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SYSTEMATIC REVIEW AND META-ANALYSIS

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

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BACKGROUND: The optimal antithrombotic therapy for patients with atrial fibrillation undergoing percutaneous coronary intervention is a topic of debate. We aimed at defining the efficacy and safety of double antithrombotic therapy with single antiplatelet therapy (SAPT) plus a non–vitamin K antagonist oral anticoagulant (NOAC) against triple antithrombotic therapy with dual antiplatelet therapy (DAPT) added to a vitamin K antagonist (VKA), illustrating the pooled cumulative distribution of events, the ranking of different NOACs tested in NOAC+SAPT combination strategies, and the state of the current evidence in the field.

METHODS AND RESULTS: Randomized controlled trials meeting the inclusion criteria were identified. The primary efficacy end point was the composite of trial-defined major adverse cardiac events. The primary safety end point was clinically significant bleeding. Secondary end points were the components of primary end points. Trial-level pairwise and Bayesian network meta-analyses, reconstructed Kaplan–Meier analyses, and trial sequential analysis were performed. Four randomized controlled trials (10 969 patients) were included. No differences were found in terms of major adverse cardiac events (hazard ratio [HR], 1.07; 95% CI, 0.94–1.22), and the NOAC+SAPT strategy showed a lower rate of clinically significant bleeding compared with VKA + DAPT (HR, 0.56; 95% CI, 0.39–0.80). These results were consistent in reconstructed Kaplan–Meier analyses. In the Bayesian network meta-analysis, different NOACs displayed diverse risk–benefit profiles. Trial sequential analyses suggest that the evidence for the similarity in major adverse cardiac events compared with VKA + DAPT and the bleeding risk reduction observed with NOAC+SAPT is likely to be conclusive.

CONCLUSIONS: NOAC+SAPT does not increase the risk of major adverse cardiac events and reduces the risk of bleeding compared with VKA + DAPT in AF patients undergoing percutaneous coronary intervention. Various NOACs may have different risk–benefit profiles in combination strategies.

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Key Words: acute coronary syndrome ■ anticoagulant therapy ■ antiplatelet therapy ■ antithrombotic therapy ■ atrial fibrillation ■ percutaneous coronary intervention

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CLINICAL PERSPECTIVE

What Is New?

- This meta-analysis of more than 10 000 patients provides robust evidence that the incidence of major adverse cardiac events does not differ between the non–vitamin K antagonist oral anticoagulant + single antiplatelet therapy and the vitamin K antagonist + dual antiplatelet therapy strategies, whereas a non–vitamin K antagonist oral anticoagulant + single antiplatelet therapy strategy reduces bleeding compared with a vitamin K antagonist + dual antiplatelet therapy regimen.

What Are the Clinical Implications?

- A strategy of double antithrombotic therapy with a non–vitamin K antagonist oral anticoagulant + single antiplatelet therapy, with a periprocedural period of aspirin, should be the first-line approach in patients with atrial fibrillation undergoing percutaneous coronary intervention.

Nonstandard Abbreviations and Acronyms

ACS	acute coronary syndrome
AF	atrial fibrillation
CHA_2DS_2-VASc	Congestive heart failure, Hypertension, Age ≥75 years, Diabetes, Prior stroke or transient ischemic attack, Vascular disease, Sex class
DAPT	dual antiplatelet therapy
HAS-BLED	Hypertension, Abnormal liver/renal function, Stroke history, Bleeding history or predisposition, Labile INR, Elderly, Drug/alcohol usage
HR	hazard ratio
MACE	major adverse cardiovascular event
MI	myocardial infarction
NOAC	non–vitamin K antagonist oral anticoagulant
PCI	percutaneous coronary intervention
PROSPERO	International prospective register of systematic reviews
RCT	randomized controlled trial
SAPT	single antiplatelet therapy
ST	stent thrombosis
VKA	vitamin K antagonist

Percutaneous coronary intervention (PCI) is the standard of care for patients with acute coronary syndrome (ACS) and a treatment option for those with stable ischemic heart disease.[1–3] Dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ inhibitor is mandatory after PCI to prevent ischemic events, including stent thrombosis (ST), but this comes at the price of an increased risk of bleeding complications.[4–8] The trade-off of thrombotic and bleeding complications is even more challenging when a patient undergoing PCI has a requirement for long-term oral anticoagulation therapy, such as atrial fibrillation (AF).[9,10] It is estimated that ≈20% to 30% of patients with AF presents with SIHD, and AF coexists in up to 7% to 10% of those undergoing PCI.[11] Because the mechanisms underpinning coronary ischemic events and ST are largely different from those responsible for cardioembolic stroke in patients with AF, both antiplatelet and anticoagulant therapy are indicated in the context of AF-PCI.[2,3,12–14] Unfortunately, the combination of DAPT and oral anticoagulation, also known as triple antithrombotic therapy, is associated with a high rate of fatal and nonfatal bleeding complications.[15]

Although non–vitamin K antagonist oral anticoagulants (NOAC) should be preferred to vitamin K antagonists (VKA) for stroke prevention in patients with AF,[16–19] triple therapy with VKA is still broadly used in clinical practice.[20,21] Four randomized controlled trials (RCTs) conducted in AF patients with ACS and/or undergoing PCI compared double antithrombotic therapy with a NOAC plus single antiplatelet therapy (SAPT) to triple antithrombotic therapy with VKA plus DAPT.[22–25] A post hoc analysis of the 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) trial was also published providing more details on ST for the comparison between NOAC+SAPT and VKA+DAPT.[26] To date, meta-analyses including these trials showed that a NOAC+SAPT strategy significantly reduces the risk of bleeding complications compared with a VKA+DAPT strategy. Cumulatively, there was no apparent greater risk for hard ischemic events but an increase in ST, although the power for such comparisons, even in the setting of a meta-analysis, was limited.[27–34] Importantly, these meta-analyses included data from NOAC+SAPT versus VKA+DAPT for all but the AUGUSTUS trial. For the latter, only data from triple versus double antithrombotic therapy (and not specifically NOAC+SAPT versus VKA+DAPT) were used, causing heterogeneity in the compared groups. It is also noteworthy that the available meta-analyses typically used standard

frequentist methodologies and lacked a Bayesian approach to investigate the relative merits of the different NOAC+SAPT strategies. In addition, the summary estimates were pooled at the study level without taking into account any time-related effect, and no subgroup analyses were performed. Finally, whether the comparison of NOAC+SAPT versus VKA+DAPT regarding bleeding and thrombotic outcomes are conclusive or susceptible to change according to future data remains unclear.

On this background, we conducted an up-to-date comprehensive meta-analysis of AF-PCI trials of NOACs using state-of-the-art frequentist and Bayesian approaches.[35] Specifically, the aims of this meta-analysis were to (1) define the treatment effect of NOAC+SAPT with respect to efficacy and safety in the overall population and in subgroups of interest; (2) illustrate the time-dependent pooled cumulative distribution of events across trials; (3) use a Bayesian approach to rank the merits of different NOAC+SAPT strategies; (4) perform a trial-sequential analysis to define the need for future studies in the field and explore whether the current evidence on efficacy of a NOAC+SAPT regimen is sufficient and conclusive.

METHODS

This meta-analysis is registered in PROSPERO (international prospective register of systematic reviews; CRD42020151089) and was designed according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines (Table S1).[36–38]. Methods used in the analysis, including the search string, are available from the corresponding author to any researcher for purposes of reproducing the results or replicating it.

Study Selection Criteria and Information Sources

For the purpose of the present meta-analysis, RCTs comparing NOAC+SAPT versus VKA+DAPT in patients with AF undergoing PCI were considered. To assess study eligibility and to perform data extraction, 2 authors (M.D.M., A.G.) independently performed a systematic review of the current literature and disagreements were discussed by the whole authorship group. A comprehensive literature exploration was undertaken using PubMed, SCOPUS, and Web of Science as searching tools from inception up to the final search date of February 1, 2020. The following keywords were used to search all the relevant studies: ("AF" or "atrial fibrillation") AND (“coronary stenting” or “coronary angioplasty” or “PCI” or “percutaneous coronary intervention” or “stenting” or “stent” or “drug-eluting stent” or “DES” or “BMS” or “bare metal stent” or “acute coronary syndrome”) AND (“antithrombotic therapy” or “DAPT” or “dual antiplatelet therapy” or “clopidogrel” or “ticagrelor” or “prasugrel” or “P2Y12 inhibitor” or “triple therapy” or “antithrombotic drugs” or “antiplatelets” or "oral anticoagulant" or "VKA" or "NOAC" or “DOAC” or "dabigatran" or "apixaban" or "edoxaban" or "rivaroxaban”). Search terms were combined using the Boolean operators “AND” and “OR.”

Initially, each article of potential interest was screened by reading the title and abstract; subsequently, articles with chances of inclusion underwent a full-text appraisal. Only the studies that met our predefined inclusion criteria were included in the final analysis: (1) RCTs with a comparison between double and triple therapy regimens; (2) study population of AF patients with ACS and/or undergoing PCI either for SIHD or ACS; (3) at least an antithrombotic regimen including a $P2Y_{12}$ inhibitor in association with a NOAC at a standard or reduced dose approved for prevention of cardioembolic stroke; (4) reported major bleeding and major adverse cardiovascular event (MACE) according to validated definitions; (5) follow-up period of at least 6 months. No language or publication date restrictions were applied. In addition, the reference lists of prior systematic reviews and meta-analyses were screened to find further potentially relevant studies, but no additional trials meeting our inclusion criteria called for attention.

Outcome Measures

The primary efficacy outcome was the composite of trial-defined MACE (Table S2), which was usually defined as a combination of either all-cause or cardiovascular death, myocardial infarction (MI), stroke, and ST. Secondary efficacy outcomes were the individual components of the primary efficacy outcome.

The primary safety outcome was trial-defined clinically significant bleeding (Table S3), typically the composite of major bleeding or clinically relevant nonmajor bleeding (Table S2). Secondary safety outcomes were major bleeding (according to the Thrombolysis in Myocardial Infarction or the International Society on Thrombosis and Haemostasis criteria) clinically relevant nonmajor bleeding, and intracranial haemorrhage.

Quality Assessment and Publication Bias

Two independent reviewers (M.D.M., A.G.) performed the trial-level qualitative assessment using the 7-domain Cochrane Collaboration tool. The risk of bias was classified as high, low or unclear. We assessed the reliability of the results for each outcome according to Grading of Recommendations, Assessment, Development and Evaluation (GRADE) approach.[38,39] Funnel plots for both the primary outcomes were

used to evaluate the presence of publication bias, heterogeneity of studies, or data irregularities. The significance of asymmetry was explored using visual inspection and tested by a rank correlation test based on Kendall's τ.[40]

Statistical Analysis

Full details about the statistical methodology are given in Data S1. In brief, trial-level and pooled estimates are reported as event rates (per 100 patient-years), hazard ratios (HRs), and 95% CIs. Both fixed-effects and random-effects were used in pairwise meta-analyses first. Heterogeneity was assessed using I^2 statistics and Cochran's Q tests. Subgroups analyses were performed to investigate the consistency of the effect sizes across subsets of interest. Reconstructed Kaplan–Meier analyses were performed extracting survival data from the published Kaplan–Meier curves of each study using the WebPlotDigitizer software[41] (4.2 version) and combining them. Landmark analyses at 30 and 180 days were performed for the primary bleeding end point. A network meta-analysis was fitted to simultaneously compare and rank multiple regimens. For the purpose of the network meta-analysis, we used the Bayesian approach, with noninformative priors, which is a conservative and commonly used method. Furthermore, the state of the current evidence was tested through the trial sequential analyses. A sensitivity analysis was performed with leave-one-out method; this technique consists in reanalyzing the results after removing each of the trials included, in order to verify whether the main result is influenced by a particular trial.

RESULTS

The preliminary search yielded a total of 2698 articles, reduced to 1567 after duplicates removal. After title and abstract screening, 1561 articles were excluded. The remaining 6 articles were read full text and 4 were found to be eligible for inclusion in our meta-analysis: PIONEER AF-PCI[22] (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[23] (Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran versus Triple Therapy with Warfarin in Patients with Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention), AUGUSTUS,[24] and ENTRUST-AF PCI[25] (Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention). The flow diagram of the study selection process is shown in Figure S1. The trials' design and inclusion/exclusion criteria are summarized in Tables S2 and S4 and Figure S2. The follow-up ranged from 6 months (AUGUSTUS) to a mean of 14 months (RE-DUAL PCI). One of the arms in PIONEER AF-PCI was excluded because it used DAPT in addition to a very low dose (2.5 mg bid) of rivaroxaban, which is not approved for cardioembolic risk prevention in AF and not endorsed by any guideline or consensus recommendation. Because AUGUSTUS had a factorial randomization (double versus triple therapy and apixaban versus VKA), for the purpose of this meta-analysis and consistency with the other trials, we prioritized comparative data of apixaban+SAPT and VKA+DAPT, if available. Where only data concerning double versus triple therapy regimens were available (ie, for patient baseline characteristics and the subgroup analyses of primary end points), the same were used, as detailed later.

A total of 10 969 patients were included in the 4 trials. The baseline characteristics of the study populations are reported in Table S5. The mean age ranged between 69.9 and 70.8 years. Male sex represented between 71.0% (AUGUSTUS) and 76.0% (RE-DUAL PCI) of patients. The overall prevalence of ACS ranged from 50.5% (AUGUSTUS) to 60.9% (RE-DUAL PCI) and all patients underwent PCI (except in AUGUSTUS, where 23.9% of cases were medically managed ACS). The mean time in the therapeutic range among patients in the warfarin groups varied from 58.6% (AUGUSTUS) to 65% (PIONEER AF-PCI). The prevalence of various comorbidities was relatively high, as well as the thromboembolic and bleeding risks, with a mild degree of variation among RCTs (CHA_2DS_2-VASc [Congestive heart failure, Hypertension, Age ≥75 years, Diabetes, Prior stroke or transient ischemic attack, Vascular disease, Sex class] from 3.8–4.0 and HAS-BLED [Hypertension, Abnormal liver/renal function, Stroke history, Bleeding history or predisposition, Labile INR, Elderly, Drug/alcohol usage] from 2.8–3.0). Clopidogrel was administered in 90.8% of patients, ticagrelor was used in 7.0%, and prasugrel in 0.8% of cases. In all the trials, aspirin was used in the peri-PCI period potentially allowing for a period of triple therapy before randomization (mean time to randomization 1.9–6.6 days, with minimum 1 day and maximum 14 days).

Primary Efficacy Outcome

The incidences of MACE are plotted in the Figure 1 and Figure S3. No significant differences were found in MACE between the NOAC+SAPT and VKA+DAPT strategies, both by random-effects (HR, 1.07; 95% CI, 0.94–1.22) and by fixed-effects (HR, 1.07; 95%

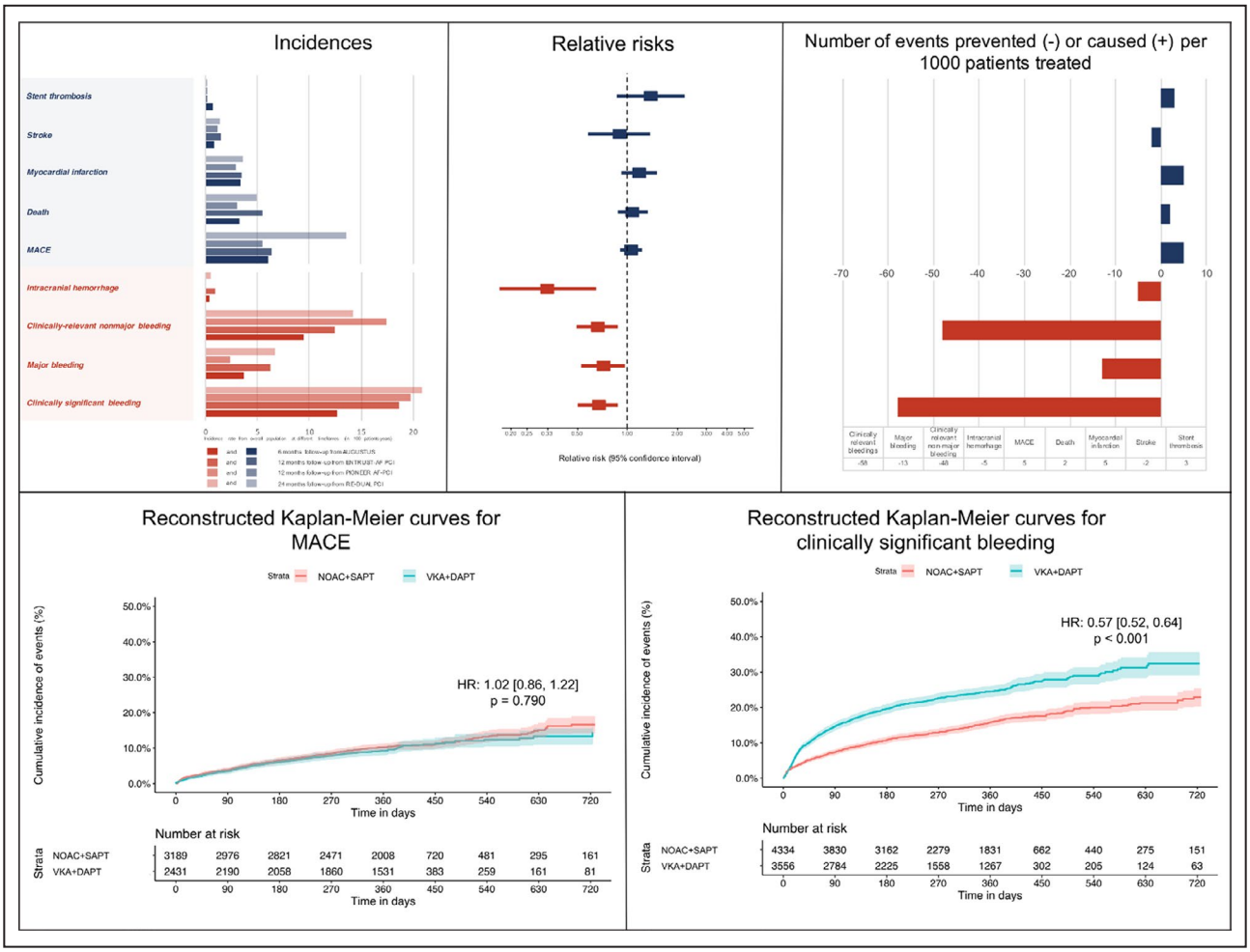

Figure 1. Incidences (%) of efficacy and safety outcomes (upper left panel), respective effects of NOAC+SAPT regimens vs VKA+DAPT (forest plot in the upper central panel), and number of events prevented or caused per 100 patients treated (upper right panel). In the bottom left (for MACE) and right (for clinically significant bleeding) panels, the reconstructed Kaplan–Meier curves represent the probability of events in the 2 strategy groups of the population included in all the trials. AUGUSTUS indicates 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 vs Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention; HR, hazard ratio (CI between squared brackets); 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-DUAL PCI, Evaluation of Dual Therapy With Dabigatran vs Triple Therapy With Warfarin in Patients With AF That Undergo a PCI With Stenting; SAPT, single antiplatelet therapy; and VKA, vitamin K antagonist.

CI, 0.94–1.22) models (Figure 2A).[22–25] The RE-DUAL PCI trial had the highest relative weight. There was no evidence of heterogeneity (I^2=0%, P=0.60 in the fixed-effects model). At the reconstructed Kaplan–Meier analysis, the AUGUSTUS trial could not be included because the survival curve for this end point was not reported in the trial. The reconstructed Kaplan–Meier analysis from the other 3 trials showed the overlap between the event-free survival curves of the 2 treatments over time (Figure 1), with an event rate of 10.6 and 9.8 per 100 patient-years, respectively. The number of MACE caused per 1000 patients treated with NOAC+SAPT versus VKA+DAPT was 5 (Figure 1). The sensitivity analysis demonstrated that the result was not affected by any specific trial (Table S6). The trial sequential analysis demonstrated that in light of the available data, significant differences in terms of MACE between the NOAC+SAPT and VKA+DAPT regimens are not likely to occur because the Z-values line was in the area of futility (Figure 3A). Thus, even though the required sample size was not achieved, it is unlikely that any eventual future study could demonstrate a significant difference in term of MACE between the 2 treatments.

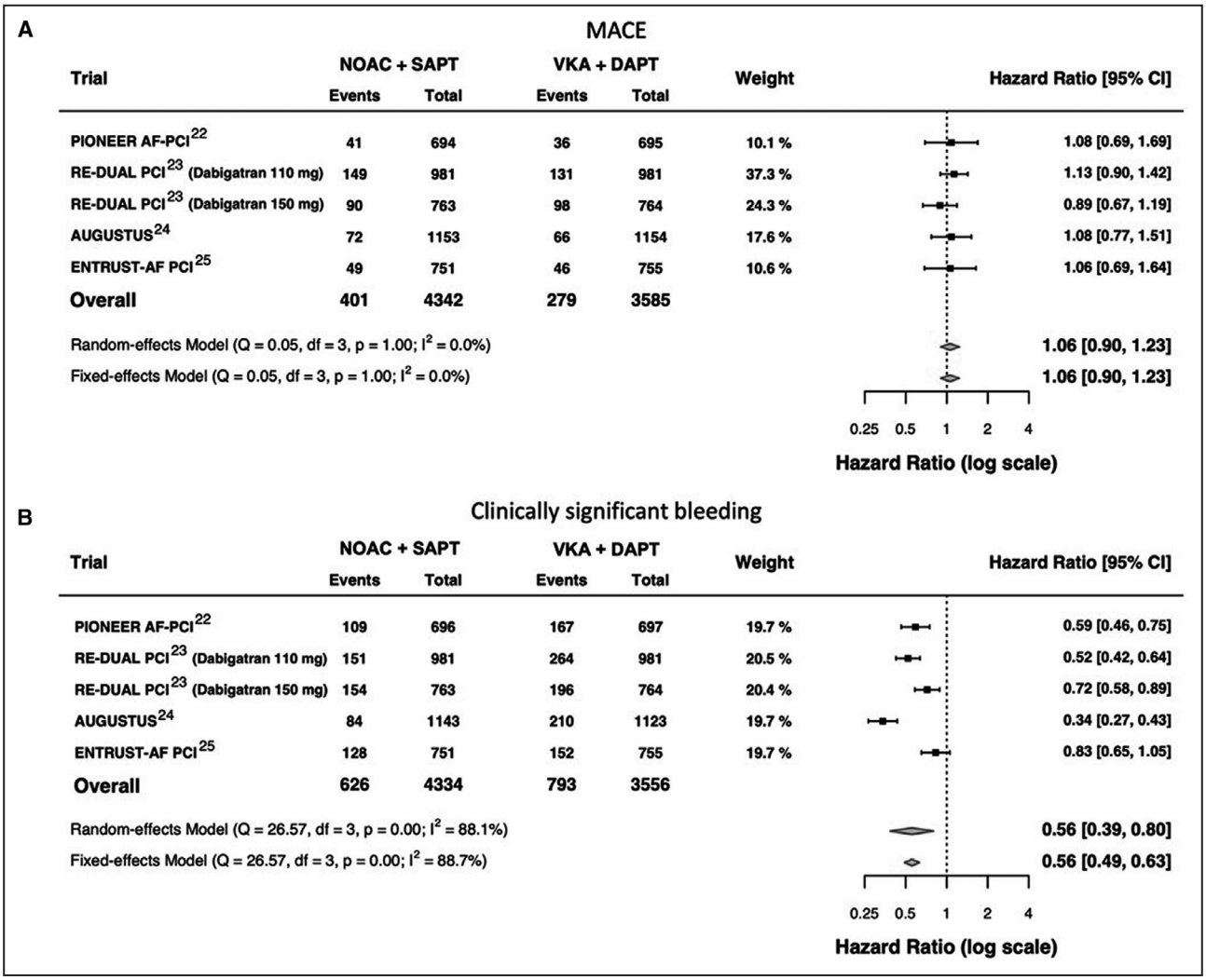

Figure 2. Forest plot for MACE (A) and clinically significant bleeding (B) end points.
In the analysis of the overall population, the number of the patients included in DAPT+VKA arms of the RE-DUAL PCI trial were not summed because the group of 764 patients compared with dabigatran 110 mg were a subset of the group of 981 patients compared with dabigatran 150 mg. Thus, only a total of 981 patients were included in the overall analysis. AUGUSTUS indicates 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; df, degrees of freedom; ENTRUST-AF PCI, Edoxaban Treatment vs Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention; 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; Q, Cochran's Q test; RE-DUAL PCI, Evaluation of Dual Therapy With Dabigatran vs Triple Therapy With Warfarin in Patients With AF That Undergo a PCI With Stenting; SAPT, Single Antiplatelet Therapy; TAT, triple antithrombotic therapy; and VKA, vitamin K antagonist.

The subgroup analysis showed that the effect was consistent in all the investigated subsets of patients, without significant interaction with the main baseline variables (Figures S4–S9).

At the Bayesian network meta-analysis, the following 6 treatments were compared: DAPT plus VKA, apixaban 5 mg plus $P2Y_{12}$ inhibitor, dabigatran 110 mg plus $P2Y_{12}$ inhibitor, dabigatran 150 mg plus $P2Y_{12}$ inhibitor, rivaroxaban 15 mg plus $P2Y_{12}$ inhibitor, and edoxaban 60 mg plus $P2Y_{12}$ inhibitor. The network of treatment regimens used in the analysis is displayed in Figure 4. Pairwise comparisons for the primary efficacy end point among regimens are displayed in the Table for the fixed effect model and in Table S7 for the random-effects model. There was no significant difference between the NOAC+SAPT and VKA+DAPT regimens in terms of MACE. All NOAC+SAPT regimens were similar to each other. The treatment ranking is represented in Figure 5A and in Figure S10 for the fixed-effect model and in

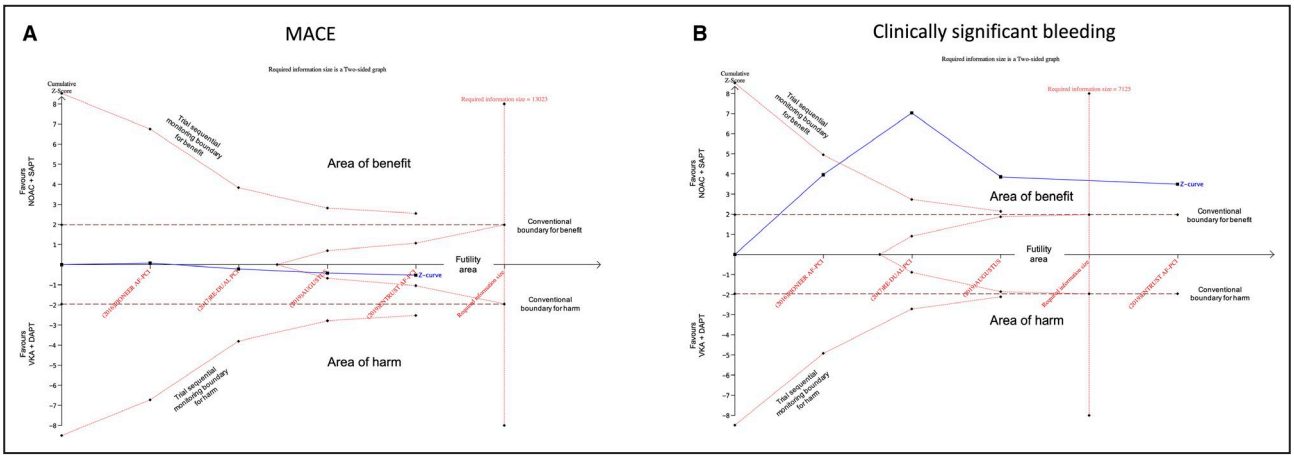

Figure 3. Trial sequential analysis for MACE (A) and clinically significant bleeding (B) end points.
The vertical red dotted line represents required information size (ie, the number of patients required) to definitely demonstrate the risk difference (alpha 5%, power 80%). The horizontal axis represents the number of patients included in the meta-analysis and is linear scaled, hence the distance of a new trial from the previous one on the axis represents the new trial population. The vertical axis represents the cumulative *z*-score. The red dotted lines represent the trial sequential monitoring boundaries (inward sloping) and the futility boundaries (outward sloping). The solid blue line represents the cumulative z-curve. According to the trial sequential analysis methodology, crossing the monitoring boundaries for the z-curve indicates a clinically meaningful effect of a specific intervention that is also supported by statistical significance; crossing the required information size line indicates that the evidence is conclusive, whereas being in the futility area suggest that the effect size is neither clinically nor statistically meaningful and it is improbable that with further trials the cumulative evidence could demonstrate a significance in the effect size. In panel A, the required information size to demonstrate or reject a 35% relative risk reduction with an incidence in the control group of 22.6% is 7125 patients (required information size line). With the ENTRUST AF-PCI trial the z-curve crossed the required information size line. In panel B, the required information size to demonstrate or reject a 20% relative risk reduction with an incidence in the control group of 7% is 13 023 patients. With the AUGUSTUS and ENTRUST AF-PCI trial the z-curve entered the futility area. AUGUSTUS indicates 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 vs Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention; MACE, major adverse cardiovascular event; NOAC, non–vitamin K antagonist oral anticoagulant; SAPT, single antiplatelet therapy; and VKA, vitamin K antagonist.

Figures S11A and S12 for the random-effects model, respectively.

Primary Safety Outcome

The incidences of clinically significant bleedings are plotted in the Figure 1 and Figure S13. All NOAC+SAPT strategies (except edoxaban+SAPT) showed a significantly lower rate of clinically significant bleeding compared with VKA+DAPT, with a significant pooled effect both by random-effects (HR, 0.56; 95% CI, 0.39–0.80) and by fixed-effects (HR, 0.56; 95% CI, 0.49–0.63) models (Figure 2B). The RE-DUAL PCI trial had the highest relative weights. There was a significant degree of heterogeneity (I^2=88.7%, P<0.01 in the fixed-effects model). Reconstructed Kaplan–Meier analysis confirmed the significant lower rate of clinically significant bleedings in the NOAC+SAPT versus VKA+DAPT groups over time and showed early separation of the curves within the first 6 months (Figure 1). The event rates were 17.8 per 100 patient-years in the NOAC+SAPT group and 32.8 per 100 patient-years in the VKA+DAPT group. The number of clinically significant bleedings prevented per 1000 patients treated with NOAC+SAPT versus VKA+DAPT was 58 (Figure 1), with a number needed to treat to avoid an event of 17 patients. Based on landmark analyses, most of the bleeding reduction was concentrated in the first 6 months; after this time frame no significant further effect was detected until 720 days (Figure S14). The sensitivity analysis demonstrated that the result was not affected by any specific trial (Table S6). The trial sequential analysis demonstrated that the results provided from the available data were in favor of NOAC+SAPT (versus VKA+DAPT) and conclusive, because the Z-values line was in the area of significant benefit and the required sample size was achieved (Figure 3B). Subgroup analyses showed that the effect size was consistent in different subsets of patients, including male or female, elderly or nonelderly, SIHD or ACS, high or low thromboembolic risk as defined by the CHA_2DS_2-VASc score, and high or low bleeding risk as defined by the HAS-BLED score, without any significant interaction with the explored baseline variables (Figures S4 through S9).

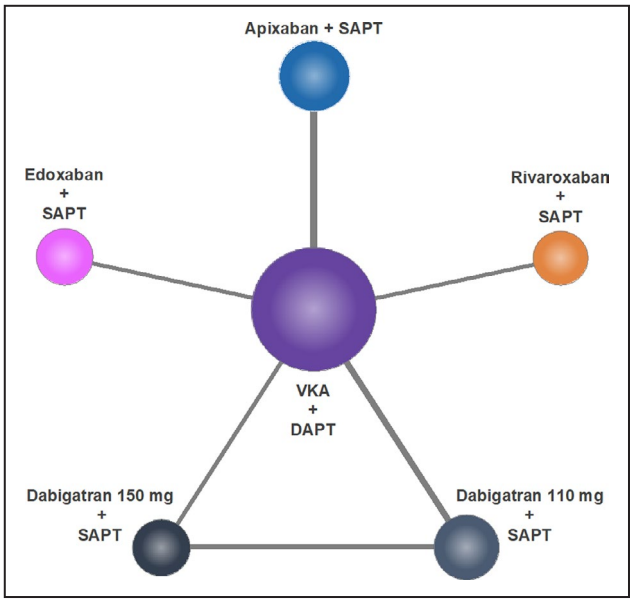

Figure 4. Network of treatments.
DAPT indicates dual antiplatelet therapy; SAPT, single antiplatelet therapy; and VKA, vitamin K antagonist.

At the Bayesian meta-analysis, the network of treatment regimens compared was the same of the primary efficacy end point (Figure 4). Pairwise comparisons for the primary safety end point among regimens are displayed in Table 1 for the fixed-effects model and in Table S7 for the random-effects model. Consistently with the frequentist approach, the NOAC+SAPT regimens resulted in a lower rate of the primary safety end point when compared with VKA+DAPT. Among NOAC+SAPT regimens, the one with apixaban demonstrated a lower risk of the primary bleeding end point. However, all these findings were no longer significant using the random-effects model. The treatment ranking is represented in Figure 5B and in Figure S10A for the fixed-effects model and in Figures S11 and S12 for the random-effects model, respectively.

Bivariate End Point and Secondary Outcomes

A plot with a bivariate outcome is presented in Figure 6. In this plot, the primary efficacy and safety end points are plotted together, visually confirming that despite a similar effect on the primary ischemic end point as compared with VKA+DAPT, the tendency toward a reduction in the primary safety end point is heterogeneous, with a more pronounced effect for apixaban+SAPT and a more modest effect for edoxaban+SAPT.

The incidences of secondary end points are plotted in the Figure 1 and Figures S3 and S13. The forest plots for secondary outcomes are displayed in Figures 7 and 8.[22–25] Among single components of MACE, data on apixaban+SAPT and VKA+DAPT were not uniformly available for stroke and MI end points

Table. Relative Effect Tables for MACE and Clinically Significant Bleeding End Points From Fixed Effect Model Analysis

		Apixaban+ SAPT	Dabigatran 110 mg+SAPT	Dabigatran 150 mg+SAPT	Edoxaban+ SAPT	Rivaroxaban+ SAPT	VKA+ DAPT
MACE	Apixaban+SAPT	…	1.05 (0.7, 1.58)	0.81 (0.53, 1.24)	0.98 (0.58, 1.66)	0.94 (0.55, 1.59)	0.92 (0.66, 1.29)
	Dabigatran 110 mg+SAPT	0.95 (0.63, 1.43)	…	0.78 (0.6, 1)	0.93 (0.59, 1.48)	0.89 (0.56, 1.44)	0.88 (0.7, 1.11)
	Dabigatran 150 mg+SAPT	1.23 (0.8, 1.89)	1.29 (1, 1.68)	…	1.2 (0.74, 1.96)	1.15 (0.71, 1.89)	1.14 (0.87, 1.49)
	Edoxaban+SAPT	1.03 (0.6, 1.73)	1.07 (0.67, 1.71)	0.83 (0.51, 1.35)	…	0.96 (0.54, 1.7)	0.95 (0.63, 1.41)
	Rivaroxaban+SAPT	1.07 (0.63, 1.82)	1.12 (0.7, 1.8)	0.87 (0.53, 1.42)	1.04 (0.59, 1.86)	…	0.99 (0.65, 1.49)
	VKA+DAPT	1.08 (0.77, 1.51)	1.13 (0.9, 1.44)	0.88 (0.67, 1.15)	1.06 (0.71, 1.58)	1.01 (0.67, 1.53)	…
Clinically significant bleeding	Apixaban+SAPT	…	1.68 (1.22, 2.32)	2.2 (1.6, 3.04)	2.38 (1.69, 3.38)	1.84 (1.3, 2.61)	2.92 (2.29, 3.78)
	Dabigatran 110 mg+SAPT	0.6 (0.43, 0.82)	…	1.31 (1.05, 1.65)	1.42 (1.04, 1.95)	1.1 (0.8, 1.5)	1.75 (1.43, 2.14)
	Dabigatran 150 mg+SAPT	0.46 (0.33, 0.62)	0.76 (0.61, 0.95)	…	1.08 (0.79, 1.48)	0.84 (0.61, 1.14)	1.33 (1.09, 1.62)
	Edoxaban+SAPT	0.42 (0.3, 0.59)	0.7 (0.51, 0.96)	0.92 (0.68, 1.26)	…	0.77 (0.55, 1.09)	1.23 (0.96, 1.57)
	Rivaroxaban+SAPT	0.54 (0.38, 0.77)	0.91 (0.67, 1.25)	1.2 (0.88, 1.64)	1.29 (0.92, 1.83)	…	1.59 (1.25, 2.03)
	VKA+DAPT	0.34 (0.26, 0.44)	0.57 (0.47, 0.7)	0.75 (0.62, 0.91)	0.81 (0.64, 1.04)	0.63 (0.49, 0.8)	…

DAPT indicates dual antiplatelet therapy; MACE, major adverse clinical event; SAPT, single antiplatelet therapy; VKA, vitamin K antagonist.

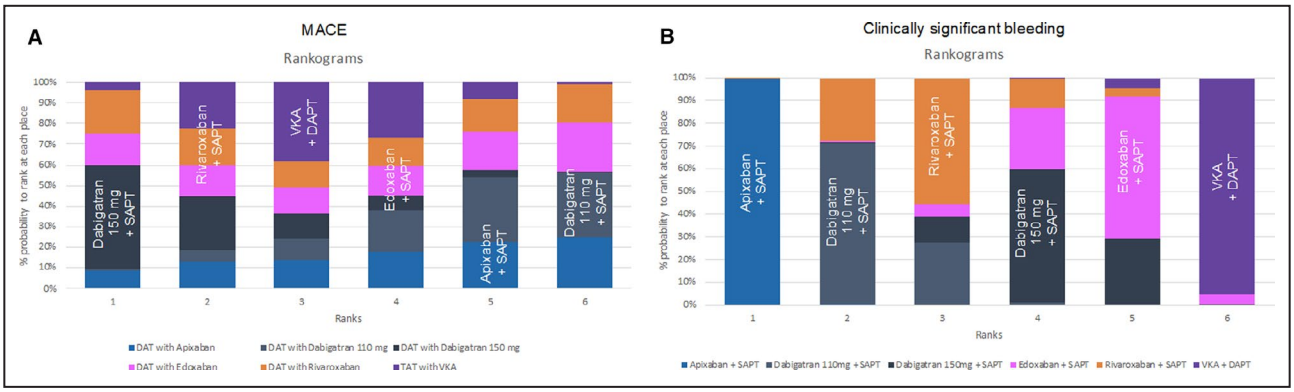

Figure 5. Rankograms according to fixed-effects model analysis for MACE (A) and clinically significant bleeding (B) end points.
In these rankograms, the probability to be ranked in each position (from the first in the left to the sixth in the right) is plotted for all NOAC+SAPT strategies. DAPT indicates dual antiplatelet therapy; MACE, major adverse clinical event; NOAC, non–vitamin K antagonist oral anticoagulant; SAPT, single antiplatelet therapy; and VKA, vitamin K antagonist.

in the AUGUSTUS trial. Thus, for death and ST, the apixaban+SAPT and VKA+DAPT groups where used, whereas the entire double and triple therapy groups were considered for stroke and MI. No significant difference in terms of death (HR, 1.07; 95% CI, 0.87–1.33), stroke (HR, 0.89; 95% CI, 0.58–1.36), MI (HR, 1.18; 95% CI, 0.92–1.52) and ST (HR, 1.38; 95% CI, 0.86–2.20) were detected between the 2 groups. All NOAC+SAPT strategies showed a lower incidence of major bleeding (HR, 0.71; 95% CI, 0.53–0.97), clinically relevant nonmajor bleeding (HR, 0.66; 95% CI, 0.49–0.88), and intracranial haemorrhage (HR, 0.46; 95% CI, 0.22–0.98) compared with the VKA+DAPT strategy. The numbers of events prevented or caused per 1000 patients treated, for all the secondary end points, are plotted in the Figure 1. The sensitivity analysis for secondary end points is shown in Table S8, again showing substantial consistency in treatment effects.

Quality Assessment and Publication Bias

The judgments of the risk of bias for every single study and as percentages across all included studies are reported in Figures S15 and S16, respectively. Visual inspection of funnel plots and the rank correlation test showed the absence of significant asymmetry both for MACE and clinically significant bleeding end points (Kendall's tau: −0.67 and 0.33, *P*: 0.333 and 0.750, respectively; Figure S17).

DISCUSSION

The main findings of the present meta-analysis, including 4 RCTs, are as follows. First, in patients undergoing PCI, the incidence of trial-defined MACE is not different between the NOAC+SAPT and the VKA+DAPT strategies, a finding unlikely to change with hypothetical further trials. Second, a NOAC+SAPT strategy reduces bleeding by 44% compared with a VKA+DAPT regimen, and this evidence can be considered conclusive. This finding is quantitatively heterogeneous as the result of the different magnitudes of treatment effect detected in the 4 trials, with AUGUSTUS showing the largest bleeding risk reduction in the apixaban+SAPT arm.

In patients with AF undergoing PCI, the general goal of antithrombotic therapy should be to minimize both the coronary ischemic risk due to PCI (with antiplatelet drugs) and the cerebral and systemic thromboembolic risk due to AF (with anticoagulant drugs). The other side of the coin is to limit the increased risk of bleeding associated with stacking of multiple antithrombotic drugs. Although the prevalence of AF-PCI is relatively low (about 7%–10%), this proportion may vary across geographies and is likely to increase in the future as the consequence of more elderly patients being offered PCI and the availability of more sensitive methods to make diagnosis of AF.[11] In the WOEST (What is the Optimal Antiplatelet & Anticoagulant Therapy in Patients With Oral Anticoagulation and Coronary Stenting) and ISAR-TRIPLE (Triple Therapy in Patients on Oral Anticoagulation After Drug Eluting Stent Implantation) trials, simplification of the reference VKA+DAPT strategy was attempted by aspirin withdrawal or shortening DAPT duration by stopping clopidogrel, respectively.[42,43] In the WOEST trial, double antithrombotic therapy with clopidogrel was associated with a significant reduction in bleeding complications and no increase in the rate of thrombotic events compared with triple therapy.[42] In the ISAR-TRIPLE trial, the primary end point, comprising a combination of ischemic and bleeding events, did not differ at 9 months between the two groups; in a landmark analysis of events between 6 weeks and

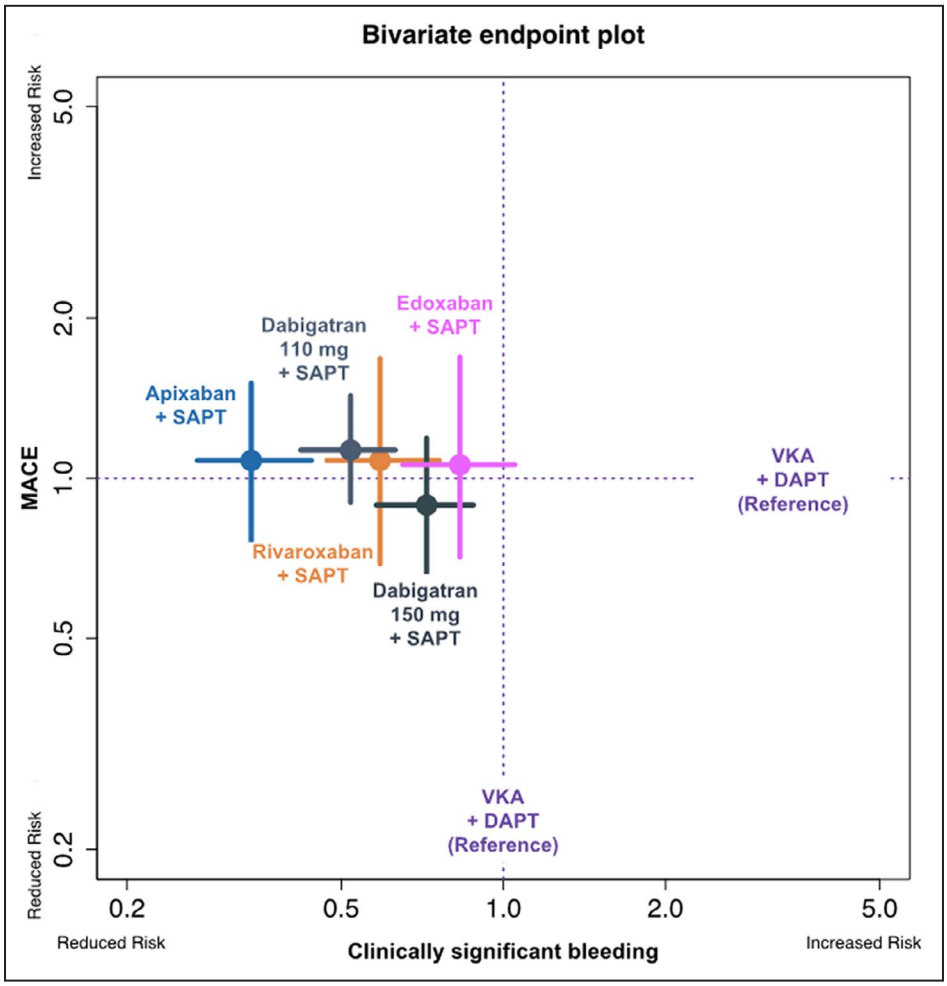

Figure 6. Bivariate end point plot for clinically significant bleeding and MACE end points. In this plot, the relative effects of different NOAC+SAPT regimens vs VKA+DAPT (set as reference, dotted lines) both in terms of MACE (vertical axis) and clinically significant bleeding (horizontal axis) are contemporary plotted. The colored points indicate the hazard ratios, whereas the colored lines indicate the CIs. DAPT indicates dual antiplatelet therapy; MACE, major adverse clinical event; NOAC, non–vitamin K antagonist oral anticoagulant; SAPT, single antiplatelet therapy; and VKA, vitamin K antagonist.

6 months, the risk of bleeding was higher in the group where clopidogrel was used longer (for 6 months), supporting the safety benefit of double versus triple antithrombotic therapy.[43] Importantly, both WOEST and ISAR-TRIPLE were relatively small and underpowered to detect significant differences in ischemic end points. Recently, the SAFE-A (Safety and Effectiveness Trial of Apixaban Use in Association with Dual Antiplatelet Therapy in Atrial Fibrillation Patients Undergoing Percutaneous Coronary Intervention) study compared 1- to 6-month $P2Y_{12}$ inhibitor-therapy on top of aspirin and apixaban in patients with AF who undergo PCI in terms of bleeding: the trial had not enough statistical power because it was prematurely terminated due to slow enrolment.[44]

Subsequently, the PIONEER AF-PCI and RE-DUAL PCI trials demonstrated that a NOAC+SAPT regimen (rivaroxaban 15 mg and dabigatran 110/150 mg, respectively) reduced clinically significant bleedings against VKA+DAPT, without any significant increase in ischemic events.[22,23] Interestingly, the design of both trials does not allow us to discriminate the effect of NOAC versus VKA from the effect of double versus triple therapy. The AUGUSTUS trial, with its 2×2 factorial design, demonstrated both a superiority of the double versus triple therapy and of the apixaban versus VKA regimens in terms of clinically significant bleedings, without significant differences in the incidence of ischemic events.[24] Closing the quartet of trials, the ENTRUST-AF PCI trial recently demonstrated the noninferiority (but not the superiority) of edoxaban+SAPT against VKA+DAPT in terms of significant bleedings, without significant differences in ischemic events.[25] It should be noted that none of these trials was powered for the ischemic end point. Interestingly, in

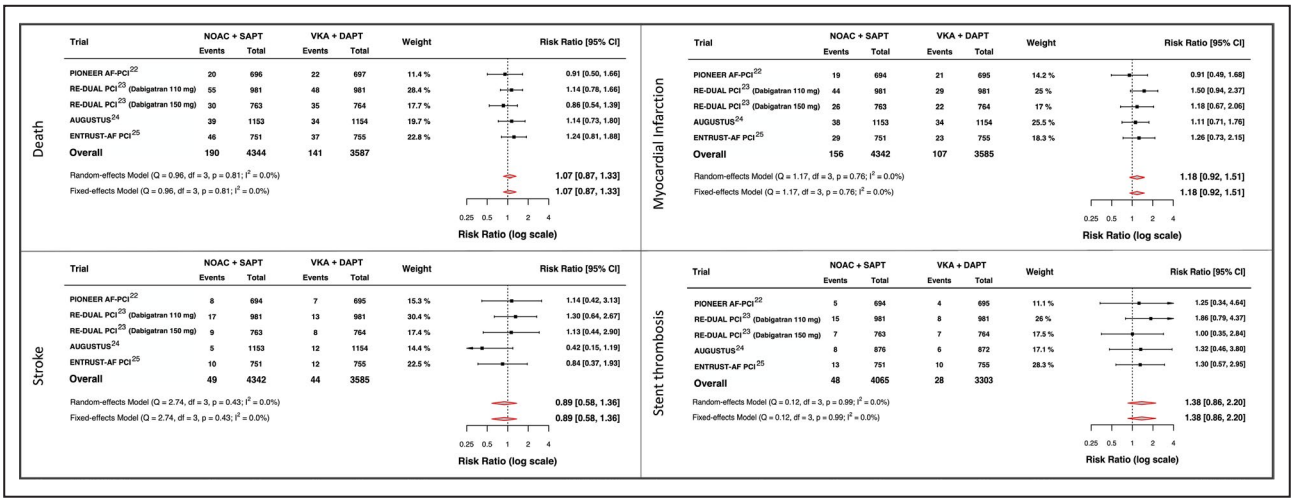

Figure 7. Forest plots for single components of MACEs.
Stent thrombosis was definite plus probable in AUGUSTUS and ENTRUST-AF PCI, definite only in RE-DUAL PCI, and it was not specified in PIONEER AF-PCI. AUGUSTUS indicates A Study of Apixaban in Patients With Atrial Fibrillation, Not Caused by a Heart 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; df, degrees of freedom; ENTRUST-AF PCI, Edoxaban Treatment vs Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention; 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; Q, Cochran's Q test; RE-DUAL PCI, Evaluation of Dual Therapy With Dabigatran vs Triple Therapy With Warfarin in Patients With AF That Undergo a PCI With Stenting; SAPT, single antiplatelet therapy; and VKA, vitamin K antagonist.

these trials, being the randomization performed several days after the index PCI, nearly all the patients likely had aspirin (hence some brief duration of triple therapy) before randomization.

The recent 2019 European Society of Cardiology guidelines on chronic coronary syndromes recommend a NOAC in preference to VKA for combination with antiplatelet therapy in patients with AF who are eligible for a NOAC (class of recommendation I). Moreover, an early cessation (≤1 week) of aspirin and continuation of double antithrombotic therapy with an oral anticoagulant and clopidogrel should be considered if the risk of ST is low or if concerns about bleeding risk prevail over the risk of ST (class of recommendation IIa).[3] On the other hand, the same class of recommendation is given for aspirin continuation up to 6 months in patients where the risk of thrombotic complications is perceived as higher than the risk of bleeding. As such, the European perspective so far is to consider both the double and triple antithrombotic therapy strategies as viable approaches to be selected depending on net benefit considerations. This is different from the North American approach, which currently recommends double therapy as the default strategy, with the triple therapy strategy restricted to very selected patients at high ischemic and low bleeding risk.[10]

Our meta-analysis confirms that a NOAC+SAPT strategy, implemented after a brief period of aspirin in the peri-PCI period does not significantly increase the combined ischemic risk and is safer than VKA+DAPT with respect to major or clinically relevant nonmajor bleedings. The trial sequential analyses suggested that further trials are not required both for primary efficacy (because it is improbable that the cumulative evidence could become clinically and statistically significant) and primary safety end points (because the required sample size to demonstrate the superiority is already achieved).

Recently, an analysis from the AUGUSTUS trial demonstrated nonsignificantly higher ST rates with placebo compared to aspirin among patients with AF with recent PCI.[26] However, it is also important to note that the overall incidence of ST was low and mostly occurring early after PCI. Importantly, in this sub-analysis, data regarding apixaban+SAPT and VKA+DAPT regimens were disclosed. Furthermore, a previous meta-analysis revealed a significant increase in the risk of ST with aspirin discontinuation compared with VKA+DAPT.[45] This evidence was not clearly visible in the 4 trials taken individually given that they were underpowered for this end point. The results of our analysis are slightly different from previous meta-analysis given that the difference in ST rates were nonsignificant (HR, 1.38; 95% CI, 0.86–2.20). This difference becomes even weaker after removing the dabigatran 110 mg arm at the sensitivity analysis (HR, 1.22; 95% CI, 0.74–2.03).[3,45,46] This is attributable to the availability of new data from AUGUSTUS, comparing the NOAC+SAPT versus VKA+DAPT groups similar to others trials, which were not included in other meta-analyses.

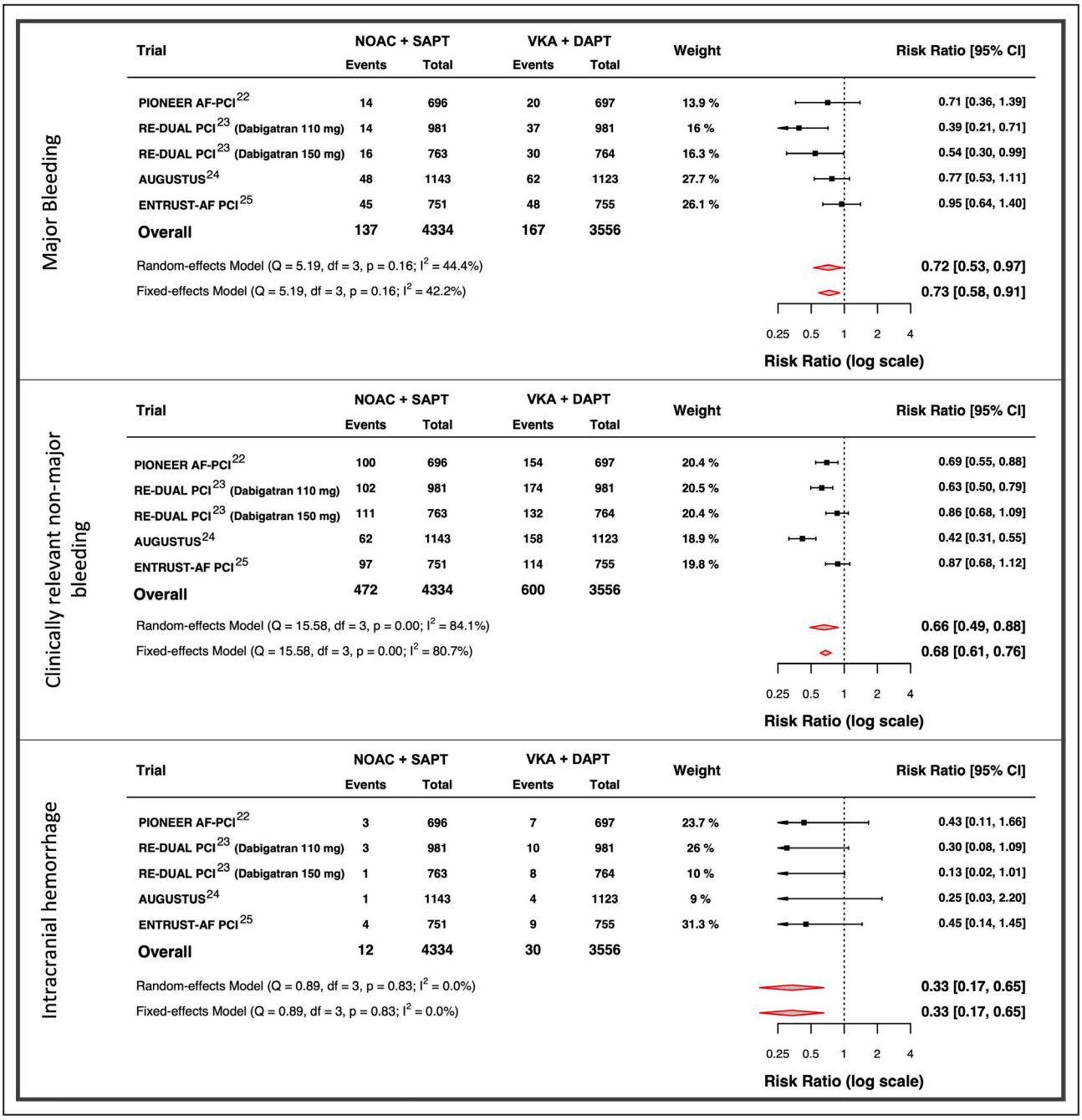

Figure 8. Forest plots for secondary bleedings end points.
AUGUSTUS indicates A Study of Apixaban in Patients With Atrial Fibrillation, Not Caused by a Heart Valve Problem, Who Are at Risk for Thrombosis (Blood Clots) Due to Having Had a Recent Coronary Event, Such as a Heart Attack or a Procedure to Open the Vessels of the Heart; DAPT, dual antiplatelet therapy; df, degrees of freedom; ENTRUST-AF PCI, Edoxaban Treatment vs Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention; 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; Q, Cochran's Q test; RE-DUAL PCI, Evaluation of Dual Therapy With Dabigatran vs Triple Therapy With Warfarin in Patients With AF That Undergo a PCI With Stenting; SAPT, single antiplatelet therapy; and VKA, vitamin K antagonist.

The pooled analysis with reconstructed patient-level data corroborates the evidence from the trial-level meta-analyses and gives insights on the distribution of the bleeding reduction with NOAC+SAPT. Understandably, bleeding was mostly reduced during the first 6 months, when the proportion of triple therapy patients in the control group was higher than in the subsequent period. Trial-level subgroup analyses

demonstrated that the effect of NOAC+SAPT versus VKA+DAPT was consistent in different settings, including presence or absence of ACS. Moreover, the trial sequential analyses demonstrated that the evidence about the absence of significant differences in the composite ischemic outcome, even though not conclusive, are not likely to change with further studies and those supporting the superiority in terms of clinically significant bleedings of NOAC+SAPT against VKA+DAPT could be considered conclusive. These results strengthen new guidelines recommendations.

About antiplatelet drugs selection, the 2019 European Society of Cardiology Chronic Coronary Syndromes guidelines recommend (class IIb) that double therapy with more potent $P2Y_{12}$ inhibitors may be considered as an alternative to triple therapy with clopidogrel in patients with a moderate or high risk of ST.[3] A North American consensus document indicates that ticagrelor, but not prasugrel, may be considered in patients at high thrombotic but low bleeding risk and only in the context of a double therapy regimen.[10] Our subgroup analysis showed that the kind of $P2Y_{12}$ inhibitor did not affect significantly the efficacy and the safety of NOAC+SAPT against VKA+DAPT. However, only 7.4% of patients were treated with more potent antiplatelet drugs; this justifies the weak recommendation of ticagrelor and prasugrel from the guidelines and its limitation (due to their known stronger antiplatelet effect) to patients with higher risk of ST. Studies are warranted to better understand the safety and efficacy profiles of prasugrel and ticagrelor in a NOAC+SAPT regimen.

Finally, the risk–benefit profiles of various NOACs have been previously analyzed in patients with AF with heterogeneous results in different settings.[47–51] In our meta-analysis, heterogeneity among different trials in the reduction of clinically significant bleeding risk could reflect a difference in individual NOACs profile. The Bayesian network meta-analysis, indirectly comparing various NOACs in double therapy regimens, revealed a trend toward a better bleeding profile of apixaban against other NOACs, which was significant in the fixed-effects model but not significant in the random-effects model. These results should be interpreted with caution. In fact, various confounders (primarily the trial design) could affect this analysis. On the other hand, these data could suggest that beyond a strategy effect (double versus triple therapy) and a class effect (NOAC versus VKA), a specific drug effect could be hypothesized. On the basis of these and other previous evidence, further investigation comparing different NOACs may be justified to directly assess the different risk–benefit profiles of all NOACs in order to select the appropriate drug for each patient rather than attempting to identify the best in class for all patients.

Some limitations of this meta-analysis should be acknowledged, which are in common with other meta-analyses. The different characteristics of the trials included could generate a certain degree of heterogeneity that cannot be adequately controlled for. These differences include the timing from the index event to randomization, inclusion and exclusion criteria, patients' characteristics, time in therapeutic range in VKA group, treatment protocol, length of treatment/follow-up, and definition of end points. This heterogeneity could potentially also affect the indirect comparisons at the network analysis. In particular, in two out of the four included trials, the MACE definition included revascularization (which is a softer end point compared with cardiovascular death, MI, stroke or ST). Notwithstanding this limitation, the heterogeneity for the MACE outcome was 0% in the fixed-effects model.

Another potential caveat is that, according to the PIONEER AF-PCI trial design, we included in our analyses data on NOAC+SAPT with rivaroxaban 15 mg, which is not approved for stroke prevention in AF. In addition, the AUGUSTUS trial had a factorial design. Our nonfactorial analysis of its results does not respect the primary aim of the trial. However, nonfactorial analysis of factorial trials is a feasible and used technique, both in context of trials and meta-analyses.[30,52,53]

It is also notable that details on timing of ST were not fully available, thus limiting the current analysis from drawing final conclusions on the optimal duration of aspirin in combination with NOAC and a $P2Y_{12}$ inhibitor in the double therapy group. Finally, reconstructed individual patient data were obtained from digitized curve reconstructions through a dedicated software, therefore our work should not be viewed as a traditional patient-level meta-analysis.

CONCLUSIONS

In patients with AF undergoing PCI, no significant differences were found between NOAC+SAPT and VKA+DAPT strategies in terms of MACE and single ischemic end points in an updated meta-analysis now encompassing ≈10 000 patients. On the other hand, a strategy of NOAC+SAPT is associated with a significantly lower incidence of both all clinically relevant bleedings and major bleedings compared with a strategy of VKA+DAPT. Finally, various NOACs showed a variable benefit–risk profile, suggesting the opportunity for tailored choices based on individual patients' profiles, which warrants future investigation.

ARTICLE INFORMATION

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Supplementary Materials

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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

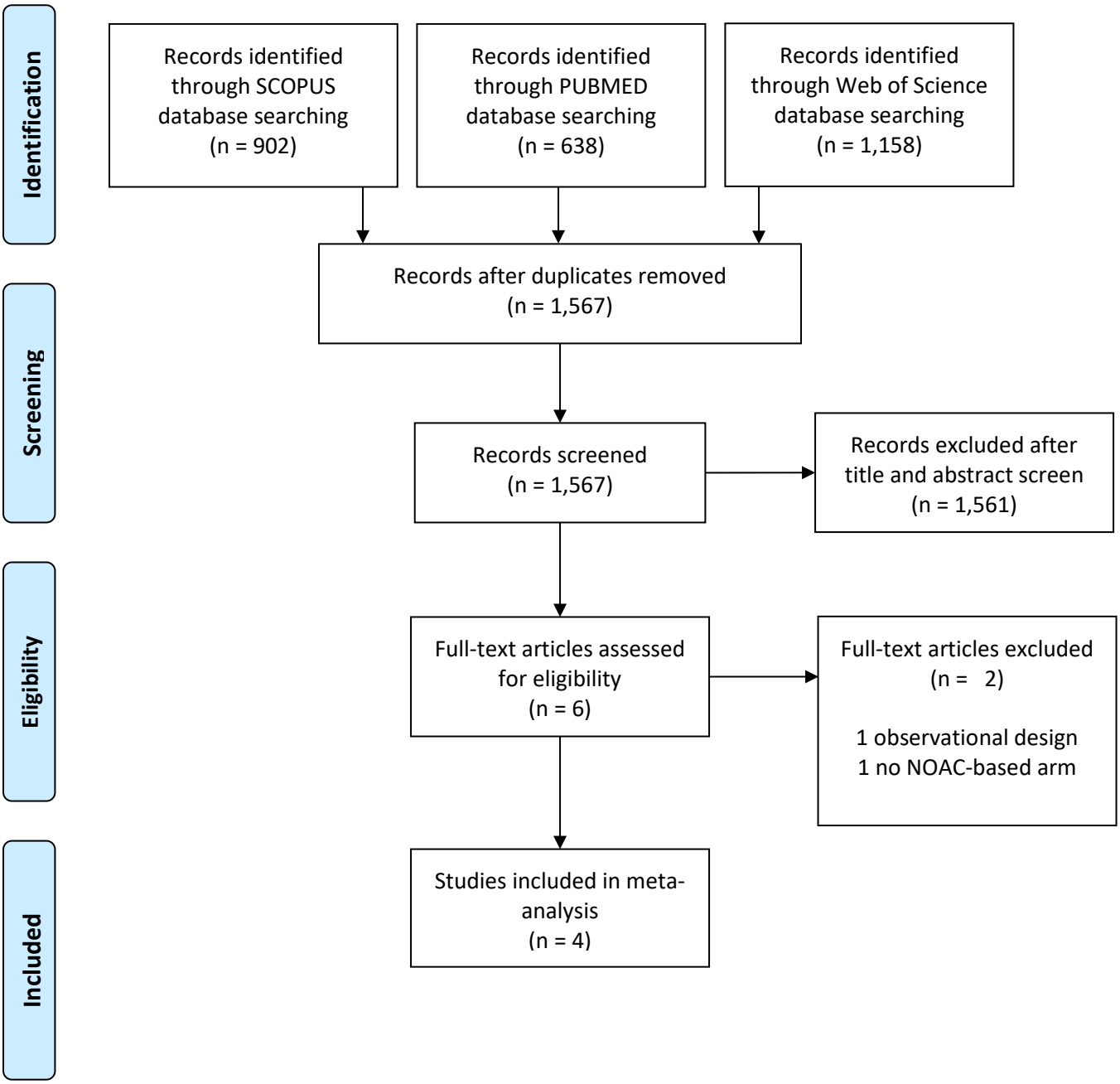
	Trial removed	HR	CI	P value for difference	I^2	P value for heterogeneity
Death	PIONEER AF-PCI	1.1	0.87-1.39	0.414	0	0.728
	RE-DUAL PCI tot	1.13	0.86-1.48	0.394	0	0.717
	AUGUSTUS	1.06	0.83-1.35	0.666	0	0.647
	ENTRUST-AF PCI	1.02	0.8-1.31	0.858	0	0.821
Stroke	PIONEER AF-PCI	0.83	0.5-1.37	0.468	12.06	0.293
	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.

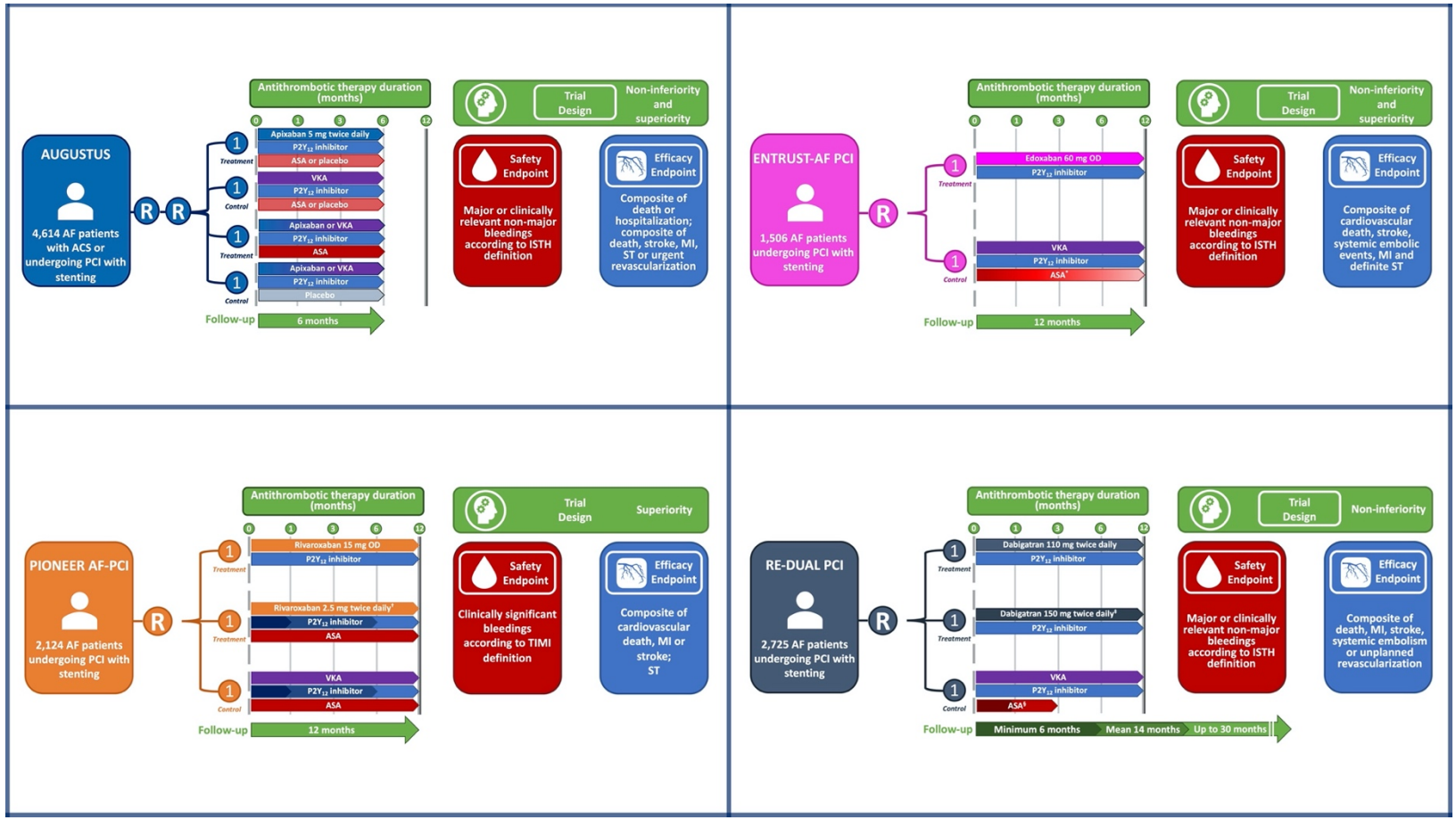
SUPPLEMENTAL FIGURES

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

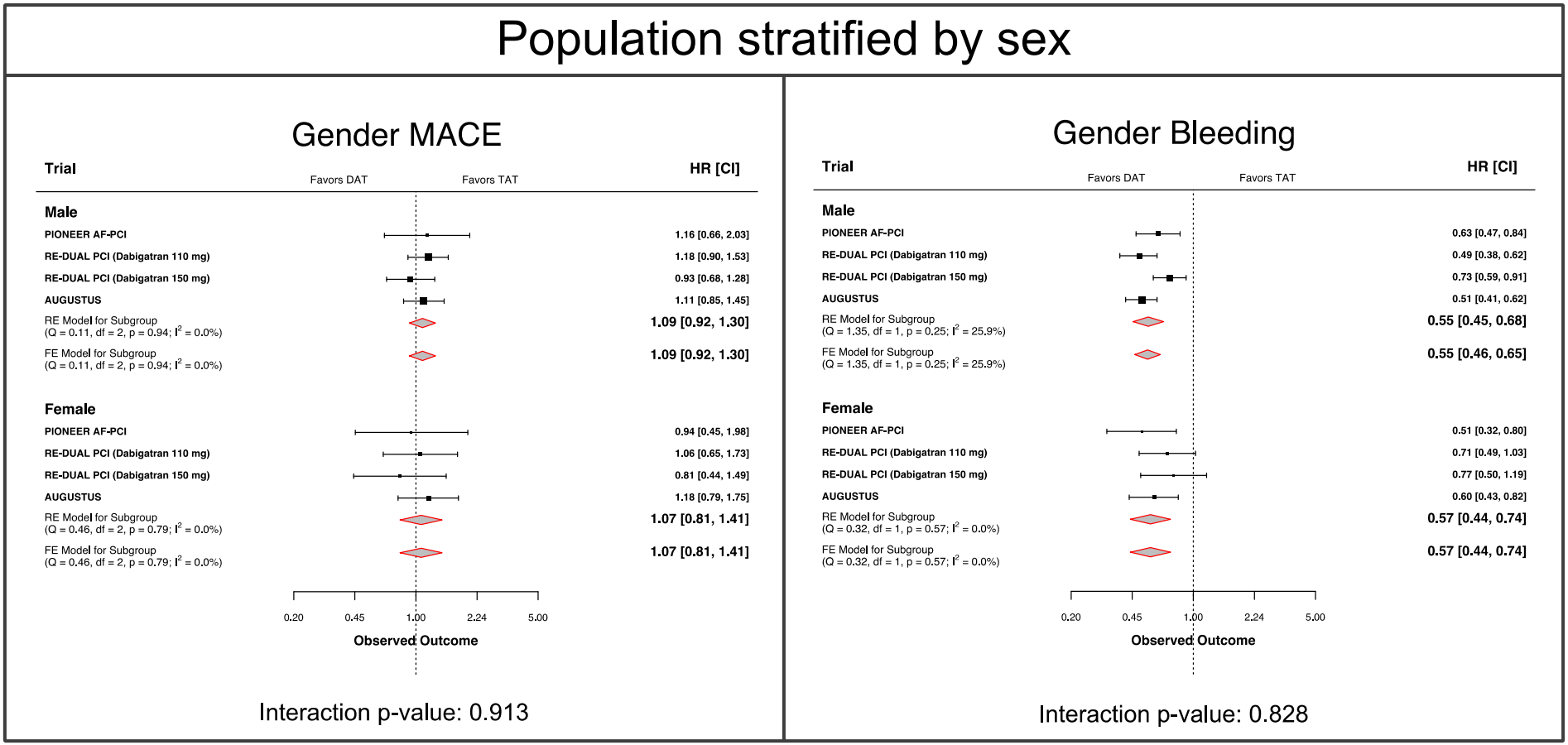
Vessels of the Heart; ENTRUST-AF PCI = Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention; ISTH = International Society on Thrombosis and Hemostasis; MI = Myocardial Infarction; OD = Once Daily; PIONEER AF-PCI = A Study Exploring 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

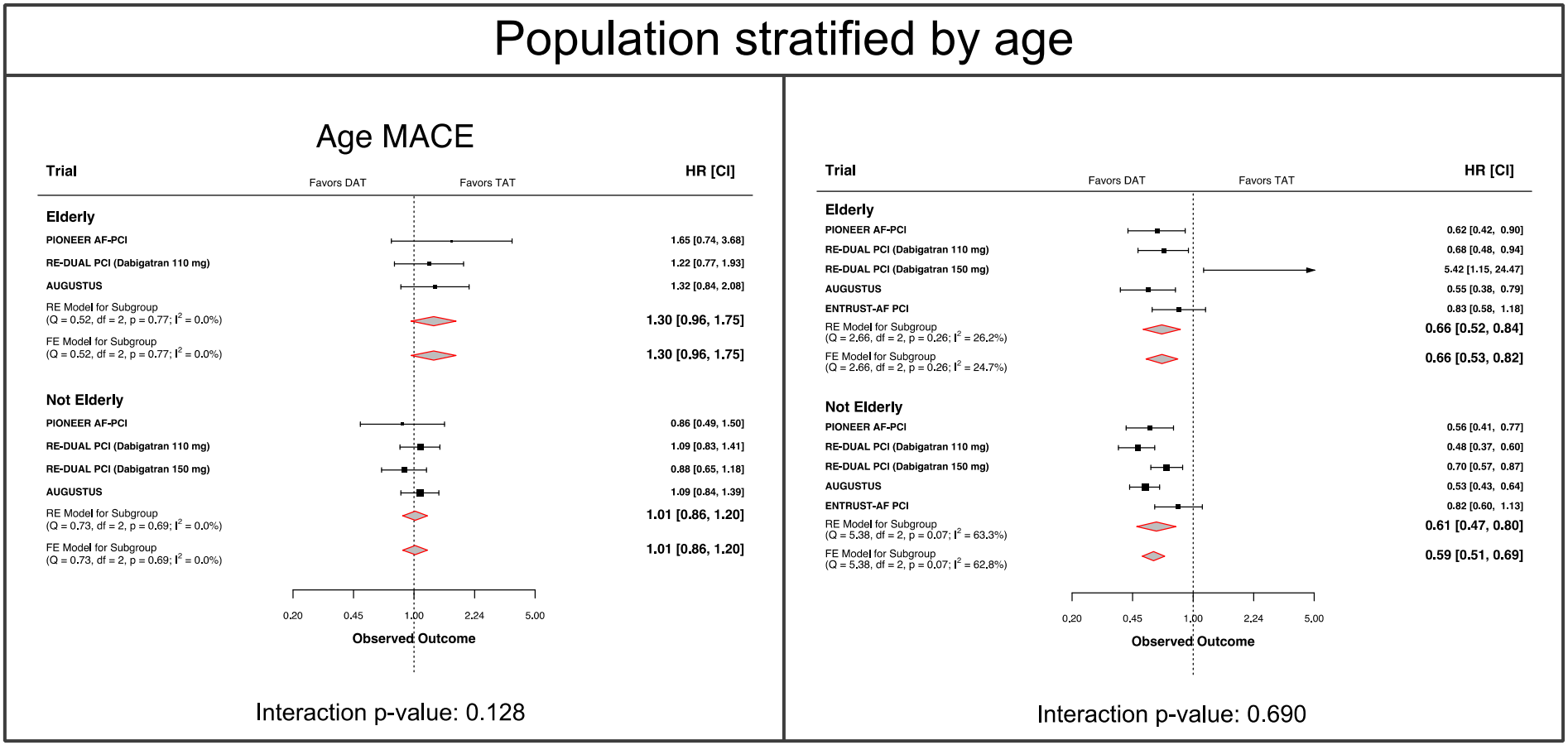


In AUGUSTUS, both double and triple therapy subgroups included patients on Apixaban or VKA, equally distributed between the two subgroups, because of its factorial randomization, whereas all other trials included exclusively patients on NOAC+SAPT and VKA+DAPT. Subgroup analyses of patients on NOAC+SAPT 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



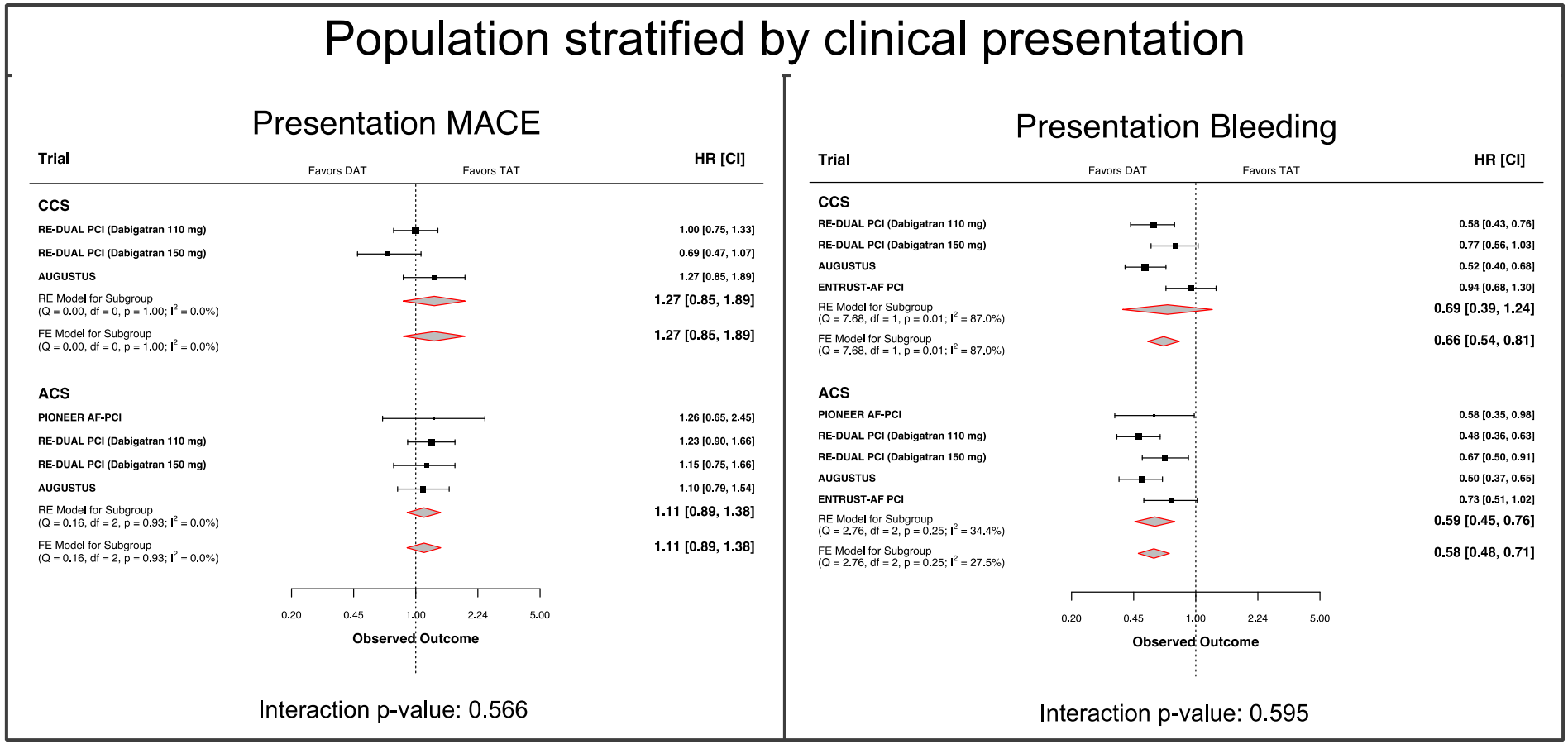
ENTRUST-AF PCI and PIONEER AF-PCI used as cutoff value for elderly vs not elderly people 75 years of age, whereas AUGUSTUS and RE-DUAL PCI used 80 years of age.

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

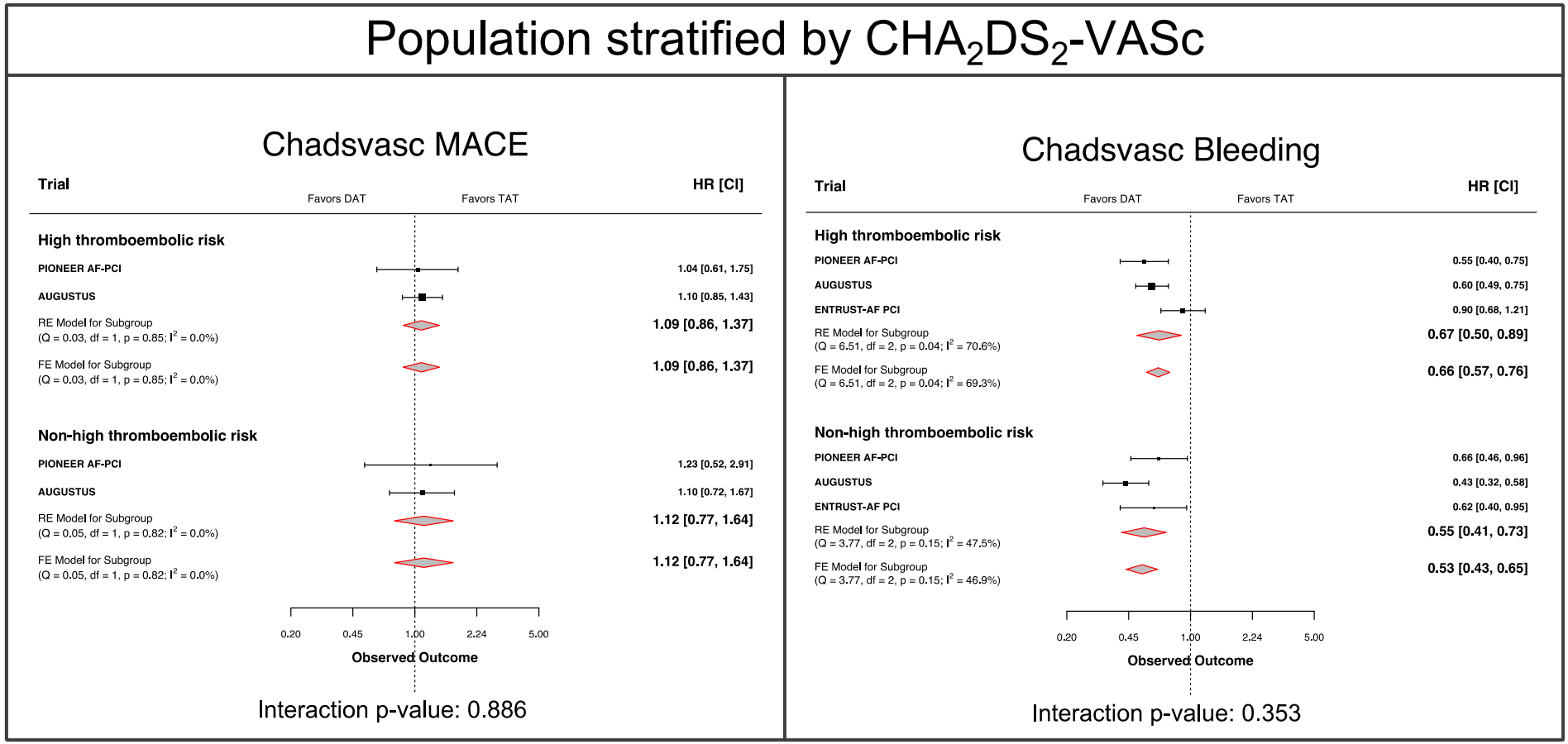


In AUGUSTUS, both double and triple therapy subgroups included patients on Apixaban or VKA, equally distributed between the two subgroups, because of its factorial randomization, whereas all other trials included exclusively patients on NOAC+SAPT and VKA+DAPT. Subgroup analyses of patients on NOAC+SAPT 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



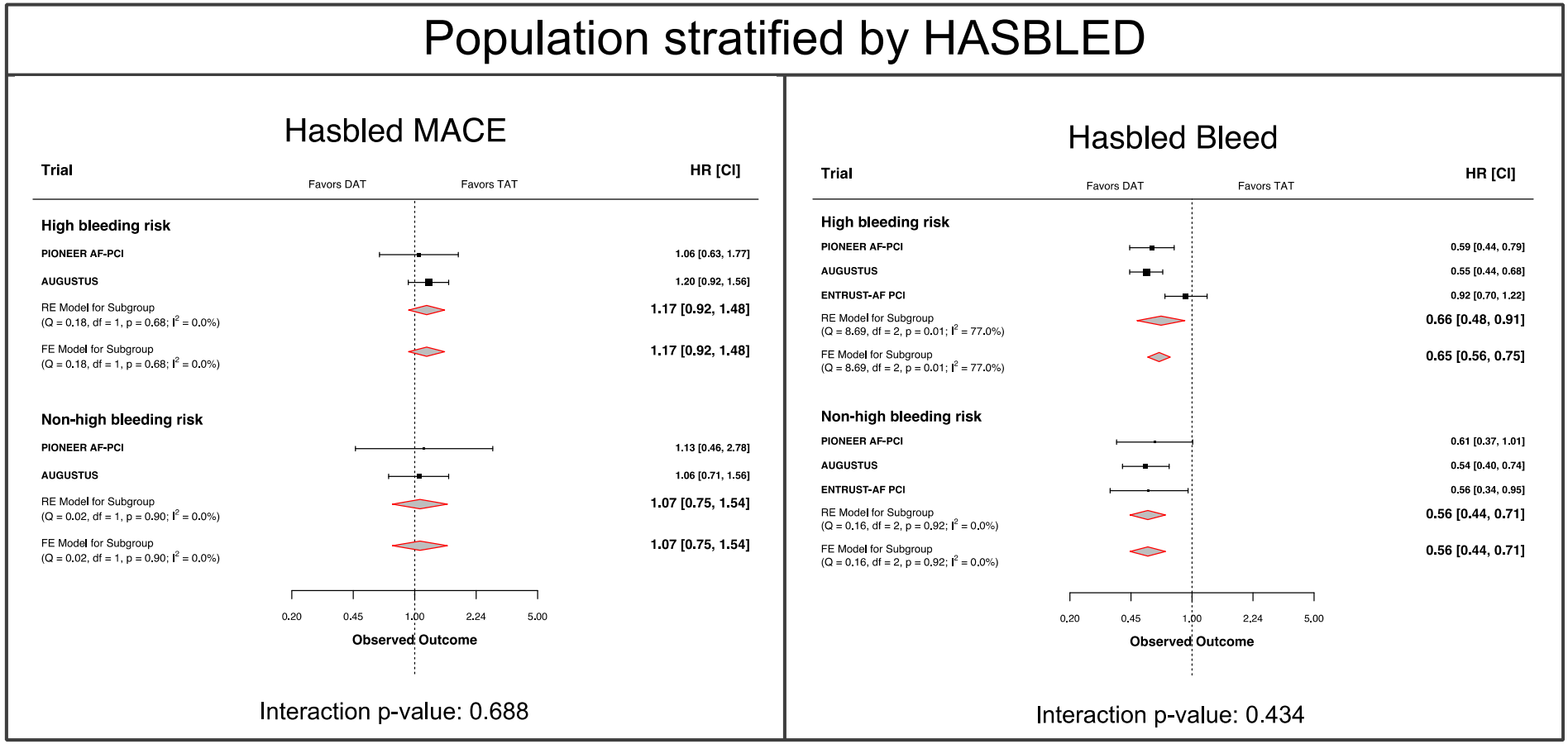
In ENTRUST-AF PCI trial a CHA_2DS_2-VAScl ≥ 3 was considered to define high thromboembolic risk, whereas in AUGUSTUS and PIONEER AF-PCI trial a value ≥ 4 was used.

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



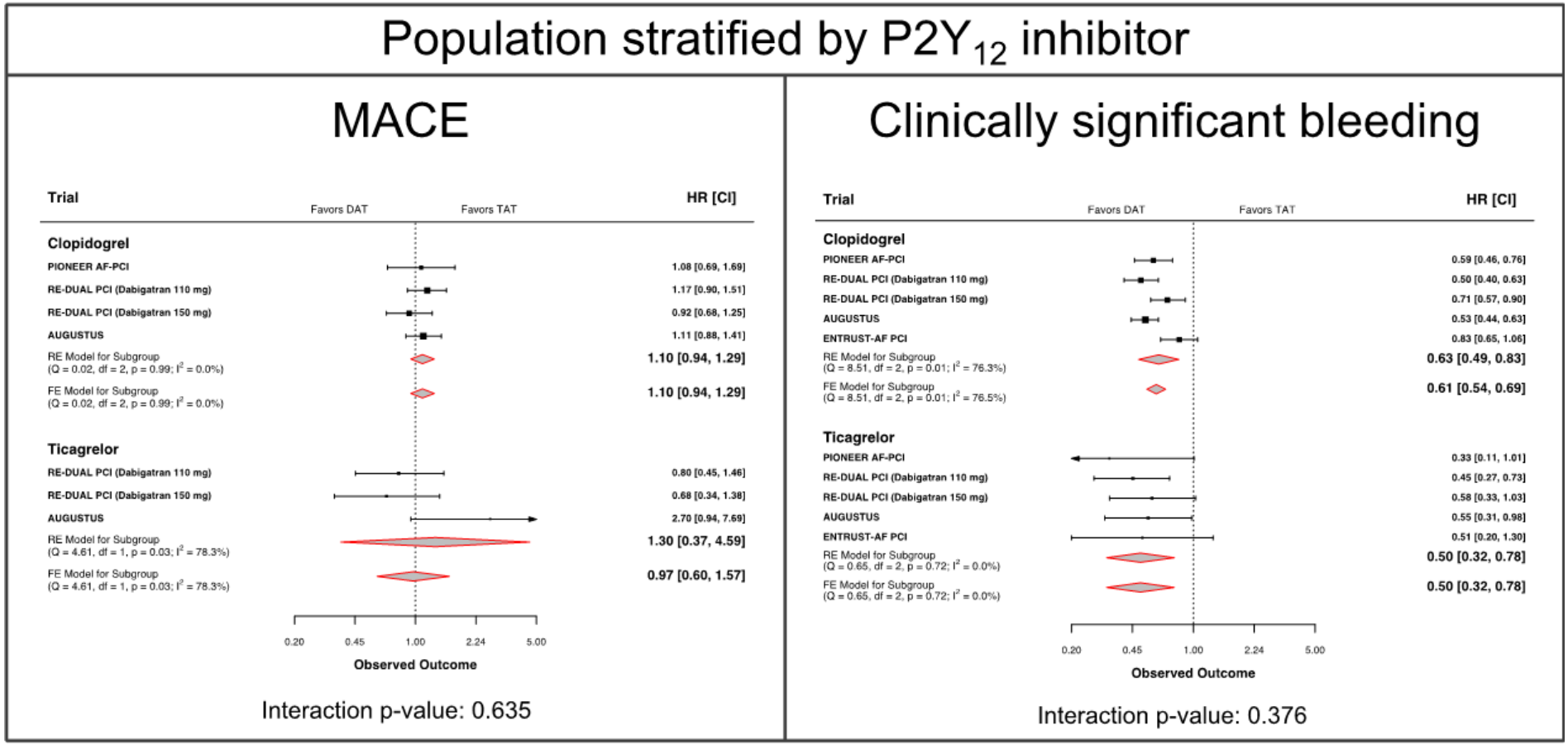
A HASBLED ≥ 3 was used to define high bleeding risk.

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



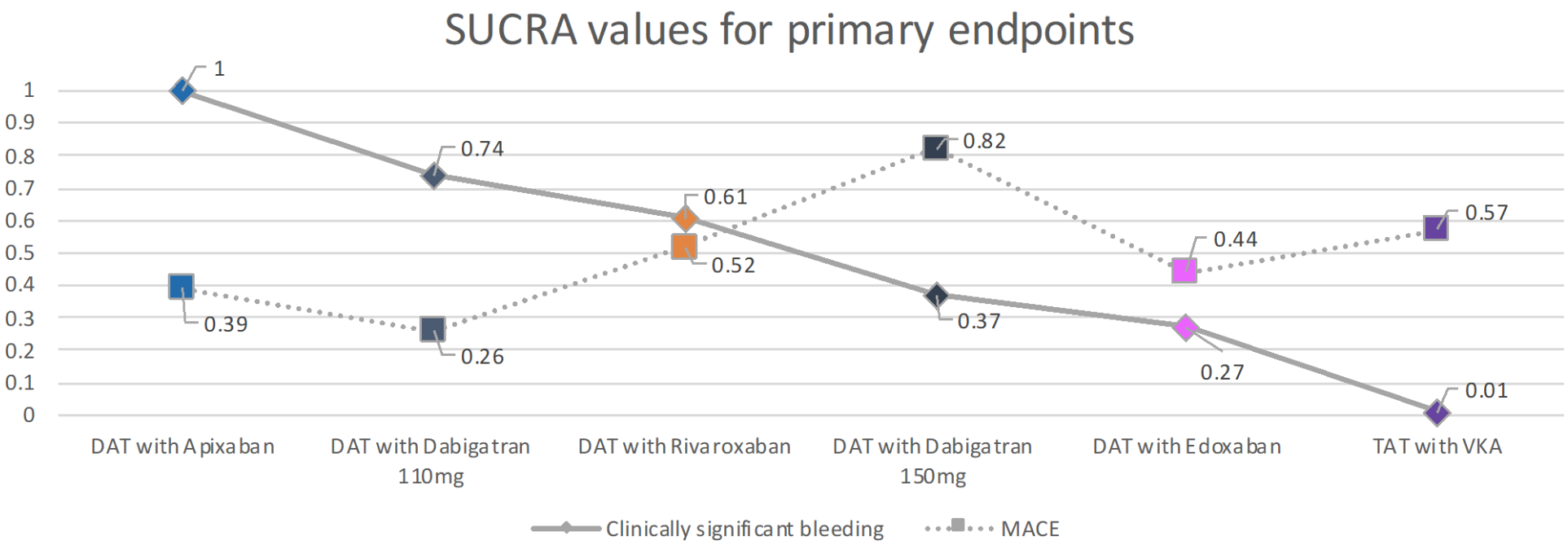
For ENTRUST-AF PCI trial, only clopidogrel vs other $P2Y_{12}$ inhibitors groups were available; for RE-DUAL PCI only ticagrelor vs other $P2Y_{12}$ inhibitors groups were available.

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

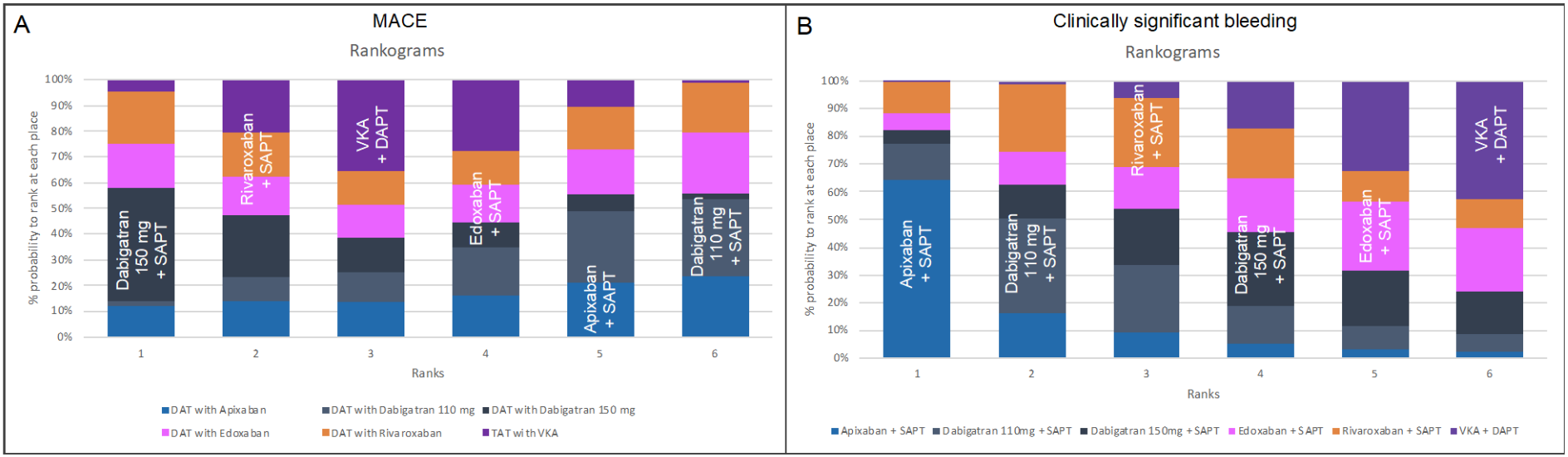
Adverse Cardiovascular Event; PIONEER AF-PCI = A Study Exploring Two Strategies of Rivaroxaban and One of Oral Vitamin K Antagonist in Patients With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention; RE = Random Effects; RE-DUAL PCI = Evaluation of Dual Therapy With Dabigatran versus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



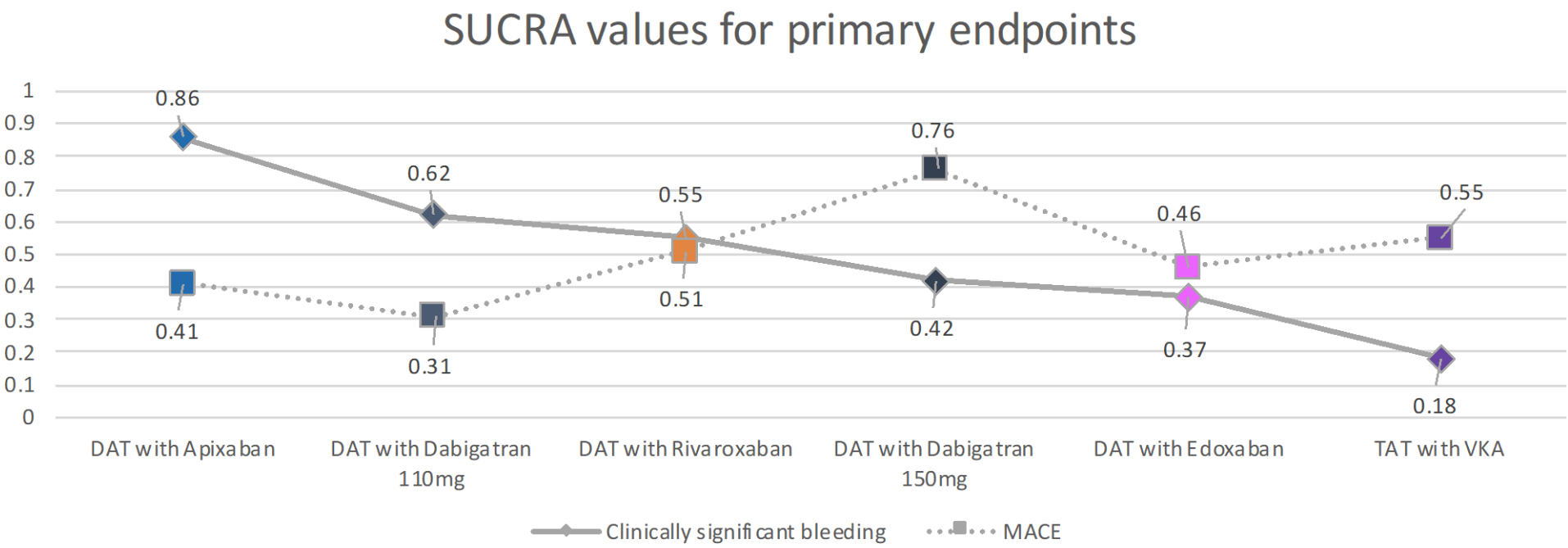
Abbreviations: DAPT = Dual Antiplatelet Therapy; MACE = Major Adverse Cardiovascular Event; SUCRA = Surface Under the Cumulative Ranking Curve; SAPT = Single Antiplatelet Therapy; VKA = Vitamin K Antagonist.

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



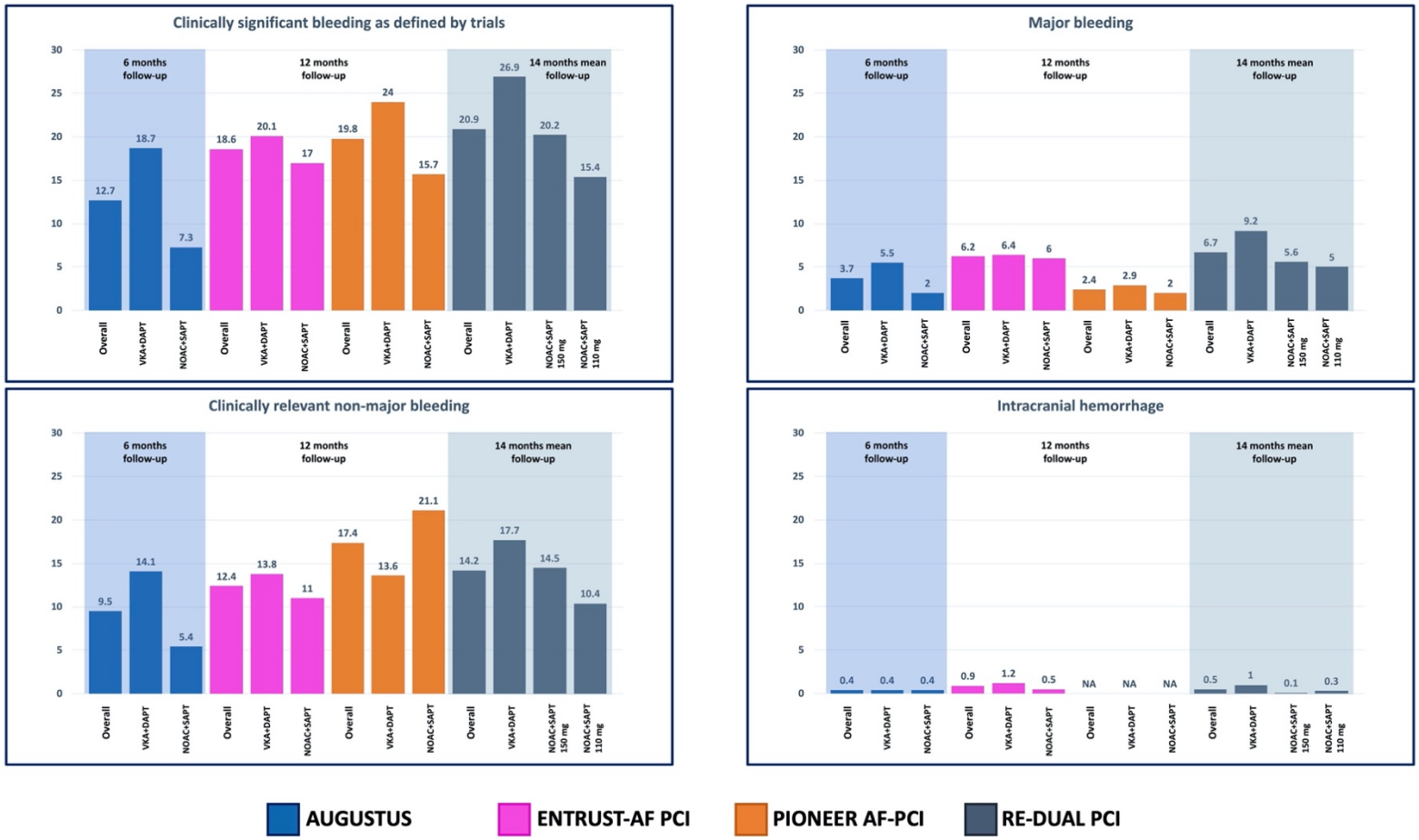
Abbreviations: DAPT = Dual Antiplatelet Therapy; MACE = Major Adverse Cardiovascular Event; SAPT = Single Antiplatelet Therapy; VKA = Vitamin K Antagonist.

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

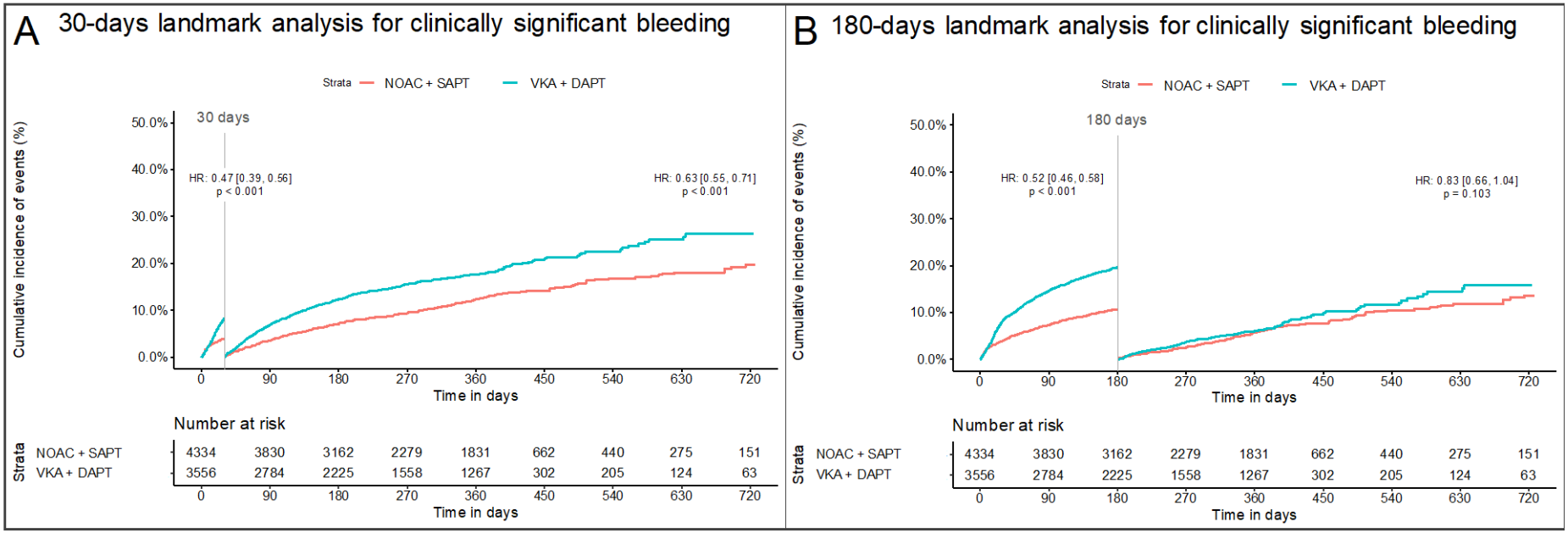


Incidences are expressed as percentages. In AUGUSTUS trial, the incidences of events for patients on NOAC+SAPT and VKA+DAPT were only available for clinically significant bleedings, major bleedings, clinically relevant non-major bleedings, whereas incidence of intracranial hemorrhage concerns the whole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

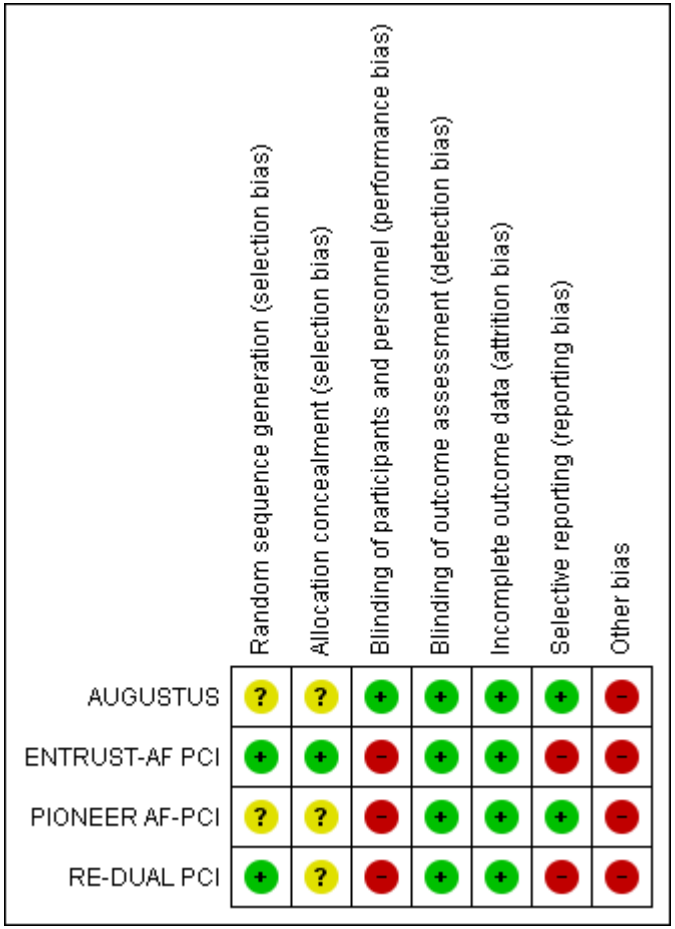
Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention; NA = Not Available; NOAC = Non-Vitamin K antagonist Oral Anticoagulant; PIONEER AF-PCI = A Study Exploring Two Strategies of Rivaroxaban and One of Oral Vitamin K Antagonist in Patients 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

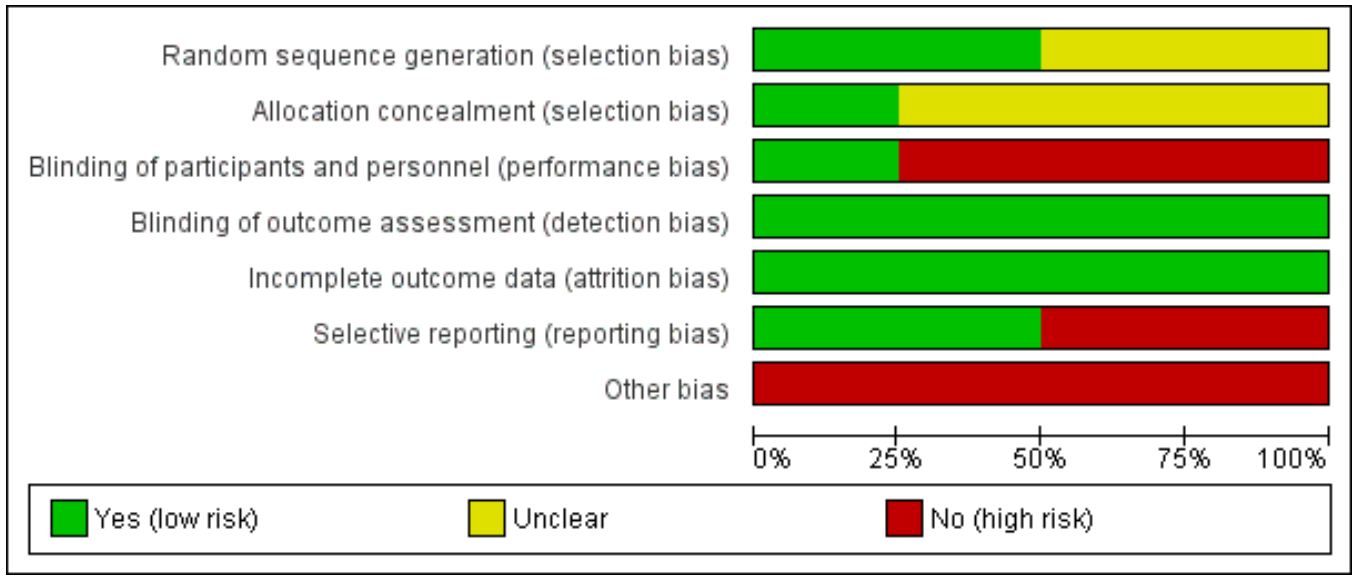
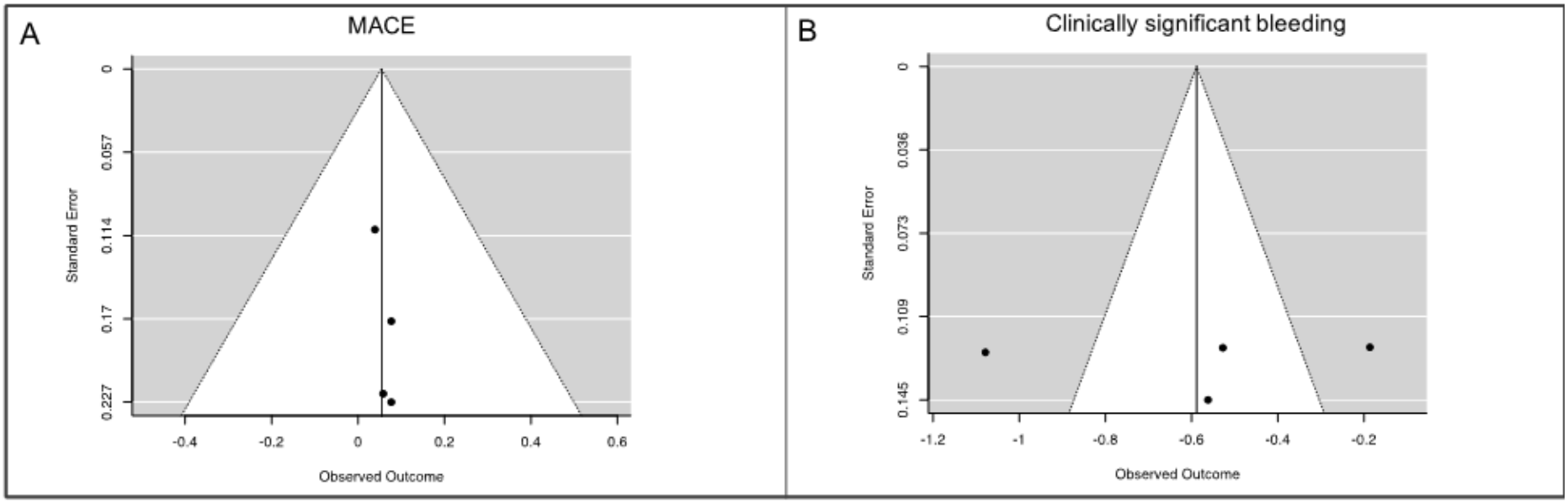


Figure S17: Funnel plots for MACE (A) and clinically significant bleeding (B) endpoints



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.