Dual Therapy Versus Triple Therapy Major Bleeding Outcomes in Patients With Atrial Fibrillation Who Developed Indications for Percutaneous Coronary Intervention: A Meta-Analysis

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DISCLOSURE: None

Abstract

INTRODUCTION: Patients with atrial fibrillation (AF) undergoing percutaneous coronary intervention (PCI) poses a therapeutic dilemma for the attending physician. Standard anticoagulation with a vitamin K antagonist (VKA) plus dual antiplatelet therapy with a $P2Y_{12}$ inhibitor and aspirin reduces the risk of stroke and thrombosis, but increases risk of bleeding. The effectiveness and safety of several novel oral anticoagulants are still unclear in these patients.

METHODS: PubMed, Cochrane and Embase databases were systematically searched for studies from 2016 until 30 November 2023. The search key terms were 'DOACs,' 'atrial fibrillation,' 'percutaneous coronary intervention' and 'bleeding.' Two independent reviewers appraised eligible studies using well-defined criteria. The main outcomes of interest were ISTH major bleeding, stent thrombosis and major adverse cardiovascular events (MACE). The random-effects model was used to derive pooled estimates.

RESULTS: The search yielded four studies which were all randomized controlled trials (RCTs). There were a total of 10,963 participants. Pooled estimates showed a statistically significant difference between direct oral anticoagulants (DOAC) + $P2Y_{12}$ and VKA + DAPT for International Society on Thrombosis and Haemostasis (ISTH) major bleeding (OR 0.62, 95% CI 0.57 – 0.69, p = <0.00001). There was no statistically significant difference between DOACs + $P2Y_{12}$ and VKA + DAPT for stent thrombosis (RR 1.17, 95% CI 0.79 – 1.72, p = 0.43) and MACE (RR 1.00, 95% CI 0.87 – 1.13, p = 0.07).

DISCUSSION: In patients with AF who had undergone PCI, the risk of bleeding was lower among those who received dual therapy with DOAC + $P2Y_{12}$ than among those who received triple therapy with warfarin, a $P2Y_{12}$ inhibitor and aspirin. However, dual therapy was noninferior to triple therapy with respect to the risk of stent thrombosis and MACE.

KEYWORDS: Dual oral anticoagulation; atrial fibrillation; percutaneous coronary intervention; major bleeding; stent thrombosis; major adverse cardiovascular events

Introduction

Atrial fibrillation (AF) is a highly prevalent arrhythmia that increases with age. Up to 40% of patients with AF also have coronary artery disease (CAD), many of whom require revascularization. Percutaneous coronary intervention (PCI) with stent implantation is the most common revascularization strategy for patients with CAD and up to 10% of these patients have AF.

Anticoagulation is the mainstay for stroke prevention in patients with AF. Many patients with AF also have a concomitant indication for either single or dual antiplatelet (aspirin plus a $P2Y_{12}$ inhibitor) therapy. For instance, about one in three patients with AF have coexistent CAD, and about one in five undergo PCI. Although anticoagulant therapy is more effective than either

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single or dual antiplatelet therapy (DAPT) for stroke prevention in AF, guidelines recommend DAPT over vitamin K antagonist (VKA) for the prevention of coronary stent thrombosis. Such a quandary prompted addition of DAPT to an anticoagulant, also known as triple therapy, with the intent of preventing both coronary ischemic and cardioembolic events.[9]

Data from randomized trials clearly demonstrate that bleeding increased with combined antithrombotic regimens. Thus, compared with aspirin, the risk of major bleeding is higher with DAPT with aspirin plus clopidogrel; and it is higher with DAPT containing a more potent $P2Y_{12}$ inhibitor such as prasugrel or ticagrelor. Adding warfarin to aspirin results in a two-fold higher risk of bleeding compared with aspirin alone.[2] Thus, in the WOEST trial, 31.7% of patients with AF treated with triple therapy experienced clinically relevant bleeding and 5.6% suffered major bleeding within one year of PCI. Consequently, bleeding is problematic with triple therapy.

There is a concern that the risk of bleeding could be even higher outside of randomized controlled trials (RCTs), but until recently, robust estimates for the rate of major bleeding with various combinations in clinical practice were scarce. The concomitant presence of these conditions represents a challenge in clinical practice, particularly with regard to their optimal antithrombotic treatment regimen. The optimal antithrombotic strategy to balance thromboembolic and bleeding events, especially acute stroke, for patients with AF following coronary stenting remains a matter of debate.[3]

In determining the best approach for antithrombotic therapy in patients with AF who are undergoing PCI, it can be difficult to balance the prevention of thrombosis with risk of bleeding.[11] DAPT with a $P2Y_{12}$ inhibitor and aspirin is superior to oral anticoagulation with a VKA in reducing the risk of thrombosis in patients undergoing placement of a first-generation stent, but oral anticoagulation is superior to DAPT in reducing the risk of ischemic stroke in patients with AF.[11]

The treatment strategy for patients with AF who have received stents must balance the risk of stent thrombosis and ischemic stroke with the risk of bleeding. A common guideline-supported practice is to combine all three drugs in a strategy; however, this approach may result in excessive major bleeding, with rates of 2.2% within the first month and 4% to 12% within the first year of treatment.[12]

General Objective

To determine whether DAPT is better compared with triple therapy in the occurrence of clinically significant bleeding among patients who have AF and underwent PCI.

PATIENTS AND METHODS

This review was reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) statement standards.

Search Strategy

PubMed, Embase and Cochrane databases were systematically searched from inception until 30 November 2023. The terms used for the search were 'DOACs', 'atrial fibrillation', 'percutaneous coronary intervention' and 'bleeding'. The search was limited to human studies, in the English language, and RCTs. Other sources searched were references of journals, grey literatures and conference proceedings.

Eligibility Criteria

Type of Studies

RCTs that investigated the outcome of patients with AF who underwent PCI and received DAPT versus triple therapy. There were no publication restrictions imposed. Abstracts, reviews, case reports and studies that did not compare DAPT versus triple therapy, or those that did not meet any of the inclusion criteria of the study were excluded.

Types of Participants

Patients who met all the following criteria were eligible for inclusion: an age of at least 18 years; previous, persistent, permanent, or paroxysmal AF and planned long-term use of an oral anticoagulant; recent acute coronary syndrome or PCI; and planned use of a $P2Y_{12}$ inhibitor for at least six months.

Language

Studies in English language or foreign journals with an English translation.

Types of Intervention

Clinical studies that compared outcomes of significant bleeding among patients who have AF and underwent PCI.

Time Frame

Studies that were published between 2016 and 30 November 2023.

Data Extraction and Risk of Bias in Included Studies

Two independent authors extracted relevant data. After removing duplicates, the two investigators (MM, JL) independently screened the remaining studies at the title/abstract level. RCTs comparing major bleeding risk outcomes between DAPT versus triple therapy in patients with AF who underwent PCI were included. The selected studies underwent full-text screening, performed by two independent investigators (MM, JL). The study selection process using PRISMA is shown in Figure 1.

End Points

The primary safety end point was the occurrence of clinically significant bleeding (a composite of major bleeding or minor bleeding according to Thrombolysis in Myocardial Infarction (TIMI) criteria or bleeding requiring medical attention during the treatment period (which was defined as the time from first administration of a trial drug to two days after the trial drugs were discontinued, through 12 months of therapy). Secondary end points included the incidence of each component of primary safety end point, as well as the following efficacy end points: occurrence of a MACE (a composite of death from

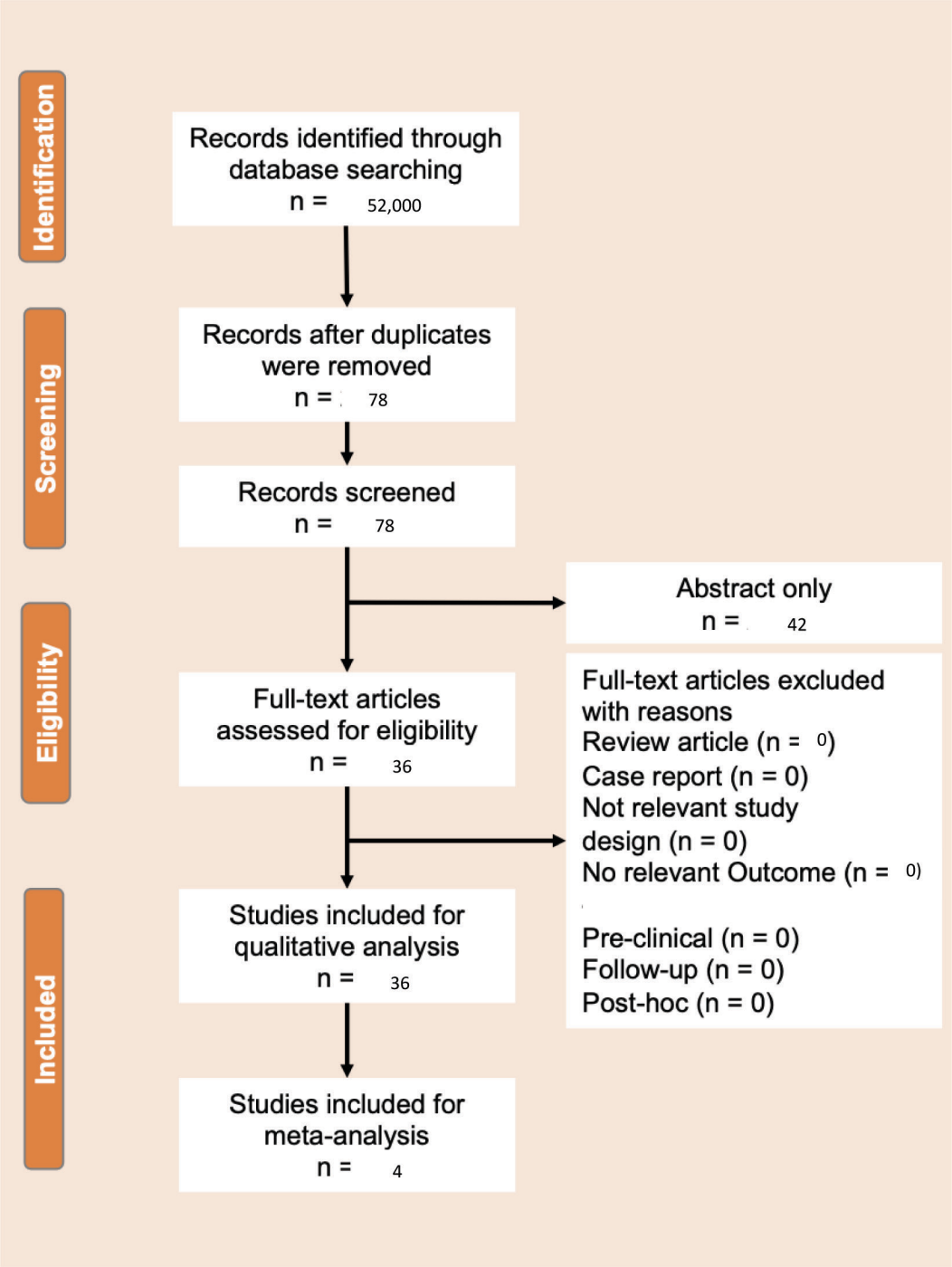

Figure 1. PRISMA flow diagram for study inclusion and exclusion

cardiovascular causes, myocardial infarction, or stroke), each component of the MACE end point and stent thrombosis. This meta-analysis compared outcomes of DAPT versus triple therapy in patients with AF who underwent PCI.

Data Collection and Analysis

Quality Assessment

Study selection and quality assessment was carried out to evaluate randomization, concealment of allocation, masking of patients and clinicians, documentation of dropouts and withdrawals and intent-to-treat analysis. The qualities of RCTs were assessed using the Cochrane Risk of Bias Tool by two independent reviewers. Details about the study design as well as aggregated patient data concerning baseline characteristics were carefully reviewed.

Data Extraction

Two independent reviewers extracted relevant data. The data from eligible studies were recorded from each trial using a standardized form pre-designed for data extraction created in

Table 1. Comparisons of Double Antithrombotic Therapy Versus Triple Antithrombotic Therapy in Trials of Non-Vitamin K Oral Antagonists in Patients with Atrial Fibrillation Undergoing Percutaneous Coronary Intervention

Characteristics	PIONEER-AF PCI	REDUAL-PCI	AUGUSTUS	ENTRUST-AF PCI
Year	2016	2017	2019	2019
Blinding	Open-label	Open-label	Open label	Open-label
Patients, n	2124	2725	4614	1506
Intervention	Rivaroxaban plus $P2Y_{12}$ inhibitor for 12 months	Dabigatran plus $P2Y_{12}$ inhibitor for 12 months	Apixaban or VKA plus $P2Y_{12}$ inhibitor for 6 months	Edoxaban plus $P2Y_{12}$ inhibitor for 12 months
Control	Warfarin plus DAPT for 1, 6, or 12 months	Warfarin plus DAPT for 1 or 3 months	Apixaban or VKA plus DAPT for 6 months	VKA plus DAPT for 1 to 12 months
Primary outcome	Clinically relevant bleeding at 12 months	Major or CRNM bleeding through follow-up (mean 14 months)	Major or CRNM bleeding at 6 months	Major or CRNM bleeding at 12 months
Treatment effect for intervention vs. control	HR, 0.59 (95% CI, 0.47-0.76); P<0.001 for superiority	HR, 0.72 (95% CI, 0.58-0.88); P<0.001 for noninferiority; P=0.002 for superiority (Dabigatran 150 mg BID); HR, 0.52 (95% CI, 0.42-0.63); P<0.001 for noninferiority, P<0.001 for superiority (Dabigatran 110 mg BID)	HR, 0.53 (95% CI, 0.45-0.63); P<0.001 for superiority	HR 0.83 (95% CI, 0.65-1.05); P<0.001 for noninferiority, P=0.1154 for superiority

AF - Atrial fibrillation; PCI - Percutaneous coronary intervention; DAPT - Dual antiplatelet therapy; VKA - Vitamin K antagonist; CRNM - Clinically relevant non-major; HR - Hazard ratio; CI – Confidence interval;

Microsoft Excel. The following characteristics were collected: authors of the study, study design, year of publication, country, study period, number of participants, duration of follow-up and study endpoints. Disagreements of reviewers on data extracted were thoroughly discussed and a third party was sought if consensus was not met.

Assessment of Heterogeneity

In pooling estimates, a homogeneity test was performed between studies using the I^2 index (a result of I^2 >50% indicates that heterogeneity exists and I^2 >70% demonstrates high heterogeneity and with a p-value of 0.05 indicating significant difference between studies). A random-effects model was used for heterogeneous studies to extrapolate a pooled estimate. A fixed-effect model was used for homogeneous studies after removing studies that caused heterogeneity.

Risk of Bias Assessment

Quality assessment of the studies was performed by two authors using the Cochrane Risk of Bias Tool. Reporting bias was minimized by a thorough literature search for eligible articles and review of full-text articles. Selection bias, performance bias, attrition bias and reporting bias were assessed and categorized as low and high risks.

Measures of Effect

The outcome on significant major bleeding used the odds ratio as the effect measure. The outcomes of MACE and stent thrombosis utilized the risk ratio. The precision of the estimate was expressed using 95% CI.

Statistical Analysis

The odds ratio and 95% CI reported in each study were used for the meta-analysis. A random-effects model with inverse-variance weights was used to combine the effect measures from all studies on a logarithmic scale. Statistical significance set at p<0.05. RevMan 5.4.1 was utilized to pool the data.

RESULTS

Our literature yielded a total of 52,000 studies. After removing duplicates, 78 studies were left. Thirty-six studies were eventually included for eligibility evaluation after careful screening of titles and abstracts. After thoroughly evaluating all 36 articles, four studies were finally included in the meta-analysis (see Figure 1).

Characteristics of Eligible Studies

The meta-analysis consisted of four RCTs published from 2016 to 2019 conducted in 33 countries (see Table 1). All four studies included patients with nonvalvular AF who underwent PCI requiring anticoagulant therapy. All patients had an end-of-treatment visit when the trial anticoagulant was discontinued; a follow-up visit took place four weeks thereafter. The trial continued until all patients had a minimum of six months of follow-up. The studies contained different outcomes of interest such as major or clinically relevant bleeding, MACE and stent thrombosis. The overall quality of included studies was high. Due to adequate randomization, the risk of sampling bias was low for RCTs. However, due to the nature of treatment, the blinding bias

Table 2. Baseline Clinical Data

	All patients	PIONEER AF-PCI	RE-DUAL PCI	AUGUSTUS	ENTRUST AF-PCI
Cohort size (n)	9463	2124	2725	4614	1500
Age (years)	NA	mean 70.1	mean 70.8	median 70.7	median 69.5
Male sex	6928 (73.2%)	1581 (74.4%)	2070 (76%)	3277 (71%)	1120 (74.6%)
CHA_2ADS_2VASc score	3.8 1.6	3.8 1.6	3.6 1.5	3.9 1.6	4.0
HAS-BLED score	2.9 0.8	3.0 0.9	2.7 0.7	2.9 0.9	3.0
Clinical setting					
Elective PCI	4441/9444 (47%)	1307 (61.5%)	1350 (49.5%)	1784/4595 (38.8%)	394 (26%)
Primary PCI	3906/9444 (41.4%)	817 (38.5%)	1375 (50.5%)	1714/4595 (37.3%)	-
Medically managed ACS	1097/4595 (23.9%)	-	-	1097/4595 (23.9%)	365 (24%)
$P2Y_{12}$ inhibitor					
Clopidogrel	8567/9345 (91.7%)	2004 (94.4)	2398 (88%)	4165/4496 (92.6%)	1391 (92.7)
Ticagrelor	699/9345 (7.5%)	92 (4.3%)	327 (12%)	280/4496 (6.2%)	106 (7.06%)
Prasugrel	79/6620 (1.2%)	28 (1.3%)	-	51/4496 (1.1%)	8 (<1%)
Time period of outcome events counting (months)	-	12	mean 12.3 (minimum 6)	6	mean 12
Primary safety outcomes	-	Composite of TIMI major or minor bleeding or BRMA	ISTH major bleeding or CRNMB	ISTH major bleeding or CRNMB	ISTH major bleeding or CRNMB
Efficacy outcomes	-	MACE (composite of CV death, MI, or stroke)	Composite of TE events (MI, stroke, or SE), death, or unplanned revascularization	Composite of death, hospitalization, or ischemic events (stroke, MI, stent thrombosis, or urgent revascularization)	MACE and stent thrombosis

AF - Atrial fibrillation; PCI - Percutaneous coronary intervention; ACS – Acute coronary syndrome; TIMI - Thrombolysis in myocardial infarction; BRMA - Bleeding requiring medical attention; ISTH - International society on thrombosis and haemostasis; DAPT - Dual antiplatelet therapy; VKA - Vitamin K antagonist; CRNMB - Clinically relevant non-major bleeding; MACE - Major adverse aardiovascular events; CV – Cardiovascular; MI – Myocardial infarction; TE – Thrombotic events; SE - Systemic embolism;

was high, although concealment allocation, risk of attrition and reporting bias were low. On visual assessment, our funnel plots were symmetrical indicating that the limited scatter was because of sampling variation and not due to publication bias.

Baseline Characteristics of the Study Population

The overall study population consisted of 10,963 patients who had nonvalvular AF (paroxysmal, persistent, or permanent) and had just undergone PCI with stent placement which are usually elderly, with median age between 68 to 71 years. Nonvalvular AF seems to have a female sex predilection. The most common risk factors were hypertension, heart failure and diabetes mellitus. The summary baseline characteristics of participants are shown in Table 2.

DOAC + $P2Y_{12}$ versus VKA + DAPT

Outcomes of ISTH Major Bleeding Versus Clinically Relevant Non-Major Bleeding

The Mantel-Haenzel (M-H) random fixed effects model pooled estimates showed a statistically significant difference between DOACs + $P2Y_{12}$ and VKA + DAPT for ISTH major bleeding or clinically relevant non-major bleeding (OR 0.62, 95% CI 0.57 – 0.69, p = <0.00001) (see Figure 2). The pooled estimates

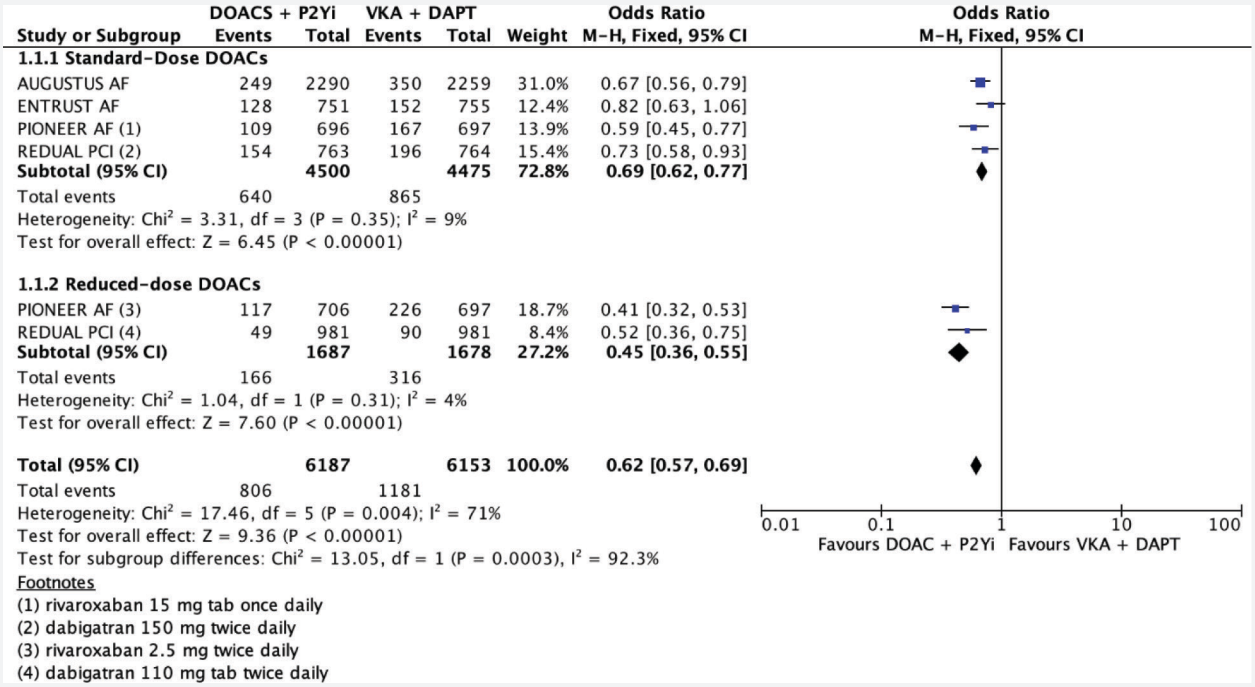

Figure 2. Forest Plot on DOAC + $P2Y_{12}$ Versus VKA + DAPT Efficacy Endpoint: ISTH Major Bleeding or Clinically Relevant Non-Major Bleeding

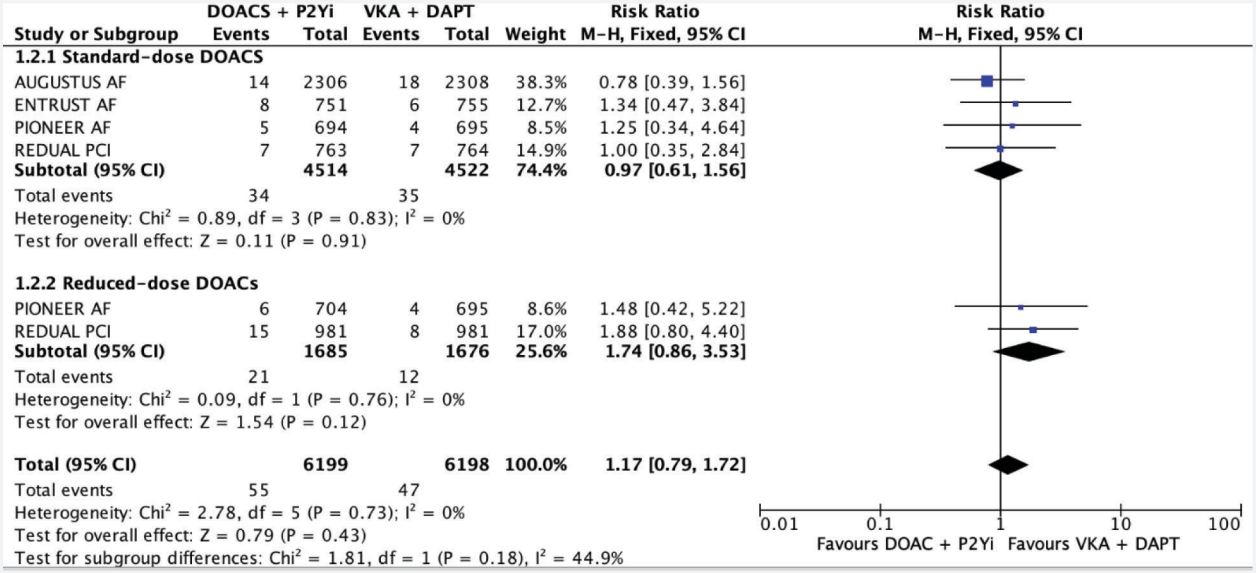

Figure 3. Forest Plot on DOAC + $P2Y_{12}$ Versus VKA + DAPT Efficacy Endpoint: Stent Thrombosis

yielded high heterogeneity with an I^2 value of 71% and significant p-value of 0.004. Weight contribution were deemed possible contributors, particularly with the lowest contribution from RE-DUAL PCI trial and narrow CIs from the PIONEER AF-PCI trial.

Subgroup sensitivity analysis for major bleeding or clinically relevant non-major bleeding

There is a significant difference with a p-value of 0.0003 in treatment effects between the two subgroups of patients receiving reduced- and standard-dose DOACs for ISTH major bleeding or clinically relevant non-major bleeding. The Forest plot demonstrated significant heterogeneity between the two subgroups with an I^2 of 92.3% (see Figure 2). Major contributors of heterogeneity were the reduced DOACs treatment arm with their narrow CI located far left from the line of no effect. Weight contributions were also deemed possible contributors of heterogeneity, particularly with the RE-DUAL PCI (reduced DOACs arm) contributing <10% of the total weight.

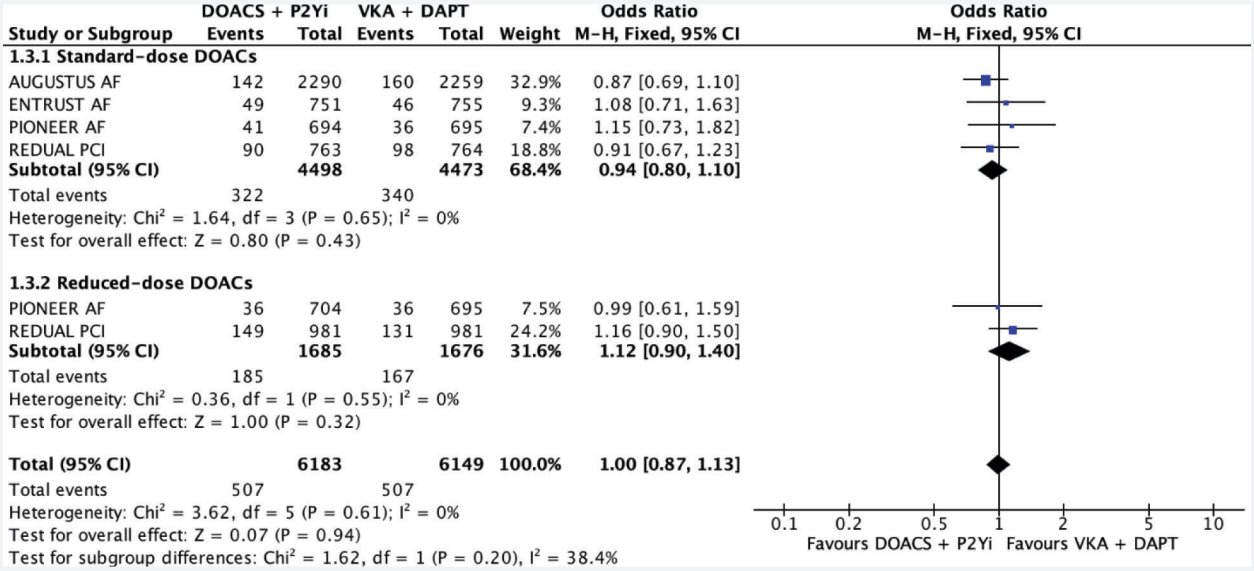

Figure 4. Forest Plot on DOAC + $P2Y_{12}$ Versus VKA + DAPT Efficacy Endpoint: Major Adverse Cardiovascular Events (MACE)

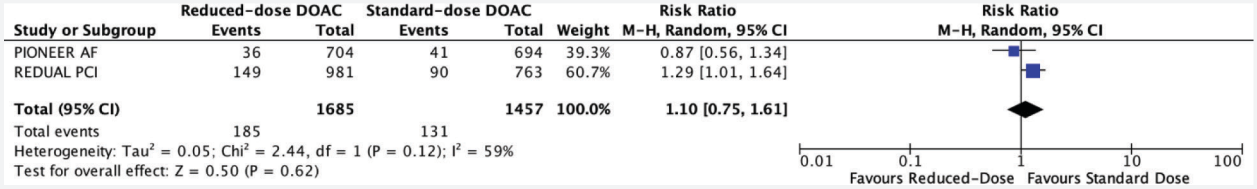

Figure 5. Forest Plot on Reduced Dose Versus Standard Dose DOACs Efficacy Endpoint: Major Adverse Cardiovascular Events

Outcomes on Stent Thrombosis

The Mantel-Haenzel (M-H) random fixed effects model pooled estimates showed no statistically significant difference between DOACs + $P2Y_{12}$ and VKA + DAPT for stent thrombosis (RR 1.17, 95% CI 0.79 – 1.72, p = 0.43) (see Figure 3). The pooled estimates yielded no heterogeneity with an I^2 value of 0 and a non-significant p-value of 0.73. Weight contributions were deemed possible contributors, particularly with the lowest contributions from the ENTRUST AF-PCI and PIONEER AF-PCI trials.

Outcomes on Major Adverse Cardiovascular Events (MACE)

The Mantel-Haenzel (M-H) random fixed effects model pooled estimates showed no statistically significant difference between DOACs + $P2Y_{12}$ and VKA + DAPT for MACE (RR 1.00, 95% CI 0.87 – 1.13, p = 0.07) (see Figure 4). The pooled estimates yielded no heterogeneity with an I^2 value of 0 and non-significant p-value of 0.61. Weight contributions were deemed possible contributors of heterogeneity, particularly with the lowest contributions from the ENTRUST AF-PCI and PIONEER AF-PCI trials.

Subgroup sensitivity analyses for stent thrombosis and major adverse cardiovascular events

There is no significant difference in treatment effects between the two subgroups of patients receiving reduced- and standard-dose DOACs for stent thrombosis (I^2 = 44.9%, p-value 0.18) and MACE (I^2 = 38.4%, p-value of 0.20) (see Figures 3 and 4). Major contributor of heterogeneity was weight contribution owing to low weight from PIONEER AF-PCI and ENTRUST AF-PCI trials.

Standard Versus Reduced Dose DOACs

Outcomes on Major Adverse Cardiovascular Events (MACE)

The Mantel-Haenzel (M-H) random fixed effects model pooled estimates showed no statistically significant difference between standard and reduced doses of DOACs on MACE (RR 1.10, 95% CI 0.75 – 1.61, p = 0.62) (see Figure 5). The pooled estimates yielded a high heterogeneity with an I^2 of 59% with a non-significant p-value of 0.12 owing to the narrow CI of the RE-DUAL PCI arm located far right from the line of no effect.

Outcomes on Stent Thrombosis

The Mantel-Haenzel (M-H) random fixed effects model pooled estimates showed no statistically significant difference between standard and reduced doses of DOACs on stent thrombosis (RR 1.48, 95% CI 0.73 – 3.01, p = 0.28) (see Figure 6). The pooled estimates yielded a low heterogeneity with an I^2 of 0% but with a non-significant p-value of 0.65 owing to major difference in weight between the two subgroups constituting a near-double weight of RE-DUAL PCI in comparison to PIONEER AF-PCI reduced dose treatment arms.

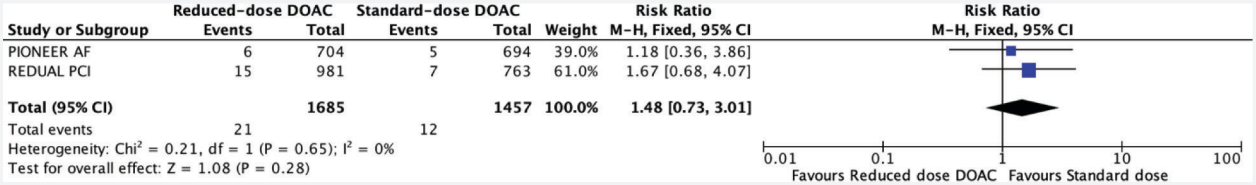

Figure 6. Forest Plot on Reduced Dose Versus Standard Dose DOACs Efficacy Endpoint: Stent Thrombosis

DISCUSSION

The four RCTs were specifically designed to assess the independent effect of anticoagulant and antiplatelet therapy in patients with AF and recent PCI. In participants with AF who had undergone PCI with stent placement, treatment that included DAPT was associated with a lower risk of clinically significant bleeding than was standard triple therapy that included a VKA. Although the choice of a $P2Y_{12}$ inhibitor was left to the treating physician, more than 90% of patients were treated with clopidogrel instead of more potent agents, which was consistent with most guidance statements.

AUGUSTUS and ENTRUST AF-PCI trials used three different regimens of full-dose anticoagulation therapy, ASA plus a $P2Y_{12}$ inhibitor for the first group; reduced-dose anticoagulation therapy, ASA plus a $P2Y_{12}$ inhibitor for the second group; and a VKA, ASA plus $P2Y_{12}$ inhibitor for the third group. The first two groups led to lower incidence of both bleeding and composite of death than did a VKA. For other outcomes included in the studies, dual versus triple therapy was not statistically significant especially with regards to both stent thrombosis and MACE.

PIONEER AF-PCI and RE-DUAL PCI trials used two different regimens of full-dose anticoagulation therapy plus a $P2Y_{12}$ inhibitor, which resulted in a risk of major or clinically relevant nonmajor bleeding events that was significantly lower than the risk with triple therapy with warfarin; in addition, dual therapy was noninferior to triple therapy with warfarin with respect to the composite efficacy end point of thromboembolic events, death or unplanned revascularization.

In summary, DAPT was non-inferior to triple therapy and had lower risks of major bleeding or clinically relevant nonmajor bleeding as compared to triple therapy. However, an individualized approach focusing on individual risk stratification is encouraged, especially among elderly patients, those with severe renal insufficiency, or other major co-existing conditions.

CONCLUSION

In patients with AF who had undergone PCI, the risk of bleeding was lower among those who received dual therapy with DOAC + $P2Y_{12}$ than among those who received triple therapy with warfarin, a $P2Y_{12}$ inhibitor, and aspirin. However, dual therapy was noninferior to triple therapy with respect to the risk of stent thrombosis and MACE. Over the past years, several NOACs, including Apixaban, Rivaroxaban, Edoxaban and Dabigatran have been studied in the setting of AF showing at least similar efficacy but also safer profiles as compared with warfarin. Ultimately, the antithrombotic and antiplatelet therapy for each individual patient must be tailored to each patient's clinical situation, and overall thrombotic and bleeding risks.

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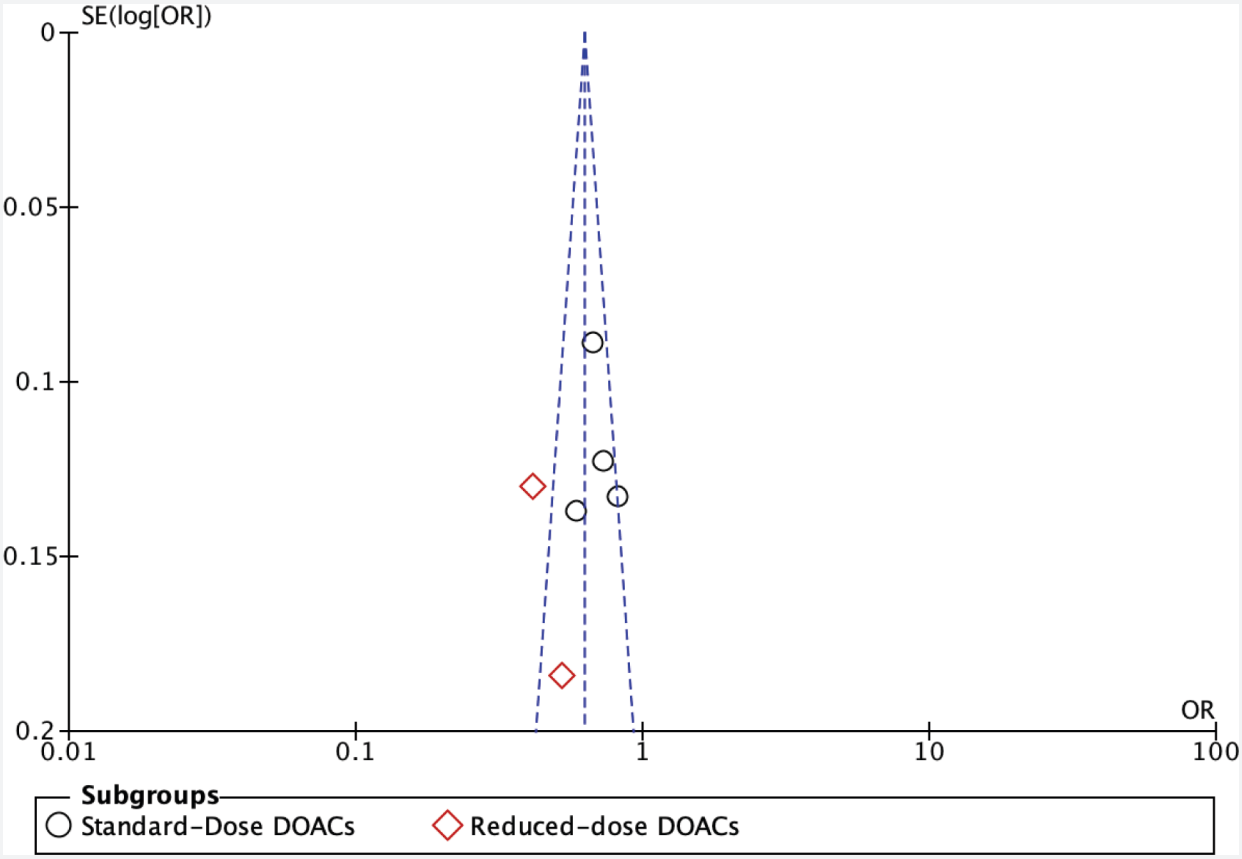
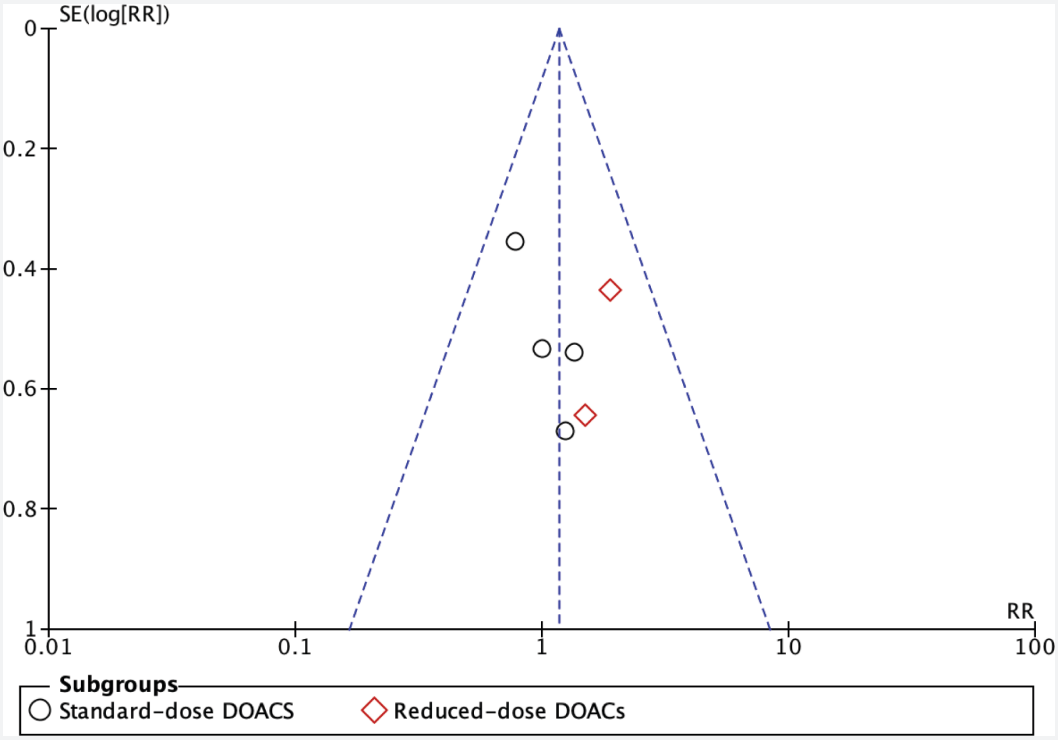
SUPPLEMENTAL FIGURE 1



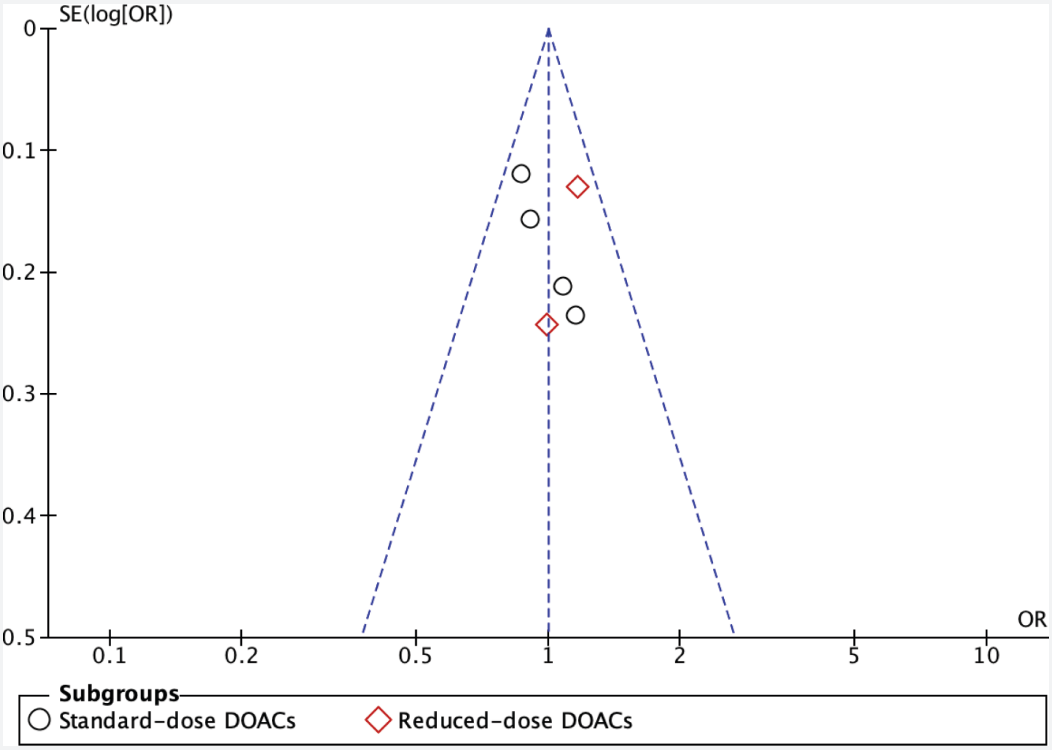
Supplemental Figure 1. Funnel Plot for Assessment of DOAC + $P2Y_{12}$ Versus VKA + DAPT on ISTH Major Bleeding or Clinically Significant Non-Major Bleeding

SUPPLEMENTAL FIGURE 2



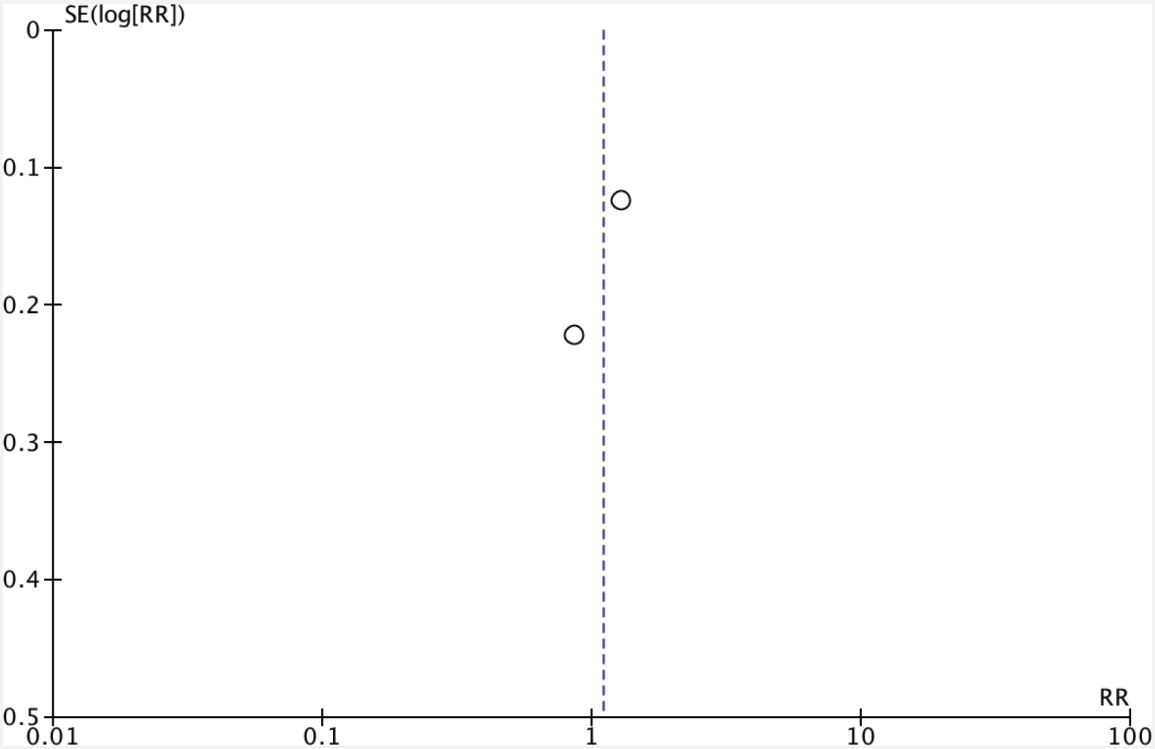
Supplemental Figure 2. Funnel Plot for Assessment of DOAC + $P2Y_{12}$ Versus VKA + DAPT on Stent Thrombosis

SUPPLEMENTAL FIGURE 3



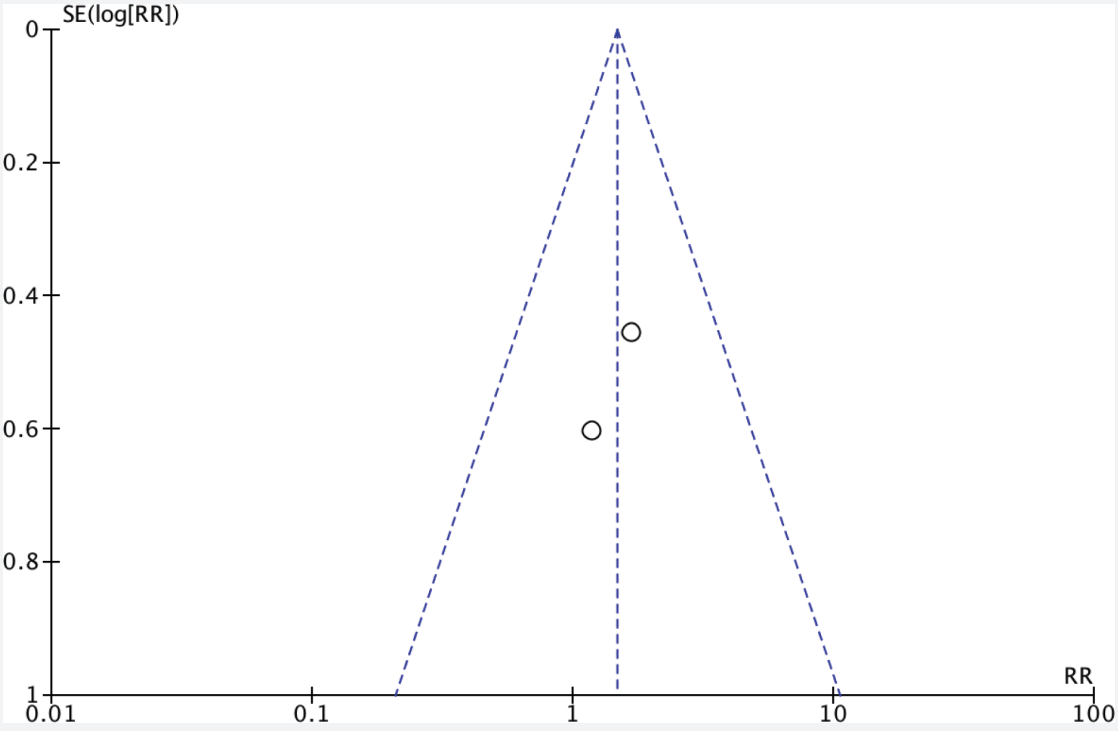
Supplemental Figure 3. Funnel Plot for Assessment of DOAC + $P2Y_{12}$ Versus VKA + DAPT on Major Adverse Cardiovascular Events

SUPPLEMENTAL FIGURE 4



Supplemental Figure 4. Funnel Plot for Assessment of Reduced Dose Versus Standard Dose DOACs on Major Adverse Cardiovascular Events

SUPPLEMENTAL FIGURE 5



Supplemental Figure 5. Funnel Plot for Assessment of Reduced Dose Versus Standard Dose DOACs on Stent Thrombosis