation, Not Caused by a Heart Valve Problem, Who Are at Risk for Thrombosis (Blood Clots) Due to Having Had a Recent Coronary Event, Such as a Heart Attack or a Procedure to Open the Vessels of the Heart; CI = Confidence Interval; DAT = Dual Antithrombotic Therapy; ENTRUST-AF PCI = Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention; FE = Fixed Effects; HR = Hazard Ratio; MACE = Major Adverse Cardiovascular Event; NOAC = Non-Vitamin K antagonist Oral Anticoagulant; PIONEER AF-PCI = A Study Exploring Two Strategies of Rivaroxaban and One of Oral Vitamin K

Antagonist in Patients With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention; RE = Random Effects; RE-DUAL PCI = Evaluation of Dual Therapy With Dabigatran versus Triple Therapy With Warfarin in Patients With AF That Undergo a PCI With Stenting; TAT = Triple Antithrombotic Therapy; VKA = Vitamin K Antagonist.

Figure S9: Subgroup analysis for both MACE and clinically significant bleeding in different $P2Y_{12}$ inhibitor risk groups



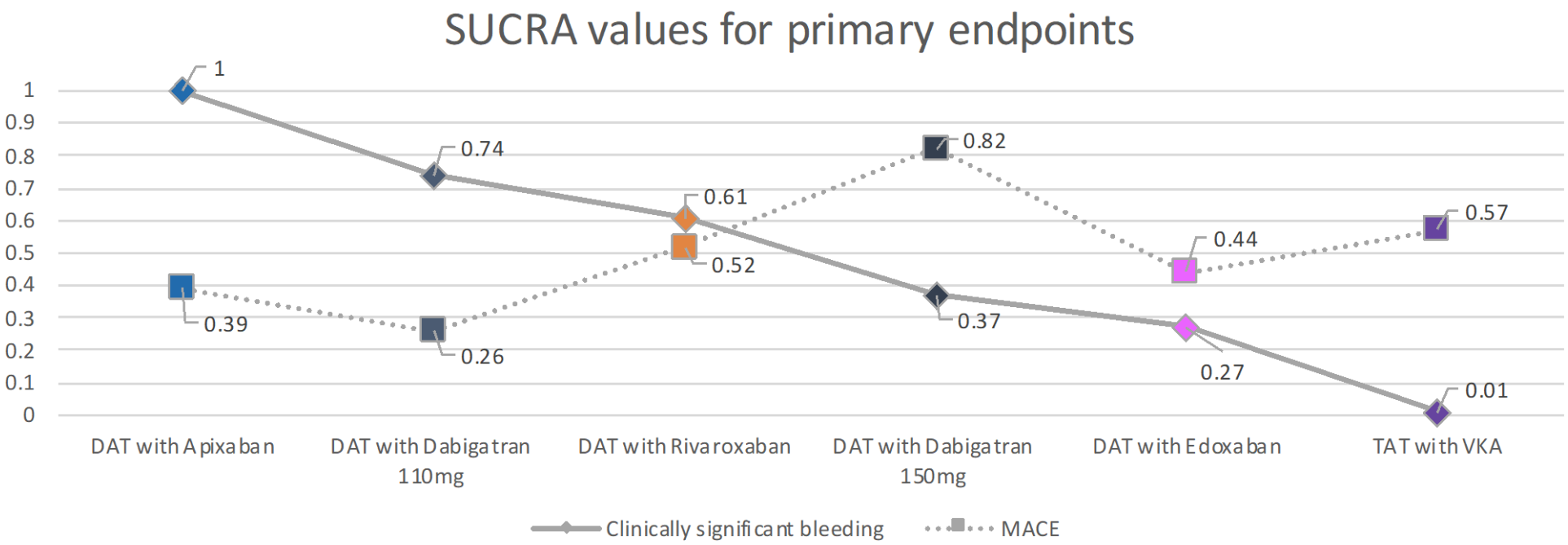
For ENTRUST-AF PCI trial, only clopidogrel vs other $P2Y_{12}$ inhibitors groups were available; for RE-DUAL PCI only ticagrelor vs other $P2Y_{12}$ inhibitors groups were available.

In AUGUSTUS, both double and triple therapy subgroups included patients on Apixaban or VKA, equally distributed between the two subgroups, because of its factorial randomization, whereas all other trials included exclusively patients on NOAC+SAPT and VKA+DAPT. Subgroup analyses of patients on NOAC+SAPT and VKA+DAPT were not available in AUGUSTUS trial.

Abbreviations: AUGUSTUS = A Study of Apixaban in Patients With Atrial Fibrillation, Not Caused by a Heart Valve Problem, Who Are at Risk for Thrombosis (Blood Clots) Due to Having Had a Recent Coronary Event, Such as a Heart Attack or a Procedure to Open the Vessels of the Heart; CI = Confidence Interval; DAT = Dual Antithrombotic Therapy; ENTRUST-AF PCI = Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention; FE = Fixed Effects; HR = Hazard Ratio; MACE = Major

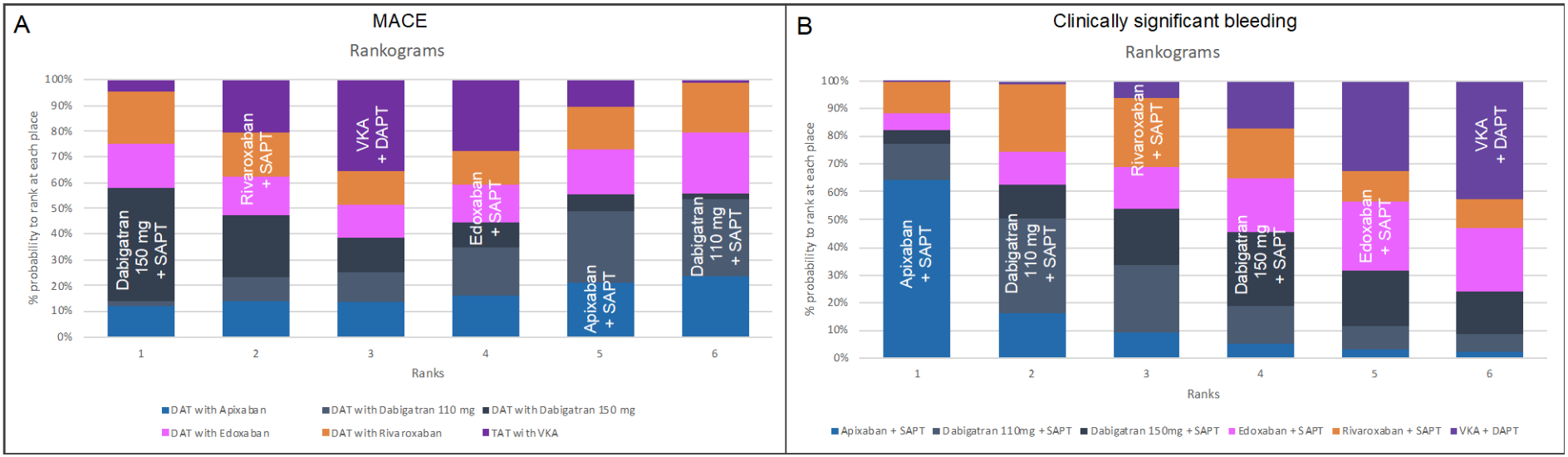
Adverse Cardiovascular Event; PIONEER AF-PCI = A Study Exploring Two Strategies of Rivaroxaban and One of Oral Vitamin K Antagonist in Patients With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention; RE = Random Effects; RE-DUAL PCI = Evaluation of Dual Therapy With Dabigatran versus Triple Therapy With Warfarin in Patients With AF That Undergo a PCI With Stenting; TAT = Triple Antithrombotic Therapy.

Figure S10: SUCRA values according to MACE and clinically significant bleeding endpoints with fixed-effects model analysis



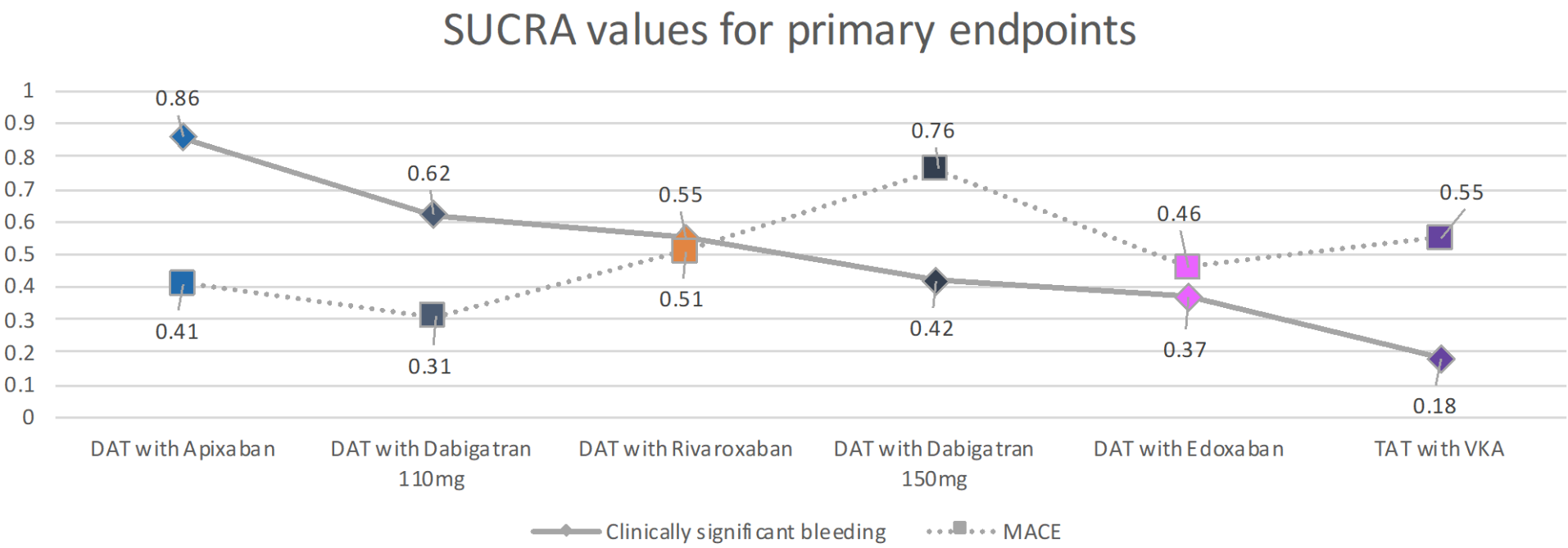
Abbreviations: DAPT = Dual Antiplatelet Therapy; MACE = Major Adverse Cardiovascular Event; SUCRA = Surface Under the Cumulative Ranking Curve; SAPT = Single Antiplatelet Therapy; VKA = Vitamin K Antagonist.

Figure S11: Rankograms according to MACE (A) and clinically significant bleeding (B) endpoints with random-effects model analysis



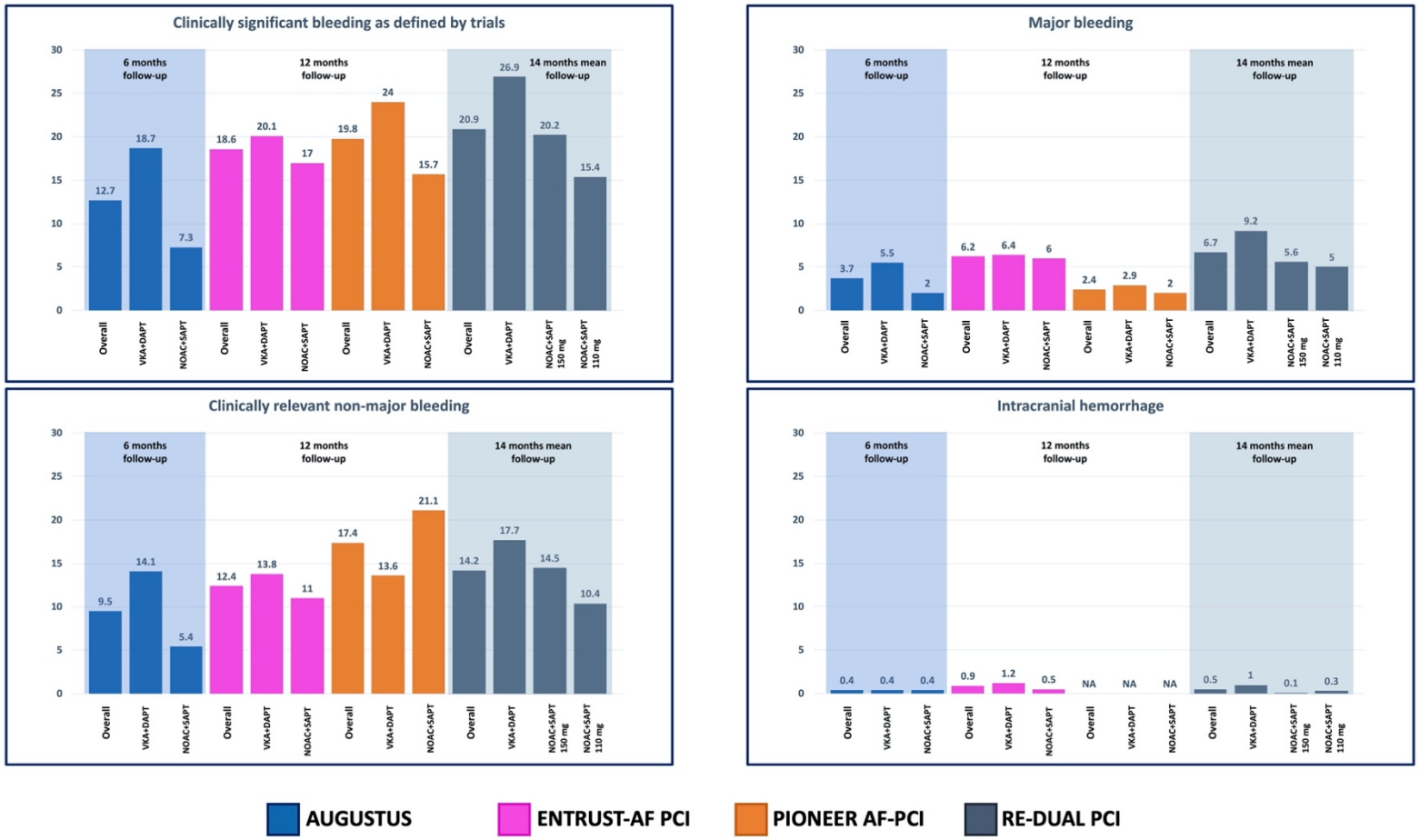
Abbreviations: DAPT = Dual Antiplatelet Therapy; MACE = Major Adverse Cardiovascular Event; SAPT = Single Antiplatelet Therapy; VKA = Vitamin K Antagonist.

Figure S12: SUCRA values according to MACE and clinically significant bleeding endpoints with random-effects model analysis



Abbreviations: DAPT = Dual Antiplatelet therapy; MACE = Major adverse cardiovascular event; SUCRA = Surface under the cumulative ranking curve; SAPT = Single Antiplatelet Therapy; VKA = Vitamin K Antagonist.

Figure S13: Incidences of bleeding endpoints through included randomized controlled trials

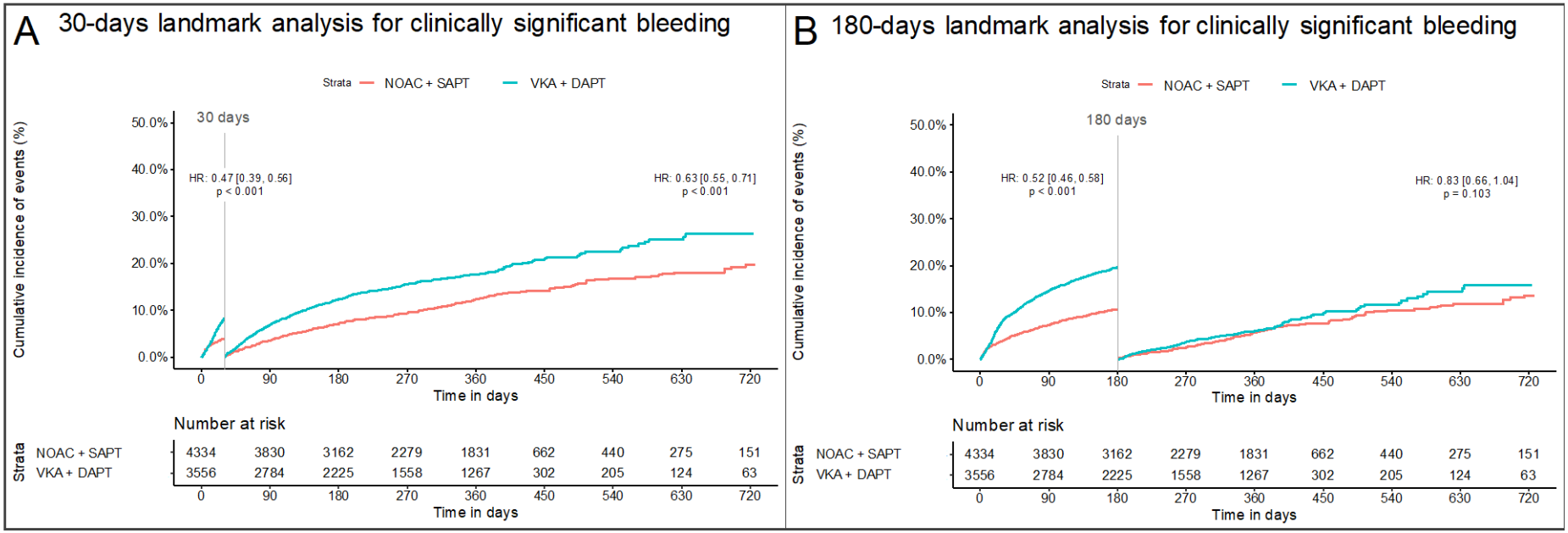


Incidences are expressed as percentages. In AUGUSTUS trial, the incidences of events for patients on NOAC+SAPT and VKA+DAPT were only available for clinically significant bleedings, major bleedings, clinically relevant non-major bleedings, whereas incidence of intracranial hemorrhage concerns the whole double and triple therapy subgroups.

Abbreviations: AUGUSTUS = A Study of Apixaban in Patients With Atrial Fibrillation, Not Caused by a Heart Valve Problem, Who Are at Risk for Thrombosis (Blood Clots) Due to Having Had a Recent Coronary Event, Such as a Heart Attack or a Procedure to Open the Vessels of the Heart; DAPT = Dual Antiplatelet Therapy; ENTRUST-AF PCI = Edoxaban

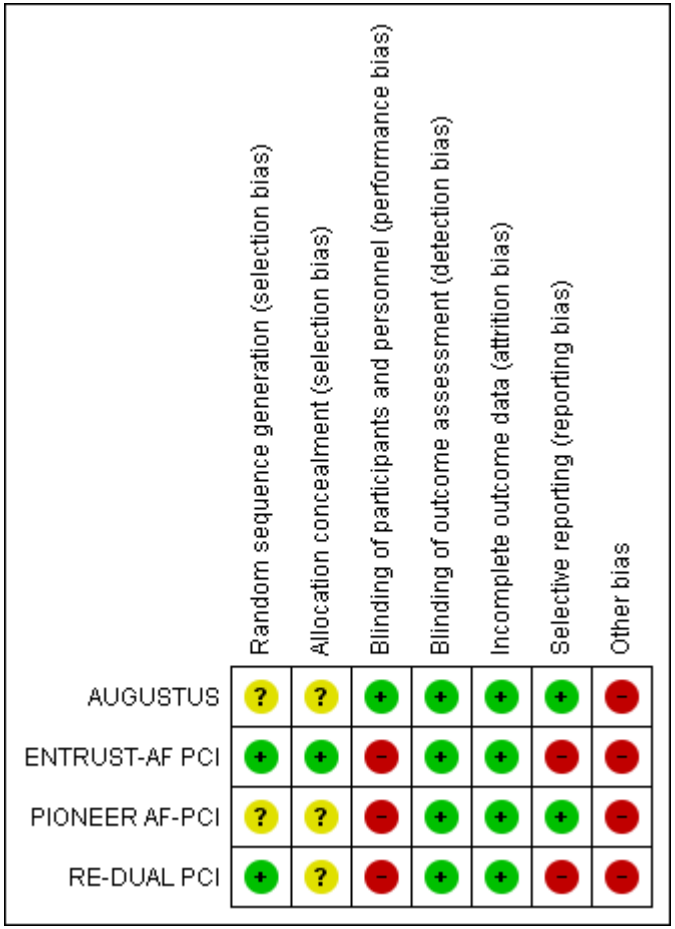
Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention; NA = Not Available; NOAC = Non-Vitamin K antagonist Oral Anticoagulant; PIONEER AF-PCI = A Study Exploring Two Strategies of Rivaroxaban and One of Oral Vitamin K Antagonist in Patients With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention; RE-DUAL PCI = Evaluation of Dual Therapy With Dabigatran versus Triple Therapy With Warfarin in Patients With AF That Undergo a PCI With Stenting; SAPT = Single Antiplatelet Therapy; VKA = Vitamin K Antagonist.

Figure S14: Kaplan-Meier curves with landmark analysis before and after 30 and 180 days for significant bleeding endpoint



Abbreviations: DAPT = Dual Antiplatelet Therapy; HR = Hazard Ratio (confidence interval between squared bracket); NOAC = Non-vitamin K antagonist Oral Anticoagulant; SAPT = Single Antiplatelet Therapy; VKA = Vitamin K Antagonist.

Figure S15: Risk of bias summary: review authors' judgements about each risk of bias item for each included study



Abbreviations: AUGUSTUS = A Study of Apixaban in Patients With Atrial Fibrillation, Not Caused by a Heart Valve Problem, Who Are at Risk for Thrombosis (Blood Clots) Due to Having Had a Recent Coronary Event, Such as a Heart Attack or a Procedure to Open the Vessels of the Heart; ENTRUST-AF PCI = Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention; PIONEER AF-PCI = A Study Exploring Two Strategies of Rivaroxaban and One of Oral Vitamin K Antagonist in Patients With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention; RE-DUAL PCI = Evaluation of Dual Therapy With Dabigatran versus Triple Therapy With Warfarin in Patients With AF That Undergo a PCI With Stenting.

Figure S16: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies

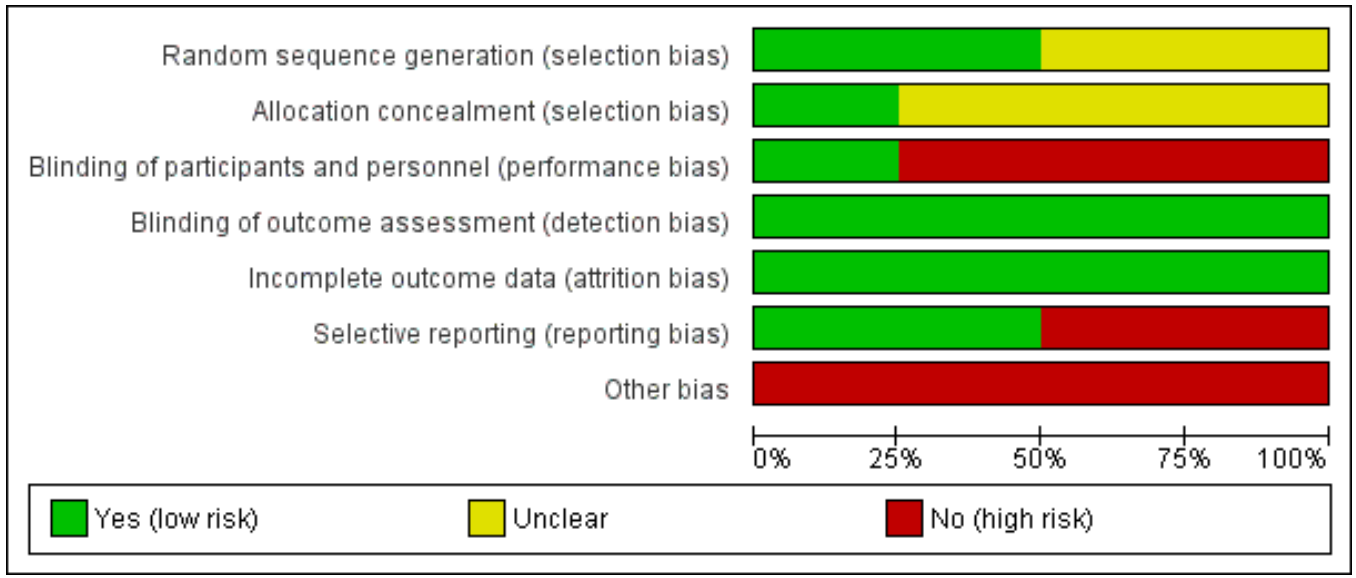
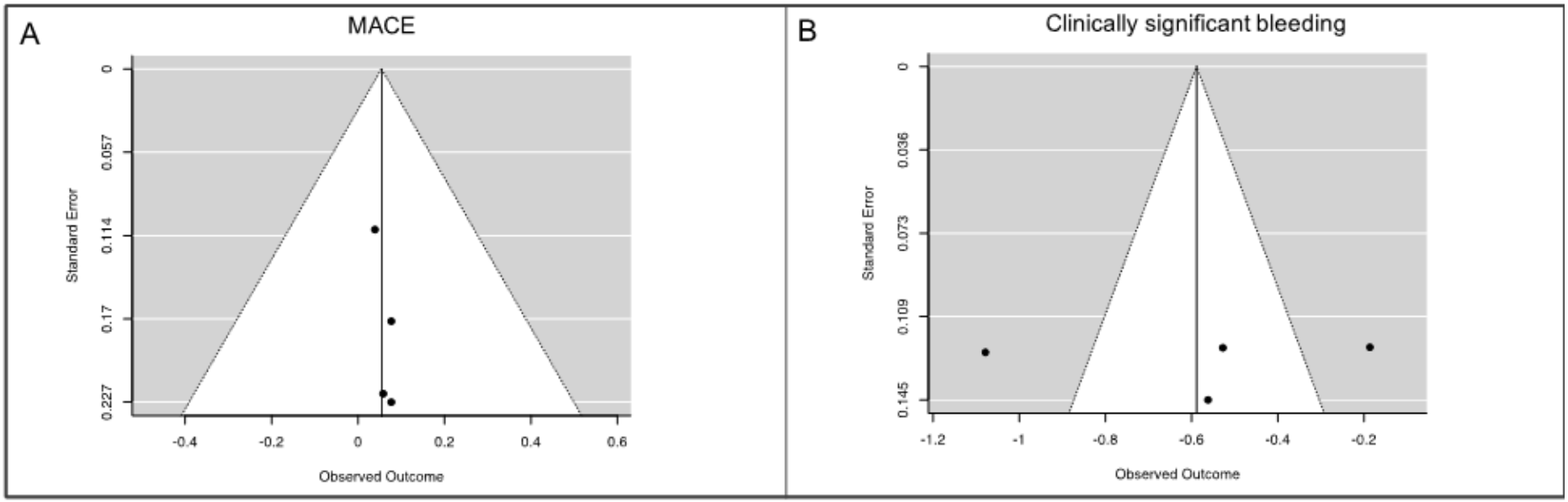


Figure S17: Funnel plots for MACE (A) and clinically significant bleeding (B) endpoints



Abbreviation: MACE = Major Adverse Cardiovascular Event.

SUPPLEMENTAL FIGURE LEGENDS

Figure S1: PRISMA Diagram Flow.

Figure S2: Comparison of included randomized controlled trials' designs.

*In the control arm of ENTRUST-AF PCI, ASA was administered for a minimum of 1 month and up to 12 months at the discretion of the investigator.

†PIONEER AF-PCI very-low dose rivaroxaban (2.5 mg twice daily) was escalated to low-dose rivaroxaban (15 mg OD) at the time of $P2Y_{12}$ inhibitor stop.

‡Elderly patients outside the US were not eligible to be assigned dabigatran 150 mg in accordance to country-specific drug labels.

§Aspirin was discontinued after 1 month in patients in whom a bare metal stent was implanted and after 3 months in patients in whom a drug-eluting stent was implanted.

Figure S3: Incidences of MACE endpoint and individual components of MACE in included randomized controlled trials.

The composite of death and ischemic events (stroke, myocardial infarction, ST, urgent revascularization) has been selected as primary efficacy outcome for AUGUSTUS trial since it is similar to other trials' primary efficacy outcomes. In AUGUSTUS trial, incidences of events for patients on NOAC+SAPT and VKA+DAPT were only available for MACEs and death, whereas incidences of stroke, myocardial infarction and ST concern the whole double and triple therapy subgroups.

Figure S4: Subgroup analysis for both MACE and clinically significant bleeding in different sex groups.

In AUGUSTUS, both double and triple therapy subgroups included patients on Apixaban or VKA, equally distributed between the two subgroups, because of its factorial randomization,

whereas all other trials included exclusively patients on NOAC+SAPT and VKA+DAPT. Subgroup analyses of patients on NOAC+SAPT and VKA+DAPT were not available in AUGUSTUS trial.

Figure S5: Subgroup analysis for both MACE and clinically significant bleeding in different age groups.

ENTRUST-AF PCI and PIONEER AF-PCI used as cutoff value for elderly vs not elderly people 75 years of age, whereas AUGUSTUS and RE-DUAL PCI used 80 years of age.

In AUGUSTUS, both double and triple therapy subgroups included patients on Apixaban or VKA, equally distributed between the two subgroups, because of its factorial randomization, whereas all other trials included exclusively patients on NOAC+SAPT and VKA+DAPT. Subgroup analyses of patients on NOAC+SAPT and VKA+DAPT were not available in AUGUSTUS trial.

Figure S6: Subgroup analysis for both MACE and clinically significant bleeding in different clinical presentation groups.

In AUGUSTUS, both double and triple therapy subgroups included patients on Apixaban or VKA, equally distributed between the two subgroups, because of its factorial randomization, whereas all other trials included exclusively patients on NOAC+SAPT and VKA+DAPT. Subgroup analyses of patients on NOAC+SAPT and VKA+DAPT were not available in AUGUSTUS trial.

Figure S7: Subgroup analysis for both MACE and clinically significant bleeding in different thromboembolic risk groups.

In ENTRUST-AF PCI trial a CHA2DS2-VAScl ≥3 was considered to define high thromboembolic risk, whereas in AUGUSTUS and PIONEER AF-PCI trial a value ≥4 was used.

In AUGUSTUS, both double and triple therapy subgroups included patients on Apixaban or VKA, equally distributed between the two subgroups, because of its factorial randomization, whereas all other trials included exclusively patients on NOAC+SAPT and VKA+DAPT. Subgroup analyses of patients on NOAC+SAPT and VKA+DAPT were not available in AUGUSTUS trial.

Figure S8: Subgroup analysis for both MACE and clinically significant bleeding in different bleeding risk groups.

A HASBLED ≥3 was used to define high bleeding risk. In AUGUSTUS, both double and triple therapy subgroups included patients on Apixaban or VKA, equally distributed between the two subgroups, because of its factorial randomization, whereas all other trials included exclusively patients on NOAC+SAPT and VKA+DAPT. Subgroup analyses of patients on NOAC+SAPT and VKA+DAPT were not available in AUGUSTUS trial.

Figure S9: Subgroup analysis for both MACE and clinically significant bleeding in different $P2Y_{12}$ inhibitor risk groups.

For ENTRUST-AF PCI trial, only clopidogrel vs other $P2Y_{12}$ inhibitors groups were available; for RE-DUAL PCI only ticagrelor vs other $P2Y_{12}$ inhibitors groups were available. In AUGUSTUS, both double and triple therapy subgroups included patients on Apixaban or VKA, equally distributed between the two subgroups, because of its factorial randomization, whereas all other trials included exclusively patients on NOAC+SAPT and VKA+DAPT. Subgroup analyses of patients on NOAC+SAPT and VKA+DAPT were not available in AUGUSTUS trial.

Figure S10: SUCRA values according to MACE and clinically significant bleeding endpoints with fixed-effects model analysis.

Figure S11: Rankograms according to MACE (A) and clinically significant bleeding (B) endpoints with random-effects model analysis.

Figure S12: SUCRA values according to MACE and clinically significant bleeding endpoints with random-effects model analysis.

Figure S13: Incidences of bleeding endpoints through included randomized controlled trials.

Figure S14: Kaplan-Meier curves with landmark analysis before and after 30 and 180 days for significant bleeding endpoint.

Figure S15: Risk of bias summary: review authors' judgements about each risk of bias item for each included study.

Figure S16: Risk of bias graph: review authors' judgements about each risk of bias item presented as percentages across all included studies.

Figure S17: Funnel plots for MACE (A) and clinically significant bleeding (B) endpoints.