REVIEW

Annals of Internal Medicine

Dual Versus Triple Therapy for Atrial Fibrillation After Percutaneous Coronary Intervention

A Systematic Review and Meta-analysis

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Background: The safety and effectiveness of dual therapy (direct oral anticoagulant [DOAC] plus P2Y12 inhibitor) versus triple therapy (vitamin K antagonist plus aspirin and P2Y12 inhibitor) in patients with nonvalvular atrial fibrillation (AF) after percutaneous coronary intervention (PCI) is unclear.

Purpose: To examine the effects of dual versus triple therapy on bleeding and ischemic outcomes in adults with AF after PCI.

Data Sources: Searches of PubMed, EMBASE, and the Cochrane Library (inception to 31 December 2019) and ClinicalTrials.gov (7 January 2020) without language restrictions; journal Web sites; and reference lists.

Study Selection: Randomized controlled trials that compared the effects of dual versus triple therapy on bleeding, mortality, and ischemic events in adults with AF after PCI.

Data Extraction: Two independent investigators abstracted data, assessed the quality of evidence, and rated the certainty of evidence.

Data Synthesis: Four trials encompassing 7953 patients were selected. At the median follow-up of 1 year, high-certainty evidence showed that dual therapy was associated with reduced risk for major bleeding compared with triple therapy (risk difference [RD], −0.013 [95% CI, −0.025 to −0.002]). Low-certainty evidence showed inconclusive effects of dual versus triple therapy on risks for all-cause mortality (RD, 0.004 [CI, −0.010 to 0.017]), cardiovascular mortality (RD, 0.001 [CI, −0.011 to 0.013]), myocardial infarction (RD, 0.003 [CI, −0.010 to 0.017]), stent thrombosis (RD, 0.003 [CI, −0.005 to 0.010]), and stroke (RD, −0.003 [CI, −0.010 to 0.005]). The upper bounds of the CIs for these effects were compatible with possible increased risks with dual therapy.

Limitation: Heterogeneity of study designs, dosages of DOACs, and types of P2Y12 inhibitors.

Conclusion: In adults with AF after PCI, dual therapy reduces risk for bleeding compared with triple therapy, whereas its effects on risks for death and ischemic end points are still unclear.

Primary Funding Source: None.

Ann Intern Med. 2020;172:474-483. doi:10.7326/M19-3763 **Annals.org**
For author affiliations, see end of text.
This article was published at Annals.org on 17 March 2020.

Revascularization by percutaneous coronary intervention (PCI) is considered the standard of care for patients with acute coronary syndrome (ACS) (1, 2). Dual antiplatelet therapy (DAPT; aspirin plus P2Y12 inhibitor) prevents major adverse cardiovascular events (MACE) after PCI for ACS or stable coronary artery disease (1–3). However, approximately 5% to 10% of patients undergoing PCI have atrial fibrillation (AF), which complicates the choice of optimal antithrombotic therapy (4–6). Evidence has favored direct oral anticoagulant (DOAC) agents over vitamin K antagonists (VKAs) in patients with nonvalvular AF for better safety (in terms of bleeding) and effectiveness (in terms of MACE) (7, 8). More recently, randomized controlled trials (RCTs) compared an alternative approach—dual therapy consisting of a DOAC and a P2Y12 inhibitor versus triple therapy comprising a VKA and DAPT—to identify an ideal antithrombotic strategy in patients with AF after PCI (6, 9–11). Theoretically, the cardiovascular benefits gained by using triple therapy could be offset by higher risk for bleeding, whereas withdrawal of aspirin might lead to higher rates of stent thrombosis and ischemic events with dual therapy (2, 12). We did a meta-analysis of contemporary RCTs to address the clinical conundrum of which antithrombotic regimen—dual (DOAC plus P2Y12 inhibitor) or triple (VKA plus DAPT) therapy—is most appropriate for the management of patients with AF and coronary artery disease who had PCI.

See also:

Editorial comment 495

METHODS

This meta-analysis was conducted following the Cochrane Collaboration guidelines and reported according to PRISMA (Preferred Reporting Items for Systematic reviews and Meta-Analyses) (13, 14). The protocol, although not registered, was submitted to PROSPERO on 21 November 2019.

Data Sources and Searches

The literature search was done without language restrictions using the electronic databases of PubMed, EMBASE, and the Cochrane Library from inception to 31 December 2019 and ClinicalTrials.gov (7 January 2020). Additional sources were Web sites of major cardiovascular and medical journals (www.onlinejacc.org, http://annals.org/aim, https://academic.oup.com/eurheartj, www.nejm.org, www.ahajournals.org/journal/circ, and https://jamanetwork.com) and bibliographies of relevant studies. The search strategy included broad search terms, such as

new oral anticoagulant, *direct oral anticoagulant*, *DOAC*, *vitamin K antagonist*, *VKA*, *antiplatelets*, *percutaneous coronary intervention*, *PCI*, *acute coronary syndrome*, *ACS*, and *atrial fibrillation* (**Appendix Tables 1** to **4**, available at Annals.org).

Study Selection

The prespecified inclusion criteria were RCTs that reported bleeding, mortality, and ischemic outcomes of interest and compared dual therapy using DOACs plus P2Y12 inhibitors versus triple therapy using VKAs plus DAPT in adult patients (aged ≥18 years) with AF receiving PCI. We placed no limitations on language, sample size, or follow-up duration. We excluded observational studies, registries, and post hoc analyses of RCTs. We also excluded RCTs that assessed dual therapy comprising a VKA plus a P2Y12 inhibitor or any oral anticoagulant plus aspirin and trials where a minority of patients (<50%) received PCI.

After removing duplicates, we screened articles first at the title and abstract level and then at the full-text level. Two investigators (M.U.K. and M.S.K.) independently screened and selected articles, and conflicts were resolved by discussion or opinion of an additional investigator (S.U.K.).

Data Extraction, Outcomes, and Quality Assessment

Two investigators (M.U.K. and M.S.K.) who were not involved in any of the selected trials independently abstracted data using prespecified collection forms, appraised the accuracy of the abstractions, and resolved any discrepancies by consensus after discussion with a third investigator (S.U.K.). The following information was abstracted: first author, journal, characteristics of the trial and participants, crude point estimates, number of events, sample size, and follow-up duration. The dual therapy group of RE-DUAL PCI (Randomized Evaluation of Dual Antithrombotic Therapy With Dabigatran vs. Triple Therapy With Warfarin in Patients with Nonvalvular AF Undergoing PCI) (10) used 2 dosages of dabigatran, 110 mg and 150 mg twice daily. As per our prespecified plan to analyze the 2 dosages separately, we abstracted outcomes from dual therapy with dabigatran, 150 mg, for our main analysis because this dose is approved in the United States for stroke prevention in patients with AF without significant renal impairment. We used data regarding dual therapy with dabigatran, 110 mg, for sensitivity analyses.

We also reviewed other meta-analyses of the selected trials for any key information not available in the original trial report (15–17). Specifically, data on all of the outcomes of interest were unavailable in the main article for AUGUSTUS (Open-Label, 2 × 2 Factorial, Randomized Controlled, Clinical Trial to Evaluate the Safety of Apixaban vs. VKA and Aspirin vs. Aspirin Placebo in Patients With AF and ACS or PCI) (6) but were subsequently provided in the meta-analysis by Lopes (the lead investigator of the trial) and colleagues (15). We abstracted the exclusive data for DOAC-based dual therapy and VKA-based triple therapy from this meta-analysis.

Two unblinded investigators (M.U.K. and M.S.K.) independently appraised the potential risk of bias of the RCTs using the Cochrane Risk of Bias Tool at the study and outcome levels (**Appendix Table 5**, available at Annals.org) (18, 19). The data abstraction of outcomes was based on the intention-to-treat principle. The main outcomes of interest were major bleeding events that met TIMI (Thrombolysis in Myocardial Infarction) criteria and all-cause mortality. The other end points were TIMI major and minor bleeding, intracerebral hemorrhage, trial-defined bleeding events, cardiovascular mortality, myocardial infarction (MI), stent thrombosis, stroke, and MACE.

Data Synthesis and Analysis

Two reviewers (M.U.K. and M.O.) assessed the certainty of the evidence under the supervision of a third reviewer (S.U.K.) using the GRADE (Grading of Recommendations Assessment, Development and Evaluation) approach (GRADEpro GDT) (https://gdt.gradepro.org/app) (**Appendix Table 6**, available at Annals.org) (20). Certainty of evidence was classified as high, moderate, low, or very low.

Estimates were pooled using an inverse-variance random-effects model. The Paule–Mandel method was used for estimation of τ^2. We applied standard or modified (in case $\tau^2 = 0$) Hartung–Knapp–Sidik–Jonkman small-sample adjustments because we had fewer than 10 studies (21). We reported effect sizes as the risk difference (RD) with 95% CI. We used I^2 statistics to measure the extent of unexplained statistical heterogeneity: I^2 greater than 50% was considered a high degree of between-study heterogeneity (22). We did not examine publication bias because the small number of studies (<10) meant that our meta-analysis was underpowered to detect it. We used "meta" commands from Stata, version 16 (StataCorp), for all analyses.

Role of the Funding Source

The study received no funding.

RESULTS

Design of Included Trials

Of 265 articles reviewed for eligibility, we selected 4 RCTs encompassing 7953 patients (**Appendix Figure 1**, available at Annals.org). The RCTs varied substantially in design and participant characteristics (**Table** and **Appendix Table 7** [available at Annals.org]). PIONEER AF-PCI (Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral VKA Treatment Strategy in Subjects With AF Who Undergo PCI) (9) randomly assigned 2124 patients with AF receiving PCI into the following 3 antithrombotic groups: rivaroxaban, 15 mg daily, plus a P2Y12 inhibitor (dual therapy); rivaroxaban, 2.5 mg twice daily, plus DAPT; and a VKA plus DAPT (triple therapy). RE-DUAL PCI (10) randomly assigned 2725 patients with AF receiving PCI (51% with ACS) to triple therapy or 1 of 2 dosages of dabigatran-based dual therapy (150 or 110 mg twice daily). AUGUSTUS (6) randomly assigned

Table. Characteristics of Included Trials

Characteristic	PIONEER AF-PCI (9)	RE-DUAL PCI (10)	AUGUSTUS (6)	ENTRUST-AF PCI (11)
Trial name	Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral VKA Treatment Strategy in Subjects With AF Who Undergo PCI	Randomized Evaluation of Dual Antithrombotic Therapy With Dabigatran vs. Triple Therapy With Warfarin in Patients With Nonvalvular AF Undergoing PCI	Open-Label, 2 × 2 Factorial, Randomized Controlled, Clinical Trial to Evaluate the Safety of Apixaban vs. VKA and Aspirin vs. Aspirin Placebo in Patients With AF and ACS or PCI	Edoxaban Treatment Versus VKA in Patients With AF Undergoing PCI
Patients, *n*	2124	2725	4614	1506
Enrollment initiation	May 2013	July 2014	June 2015	February 2017
Enrollment completion	July 2015	October 2016	April 2018	June 2019
Year of publication	2016	2017	2019	2019
Population	Patients who had paroxysmal, persistent, or permanent nonvalvular AF and who had received PCI with stent placement within 72 h	Patients who had nonvalvular AF and had successfully undergone PCI with a bare-metal or drug-eluting stent within the previous 6–120 h	Patients with AF with recent ACS (within 14 d) and/or PCI	Patients with AF who had a successful PCI for stable CAD or ACS (within 4–5 d)
Trial type	Open-label, multicenter RCT	Open-label, multicenter RCT	Open-label, multicenter RCT	Open-label, multicenter RCT
Inclusion criteria	Age ≥18 y AF that occurred within past 1 y, or AF that occurred >1 y ago and the participants had been receiving an OAC for AF for the past 3 mo	Age ≥18 y Patients with nonvalvular AF who just had PCI with a bare-metal or drug-eluting stent for ACS or unstable angina Patients who have been receiving an OAC or who were treatment-naive before PCI	Age ≥18 y Patients with either active or a history of AF or flutter with planned or existing use of an OAC for prophylaxis of thromboembolism Patients who have had ACS and/or PCI within the prior 14 d Planned use of an approved P2Y12 inhibitor for ≥6 mo	Age ≥18 y Nonvalvular AF and PCI for stable CAD or ACS OAC for >12 mo
Exclusion criteria	History of stroke or transient ischemic attack Significant gastrointestinal bleeding within 12 mo Calculated creatinine clearance <30 mL/min/1.73 m^2 Anemia with a hemoglobin level <100 g/L	Presence of bioprosthetic or mechanical heart valves Creatinine clearance <30 mL/min/1.73 m^2	Patients with other conditions that require anticoagulation (such as prosthetic valves or moderate or severe mitral stenosis) Severe renal insufficiency History of intracranial hemorrhage	Other conditions that require anticoagulation, such as moderate to severe mitral stenosis, mitral valve rheumatic disease, mechanical heart valve, or pulmonary embolism History of LAA closure, left ventricular or LAA thrombus High risk for bleeding Contraindication to anticoagulation Anemia with a hemoglobin level <80 g/L and platelet count <50 × 10^9 cells/L Renal failure, liver disease
Randomization sequence	Central randomization, computer-generated	Interactive response technology	Interactive voice response system	Web-based, central randomization, computer-generated
Treatments	DOAC + P2Y12 inhibitor (rivaroxaban, 15 mg/d; clopidogrel, 75 mg/d) DOAC + DAPT (rivaroxaban, 2.5 mg twice daily; aspirin, 75–100 mg/d; clopidogrel, 75 mg/d) VKA + DAPT (warfarin*; aspirin, 75–100 mg/d; clopidogrel, 75 mg/d)	DOAC (low dose) + P2Y12 inhibitor (dabigatran etexilate, 110 mg twice daily; either clopidogrel or ticagrelor) DOAC (high dose) + P2Y12 inhibitor (dabigatran etexilate, 150 mg twice daily; either clopidogrel or ticagrelor) VKA + DAPT (warfarin; aspirin, ≤100 mg/d; either clopidogrel or ticagrelor)	DOAC + DAPT (apixaban, 5 mg twice daily; aspirin, 81 mg/d; clopidogrel or ticagrelor or prasugrel) DOAC + P2Y12 inhibitor (apixaban, 5 mg twice daily; clopidogrel or ticagrelor or prasugrel) VKA + DAPT (warfarin; aspirin, 81 mg/d; clopidogrel or ticagrelor or prasugrel) VKA + P2Y12 inhibitor (warfarin; clopidogrel or ticagrelor or prasugrel)	DOAC + P2Y12 inhibitor (edoxaban, 60 mg/d or 30 mg/d; clopidogrel, 75 mg/d, or prasugrel, 5–10 mg/d, or ticagrelor, 90 mg twice daily) VKA + DAPT (warfarin; aspirin, 100 mg/d; clopidogrel, 75 mg/d, or prasugrel, 5–10 mg/d, or ticagrelor, 90 mg twice daily)

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Table–Continued

Characteristic	PIONEER AF-PCI (9)	RE-DUAL PCI (10)	AUGUSTUS (6)	ENTRUST-AF PCI (11)
Definition of primary bleeding outcome	Composite of major bleeding or minor bleeding according to TIMI or bleeding requiring medical attention	Major or CRNM bleeding event according to ISTH	Composite of major or CRNM bleeding event according to ISTH	Composite of major or CRNM bleeding event according to ISTH
Definition of MACE	Composite of death from cardiovascular causes, MI, or stroke	Thromboembolic events, death, or unplanned revascularization	Composite of all-cause death or ischemic event	Composite of cardiovascular death, stroke, systemic embolic events, MI, or definite stent thrombosis
Definition of stent thrombosis	Definite stent thrombosis (not clearly reported)	Definite stent thrombosis	Definite/probable stent thrombosis	Definite stent thrombosis
Type of index event, %†				
Non-STEMI	18.1	21.7	–	52
STEMI	11.5	14.7	–	52
Unstable angina	22.2	17.7	–	52
Type of stent, %				
Bare-metal	32.2	14.9	–	12.2
Drug-eluting	65.9	82.7	–	84.7
Bare-metal and drug-eluting	1.9	1.5	–	1.5
Type of P2Y12 inhibitor, %				
Clopidogrel	94.7	87.8	–	92.5
Prasugrel	1.2	0	–	<1
Ticagrelor	4.1	12.2	–	7.5
Analysis	Modified ITT	ITT	Modified ITT and ITT	ITT
Follow-up	12 mo	14 mo	6 mo	12 mo
Funding	Janssen Scientific Affairs and Bayer Pharmaceuticals	Boehringer Ingelheim	Bristol-Myers Squibb and Pfizer	Daiichi Sankyo

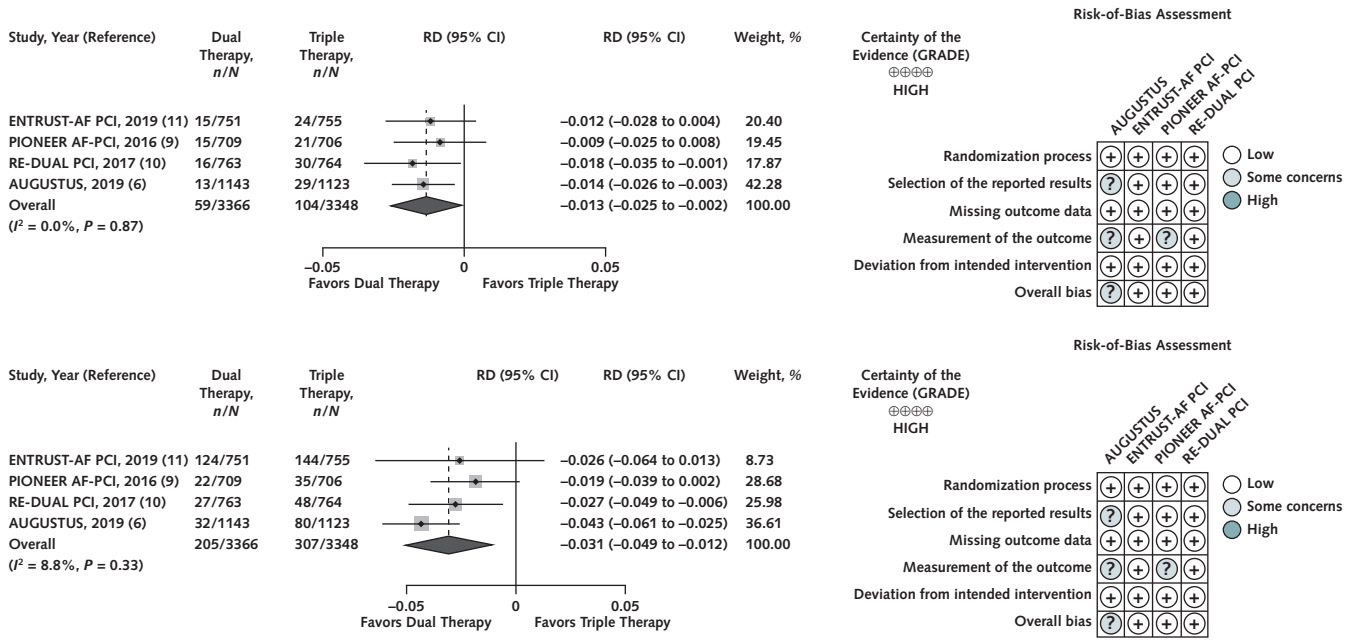
ACS = acute coronary syndrome; AF = atrial fibrillation; AUGUSTUS = Open-Label, 2 × 2 Factorial, Randomized Controlled, Clinical Trial to Evaluate the Safety of Apixaban vs. Vitamin K Antagonist and Aspirin vs. Aspirin Placebo in Patients With Atrial Fibrillation and Acute Coronary Syndrome or Percutaneous Coronary Intervention; CAD = coronary artery disease; CRNM = clinically relevant nonmajor; DAPT = dual antiplatelet therapy; DOAC = direct OAC (non-VKA); ENTRUST-AF PCI = Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention; ISTH = International Society on Thrombosis and Haemostasis; ITT = intention-to-treat; LAA = left atrial appendage; MACE = major adverse cardiovascular events; MI = myocardial infarction; OAC = oral anticoagulant; PCI = percutaneous coronary intervention; PIONEER AF-PCI = Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention; RCT = randomized controlled trial; RE-DUAL PCI = Randomized Evaluation of Dual Antithrombotic Therapy With Dabigatran vs. Triple Therapy With Warfarin in Patients With Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention; STEMI = ST-segment elevation MI; TIMI = Thrombolysis in Myocardial Infarction; VKA = vitamin K antagonist.
* Target international normalized ratio, 2–3.
† 100% of patients had ACS in AUGUSTUS.

4614 patients with AF presenting with ACS or having PCI in a 2 × 2 factorial design to either 5 mg of apixaban twice daily versus VKA or aspirin versus placebo, both on a background of P2Y12 inhibitor therapy. The ENTRUST-AF PCI (Edoxaban Treatment Versus VKA in Patients With AF Undergoing PCI) trial (11) randomly assigned 1506 patients with AF and recent PCI to full-dose edoxaban-based dual therapy versus VKA-based triple therapy. Follow-up was 12 months in PIONEER AF-PCI and ENTRUST-AF PCI, 14 months in RE-DUAL PCI, and 6 months in AUGUSTUS. The definition of the primary bleeding end point varied across trials: RE-DUAL PCI, AUGUSTUS, and ENTRUST-AF PCI defined it as a major or clinically relevant nonmajor bleeding event according to criteria from the International Society on Thrombosis and Haemostasis, whereas PIONEER AF-PCI defined it as a composite of TIMI major or minor bleeding or bleeding requiring medical attention. All patients received PCI except in AUGUSTUS, where 23.9% were treated with medical therapy (6).

Overall, mean patient age ranged from 68.6 to 71.7 years, and the proportion of enrolled women varied from 23.6% to 30.7%. Disease prevalence ranged from 73.3% to 91.0% for hypertension, 28.8% to 37.9% for diabetes, and 17.1% to 52.0% for ACS. Between 65.4% and 86.2% of patients received a drug-eluting stent. Most patients had annual thromboembolic and bleeding risks greater than 3%. The median follow-up duration across the trials was 1 year (interquartile range, 0.87 to 1.04 years).

All trials were industry-funded, and all used an open-label design that could affect treatment or reporting bias. In PIONEER AF-PCI (9), randomization was adequate across main comparative groups but patients were not randomly assigned to a stratum of DAPT duration (1, 6, or 12 months); this stratum was allocated at the clinician's discretion, generating risk for selection bias. All trials reported minimal loss to follow-up and had minimal missing outcome data (the figures show full risk-of-bias assessments).

Figure 1. Effect of dual versus triple therapy on TIMI major bleeding (*top*) and TIMI major and minor bleeding (*bottom*).



AUGUSTUS = Open-Label, 2 × 2 Factorial, Randomized Controlled, Clinical Trial to Evaluate the Safety of Apixaban vs. Vitamin K Antagonist and Aspirin vs. Aspirin Placebo in Patients With Atrial Fibrillation and Acute Coronary Syndrome or Percutaneous Coronary Intervention; ENTRUST-AF PCI = Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention; GRADE = Grading of Recommendations Assessment, Development and Evaluation; PIONEER AF-PCI = Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention; RD = risk difference; RE-DUAL PCI = Randomized Evaluation of Dual Antithrombotic Therapy With Dabigatran vs. Triple Therapy With Warfarin in Patients With Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention; TIMI = Thrombolysis in Myocardial Infarction.

Outcomes

High-certainty evidence showed that dual therapy was associated with lower risks for TIMI major bleeding (RD, −0.013 [95% CI, −0.025 to −0.002]) (**Figure 1**, *top*), TIMI major and minor bleeding (RD, −0.031 [−0.049 to −0.012]) (**Figure 1**, *bottom*), and trial-defined bleeding (RD, −0.072 [CI, −0.129 to −0.015]) (**Appendix Figure 2** [*top*], available at Annals.org) compared with triple therapy. We found no statistically significant difference between dual and triple therapy in terms of intracerebral hemorrhage (RD, −0.004 [CI, −0.009 to 0.000]; moderate-certainty evidence) (**Appendix Figure 2**, *bottom*).

Low-certainty evidence showed that dual therapy had an inconclusive effect compared with triple therapy on risks for all-cause mortality (RD, 0.004 [CI, −0.010 to 0.017]) (**Figure 2**, *top*), cardiovascular mortality (RD, 0.001 [CI, −0.011 to 0.013]) (**Figure 2**, *bottom*), MI (RD, 0.003 [CI, −0.010 to 0.017]) (**Figure 3**, *top*), stent thrombosis (RD, 0.003 [CI, −0.005 to 0.010]) (**Figure 3**, *bottom*), and MACE (RD, 0.003 [CI, −0.016 to 0.023]) (**Figure 4**, *top*). The upper bounds of the CIs of these estimates were compatible with a possible increased risk for ischemic outcomes with dual versus triple therapy. Low-certainty evidence showed no statistically significant difference in effect on stroke risk between dual and triple therapy (RD, −0.003 [CI, −0.010 to 0.005]) (**Figure 4**, *bottom*).

Sensitivity analyses after pooling dual therapy using dabigatran, 110 mg, showed consistent bleeding and ischemic outcomes compared with triple therapy (**Appendix Figures 3** to **7**, available at Annals.org).

DISCUSSION

The following are the 2 principal findings of our meta-analysis: high-certainty evidence shows that DOAC-based dual therapy reduces risk for bleeding events compared with VKA-based triple therapy, and low-certainty evidence shows inconclusive effects of dual versus triple therapy on risks for death and ischemic end points, such as MI, stent thrombosis, stroke, and MACE. Results including sensitivity analyses, however, were compatible with a possible increased risk for ischemic end points with use of dual versus triple therapy.

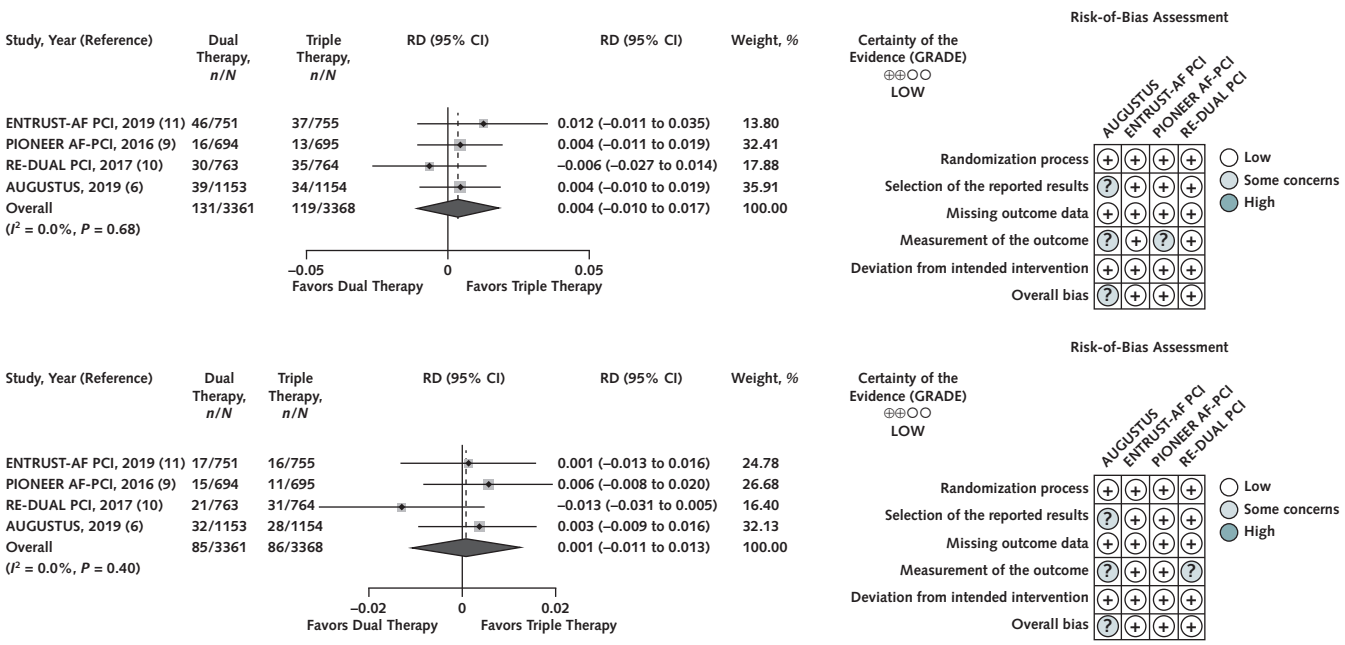
Our results reflect the outcome trends in all 4 included RCTs. In PIONEER AF-PCI (9), both rivaroxaban-based antithrombotic regimens showed lower risk for clinically significant bleeding than triple therapy (16.8% vs. 18.0% vs. 26.7%) at 12 months. In RE-DUAL PCI (10) at 14 months, triple therapy was associated with a 5.5–percentage point increase in major or clinically relevant nonmajor bleeding events compared with dabigatran, 150 mg; the corresponding increase compared with dabigatran, 110 mg, was 11.5 percentage points.

These findings were consistent regardless of index PCI subgroup (such as ACS or stable coronary artery disease), stent type, or type of P2Y12 inhibitor therapy. What remained unclear from these 2 trials was whether the decreased bleeding risk seen with dual therapy was exclusively driven by using a DOAC instead of a VKA or was due to an aspirin-free strategy (12). AUGUSTUS (6) explored this issue: At 6 months, apixaban was associated with a 4.2–percentage point reduction in major or clinically relevant nonmajor bleeding compared with VKA; addition of aspirin was associated with a 7.1–percentage point increase in bleeding compared with placebo. Contrary to all previous trials, ENTRUST-AF PCI showed no significant differences for major or clinically relevant nonmajor bleeding events between dual therapy (17%) and triple therapy (20%) (11). These results could have been driven by lower bleeding rates in the VKA group during the first 2 weeks of treatment, when a high proportion of patients did not achieve an international normalized ratio of 2 (69% in the first week and 42% in the second week).

All RCTs showed a numerical increase in ischemic end points with dual therapy. These findings should be cautiously interpreted in light of the limitations of the individual RCTs. In PIONEER AF-PCI, statistical power to detect important differences between groups for all efficacy end points was low, varying between 5.4% and 13% (9). The stent thrombosis end point was not centrally adjudicated, and the directionality of efficacy end points was inconsistent among antithrombotic groups. All dosing regimens of rivaroxaban were less than the 20-mg daily dose approved for stroke prevention in AF for patients without significant renal impairment. In RE-DUAL PCI, the composite efficacy end point was underpowered to detect clinical differences (10). Of note, a pooled analysis of both doses of dabigatran-based dual therapy in RE-DUAL PCI showed a 1.1–percentage point increase in the efficacy end point (10). However, the rate of the efficacy end point was numerically lower in the comparison of dual therapy using 150 mg of dabigatran (11.8%) versus triple therapy (12.8%) than in the comparison of dual therapy using 110 mg of dabigatran (13.7%) versus triple therapy (13.4%); thus, it can be inferred that higher thromboembolic tendency might be solely limited to the 110-mg–based regimen. In AUGUSTUS, rates of MI and stent thrombosis increased by 0.5% and 0.4%, respectively, among patients who were not receiving aspirin (6). Nevertheless, low event rates, inadequate power to assess cardiovascular outcomes, and limited follow-up duration were major limitations of this trial.

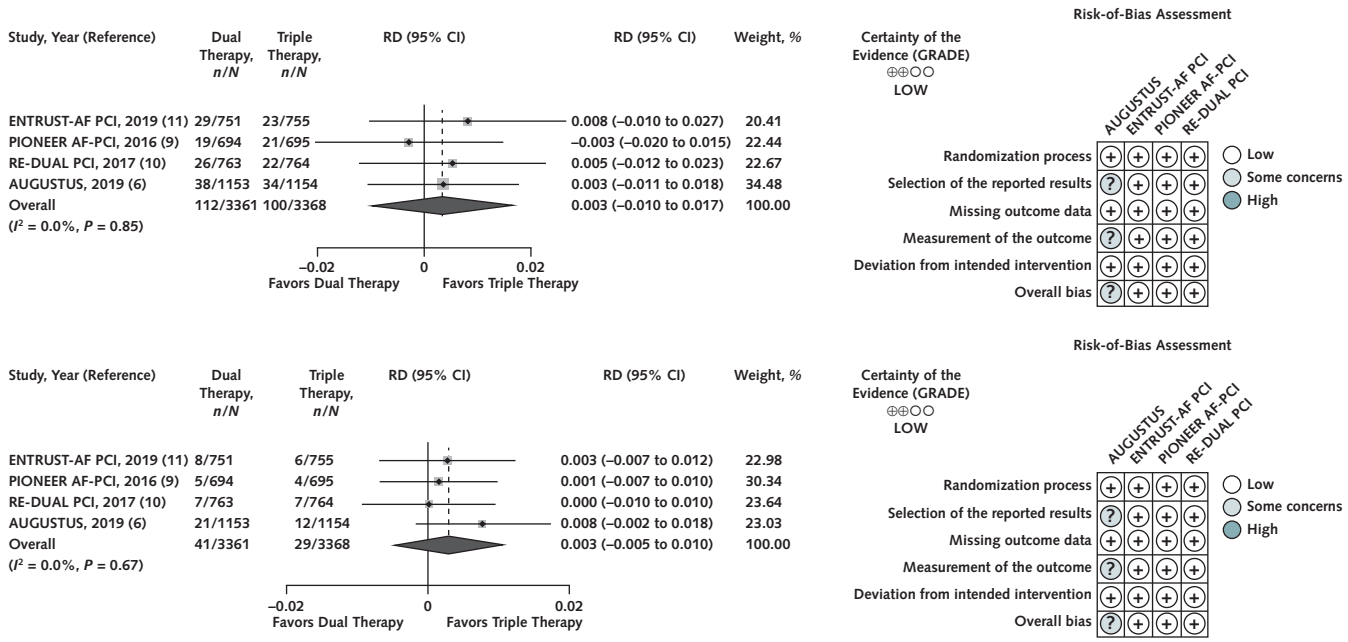
The management of AF after PCI is a common clinical conundrum. Fundamental questions include the timing of aspirin withdrawal, whether discontinuation of aspirin therapy can compromise any potential cardiovascular benefits, and the choice of DOAC versus VKA

Figure 2. Effect of dual versus triple therapy on all-cause mortality (*top*) and cardiovascular mortality (*bottom*).



AUGUSTUS = Open-Label, 2 × 2 Factorial, Randomized Controlled, Clinical Trial to Evaluate the Safety of Apixaban vs. Vitamin K Antagonist and Aspirin vs. Aspirin Placebo in Patients With Atrial Fibrillation and Acute Coronary Syndrome or Percutaneous Coronary Intervention; ENTRUST-AF PCI = Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention; GRADE = Grading of Recommendations Assessment, Development and Evaluation; PIONEER AF-PCI = Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention; RD = risk difference; RE-DUAL PCI = Randomized Evaluation of Dual Antithrombotic Therapy With Dabigatran vs. Triple Therapy With Warfarin in Patients With Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention.

Figure 3. Effect of dual versus triple therapy on myocardial infarction (*top*) and stent thrombosis (*bottom*).



AUGUSTUS = Open-Label, 2 × 2 Factorial, Randomized Controlled, Clinical Trial to Evaluate the Safety of Apixaban vs. Vitamin K Antagonist and Aspirin vs. Aspirin Placebo in Patients With Atrial Fibrillation and Acute Coronary Syndrome or Percutaneous Coronary Intervention; ENTRUST-AF PCI = Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention; GRADE = Grading of Recommendations Assessment, Development and Evaluation; PIONEER AF-PCI = Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention; RD = risk difference; RE-DUAL PCI = Randomized Evaluation of Dual Antithrombotic Therapy With Dabigatran vs. Triple Therapy With Warfarin in Patients With Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention.

for oral anticoagulation. All included RCTs tested the safety of early withdrawal of aspirin—that is, before hospital discharge—on the basis of the rationale that risk for bleeding is generally higher during the first month after PCI because of periprocedural use of antithrombotic therapy (6, 9–12, 23). A guideline from the American College of Cardiology, American Heart Association, and Heart Rhythm Society recommends limiting aspirin use in the preprocedural period and during hospitalization (24). However, 2018 guidelines from the European Society of Cardiology restrict use of dual therapy only in patients with high bleeding risk at baseline and recommend 1 to 6 months of triple therapy for all other patients, based on thrombotic and bleeding risk assessment (class of recommendation, IIa for both guidelines). These recommendations were generated before the AUGUSTUS and ENTRUST-AF PCI trials (6, 11). Our meta-analysis might promote more consistency between American and European society guidelines regarding the safety of early withdrawal of aspirin from triple therapy.

Historically, aspirin has remained the cornerstone of the secondary prevention strategies after PCI (23). However, an emerging paradigm shift favors P2Y12 inhibitor monotherapy over aspirin monotherapy after discontinuation of DAPT. Four recent RCTs (25–28) compared an early deescalation of DAPT to P2Y12 inhibitor monotherapy (1 to 3 months) versus 12 months of DAPT; these trials unanimously showed better safety in terms of bleeding events without worsening MACE. Aspirin has very limited efficacy in preventing cardioembolic stroke particular to AF given the specific nature of thrombi (that is, less platelet mass than arterial thrombi) (23). The post hoc analysis of the SPAF (Stroke Prevention in Atrial Fibrillation) trial confirmed that aspirin therapy resulted in greater reductions in the incidence of noncardioembolic than cardioembolic stroke (risk reduction, 100% vs. 31%; P = 0.01) (23, 29).

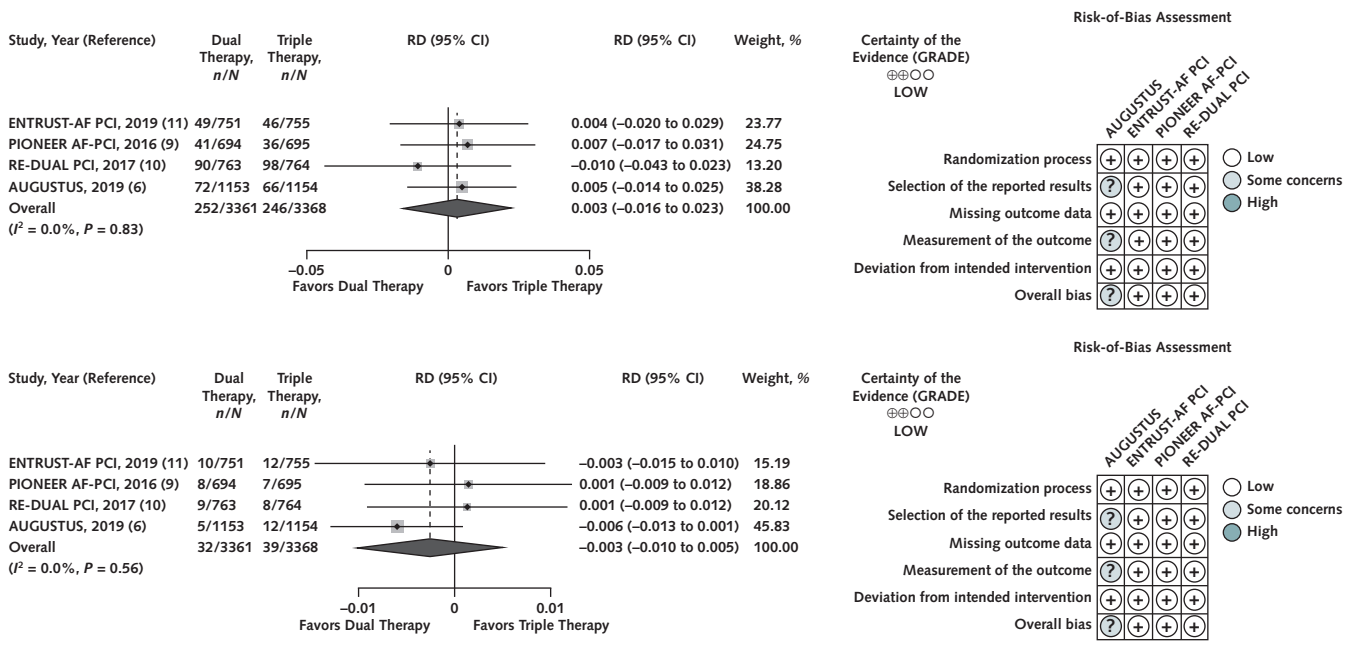
Regarding oral anticoagulation, DOACs have shown a more favorable risk–benefit profile than VKAs in AF (7). AUGUSTUS (6) showed that apixaban was associated with lower rates of death and hospitalization, driven by the incident hospitalization rate and 50% relative risk (RR) reduction in stroke compared with VKA. Current American and European guidelines also favor DOACs over VKAs for AF management in the absence of contraindications (1, 24). Finally, the factorial design of AUGUSTUS signaled that perhaps both aspects of antithrombotic strategies—early withdrawal of aspirin and preference for DOACs over VKAs—offer the optimal balance of safety and effectiveness in the management of AF after PCI.

Our results are generally consistent with those of other meta-analyses using the same RCT data (11, 15). However, a recent meta-analysis by Gargiulo and colleagues (30) showed a statistically significant 59%

higher RR for stent thrombosis with dual therapy than triple therapy. Their study varied from the current meta-analysis in several ways. Given the unique design of AUGUSTUS, it was critical to pool data specific to the DOAC-based dual therapy and VKA-based triple therapy groups (6). Pooling this data set using a DerSimonian–Laird random-effects model (a method used by Gargiulo and colleagues) will generate an RR of 1.55 (CI, 0.99 to 2.41) with dual versus triple therapy, as shown in the secondary analysis by Gargiulo and colleagues (30). However, they pooled the aspirin and placebo groups for their primary analyses without accounting for the fact that participants in both oral anticoagulant groups were randomly assigned to aspirin or placebo. The DerSimonian–Laird random-effects model is known to substantially underestimate the 95% CI when only a few studies report effect estimates (31). In the study by Gargiulo and colleagues (30), the RR for stent thrombosis was 1.59 (CI, 1.01 to 2.50), which barely excluded 1. This marginal effect could easily be due to the use of the DerSimonian–Laird estimator. We used a more robust statistical method that is consistent with general recommendations from Hartung and Knapp (32) and Veroniki and colleagues (21). Another meta-analysis by Vranckx and colleagues (11) had findings consistent with our own.

The included trials in our meta-analysis had methodological heterogeneities. In AUGUSTUS, patients were enrolled and randomly assigned to a group within 14 days (median time to randomization, 6.6 days) after an ACS episode or PCI. Time to randomization was shorter in other trials. In RE-DUAL PCI, aspirin therapy was discontinued after 1 month in patients with a bare-metal stent or after 3 months in patients with a drug-eluting stent. In PIONEER AF-PCI, patients received DAPT for 1, 6, or 12 months. Because we relied on trial-level information, we could not analyze results according to type of DOAC or P2Y12 inhibitor, age, or comorbid conditions (for example, diabetes; renal failure; or history of bleeding or procedure-related factors, such as coronary anatomy complexity, stent length, or left main stenting). Clopidogrel was used in more than 90% of participants, and a very small proportion received ticagrelor and prasugrel. Thus, we could not examine the influence of different P2Y12 inhibitors on outcomes. However, the component RCTs of this meta-analysis did not find statistically significant subgroup interactions across different P2Y12 inhibitors with regard to bleeding or cardiovascular end points (6, 10, 11). Such differences can be comprehensively addressed by pooling individual patient data across trials. In all RCTs, lower rates of ischemic events were observed than anticipated, resulting in limited statistical power to detect differences between groups in ischemic and mortality outcomes. All RCTs excluded patients with renal dysfunction and enrolled patients with

Figure 4. Effect of dual versus triple therapy on major adverse cardiovascular events (*top*) and stroke (*bottom*).



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relatively low bleeding risk, limiting the generalizability of the findings. The open-label design of the trials might bias the results in favor of dual therapy.

In conclusion, our meta-analysis shows high-certainty evidence that supports the use of DOAC-based dual therapy over VKA-based triple therapy for reducing bleeding risk in patients with AF who received PCI. The use of dual therapy versus triple therapy had an inconclusive effect on risks for death and ischemic outcomes. The certainty of this evidence was low, and upper bounds of CIs signaled a possible increased risk for the ischemic end points. Future RCTs, such as COACH-AF-PCI (Dabigatran vs. Warfarin With Nonvalvular AF Who Undergo PCI) (NCT03536611), APPROACH-ACS-AF (APixaban vs. PhenpRocoumon in Patients With ACS and AF) (NCT02789917), OPTIMAL (Optimal Antithrombotic Therapy for ACS Patients Concomitant AF Undergoing New Generation Drug-Eluting Stent Implantation) (NCT03234114), and the Japanese SAFE-A (SAFety and Effectiveness Trial of Apixaban Use in Association With DAPT in Patients With AF Undergoing PCI) study (33), will be valuable to gain further insight regarding ischemic end points.

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Financial Support: Drs. Michos and Zhao are funded by the Blumenthal Scholars Fund in Preventive Cardiology at Johns Hopkins University.

Disclosures: Authors have disclosed no conflicts of interest. Forms can be viewed at www.acponline.org/authors/icmje/ConflictOfInterestForms.do?msNum=M19-3763.

Reproducible Research Statement: *Study protocol:* Submitted to PROSPERO. *Statistical code and data set:* Available from Dr. Khan (e-mail, safinmc@gmail.com).

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Appendix Table 1. PubMed and Medline Search

Number	Search Terms	Search String	Records, *n*
1	PCI OR acute coronary syndrome	((((((Percutaneous coronary intervention[MeSH Major Topic]) OR "percutaneous coronary intervention"[tiab]) OR angioplasty, transluminal, percutaneous coronary[MeSH Terms]) OR "PCI"[tiab]) OR "coronary stenting"[tiab])))) OR acute coronary syndrome[MeSH Terms]) OR "acute coronary syndrome"[tiab] OR "ACS"[tiab]))	98 420
2	Atrial fibrillation	(((Atrial Fibrillation[MeSH Major Topic]) OR atrial fibrillation[MeSH Terms]) OR "atrial fibrillation"[Tiab]) OR "AF"[Tiab))	91 569
3	Antiplatelets	((((((((((antiplatelet agents[MeSH Terms]) OR antiplatelet drugs[MeSH Terms]) OR "antiplatelet agents"[Tiab]) OR "antiplatelet drugs"[Tiab]) OR "antiplatelets"[Tiab]) OR "aspirin"[Tiab]) OR "thienopyridine"[Tiab]) OR "clopidogrel"[Tiab]) OR Platelet Aggregation Inhibitors[MeSH Major Topic]) OR "dual antiplatelet therapy"[Tiab]) OR "DAPT"[Tiab]) OR "triple therapy"[Tiab]) OR "TAT"[Tiab]))	100 258
4	NOAC OR VKA	((((((((((((((((((((new oral anticoagulants[Tiab]) OR direct oral anticoagulants[Tiab]) OR direct thrombin inhibitors[Tiab]) OR factor Xa inhibitor[Tiab]) OR dabigatran[Tiab]) OR rivaroxaban[Tiab]) OR apixaban[Tiab]) OR edoxaban[Tiab]) OR novel oral anticoagulants[Tiab]) OR non-vitamin K antagonist oral anticoagulant[Tiab]) OR NOAC[Tiab]) OR direct acting oral anticoagulant[Tiab]) OR DOAC[Tiab]) OR warfarin[MeSH Terms]) OR "warfarin"[Tiab]) OR "vitamin K antagonist"[Tiab]) OR anticoagulants[MeSH Terms]) OR anticoagulants[tiab]) OR anticoagulant drugs[MeSH Terms]) OR anticoagulant agents[MeSH Terms]) OR "anticoagulant drugs"[Tiab]) OR "anticoagulant agents"[Tiab]))	105 042
5	*(PCI OR acute coronary syndrome) AND *(Atrial fibrillation) AND *(antiplatelets) AND *(NOAC OR VKA)	("N(4)-oleylcytosine arabinoside"[Supplementary Concept] OR "N(4)-oleylcytosine arabinoside"[All Fields] OR "noac"[All Fields]) OR VKA[All Fields]	2715

NOAC = new oral anticoagulant; PCI = percutaneous coronary intervention; VKA = vitamin K antagonist.

Appendix Table 2. EMBASE Search

Number	Search Terms	Search String	Records, *n*
1	PCI or acute coronary syndrome	percutaneous coronary intervention.sh. or percutaneous coronary intervention.af. or percutaneous transluminal coronary angioplasty.af. or PCI.af. or coronary stenting.af. or Acute coronary syndrome.sh. or acute coronary syndrome.af. or ACS.af.	164 535
2	Atrial fibrillation	Atrial fibrillation.sh. or atrial fibrillation.af. or AF.af.	168 830
3	NOAC or VKA	new oral anticoagulants or direct oral anticoagulants or direct thrombin inhibitors or factor Xa inhibitor or dabigatran or rivaroxaban or apixaban or edoxaban or novel oral anticoagulants or non-vitamin K antagonist oral coagulant or NOAC or direct acting oral anticoagulant or DOAC.af. or warfarin.sh. or warfarin.af. or vitamin K antagonist.af. or anticoagulants.sh. or anticoagulants.af. or anticoagulant drugs.sh. or anticoagulant agents.sh. or anticoagulant drugs.af. or anticoagulant agents.af.	128 043
4	Antiplatelets	antiplatelet agents or antiplatelet drugs.sh. or antiplatelet agents.af. or antiplatelet drugs.af. or antiplatelets.af. or aspirin.af. or thienopyridine.af. or clopidogrel.af. or platelet aggregation inhibitors.sh. or dual antiplatelet therapy.af. or DAPT.af. or triple therapy.af. or TAT.af.	195 369
5	Combined search	#1 AND #2 AND #3 AND #4	1022

NOAC = new oral anticoagulant; PCI = percutaneous coronary intervention; VKA = vitamin K antagonist.

Appendix Table 3. Cochrane Library Search

Number	Search Terms	Records, *n*
1	Acute coronary syndrome AND antiplatelet therapy AND oral anticoagulant therapy AND atrial fibrillation (word variations have been searched)	17
2	Percutaneous coronary intervention AND antiplatelet therapy AND oral anticoagulant therapy AND atrial fibrillation (word variations have been searched)	30
3	#1 AND #2	47

Appendix Table 4. Randomized Controlled Trials Identified From ClinicalTrials.gov

Characteristic	COACH-AF-PCI	APPROACH-ACS-AF	OPTIMAL*
Trial name	Dabigatran vs. Warfarin With NVAF Who Undergo PCI	APixaban vs. PhenpRocoumon in Patients With ACS and AF	Optimal Antithrombotic Therapy for ACS Patients Concomitant AF Undergoing New Generation DES Implantation
Identifier	NCT03536611	NCT02789917	NCT03234114
Recruitment status	Recruiting	Recruiting	Recruiting
Estimated enrollment, *n*	1120	400	1550
Study start date	1 September 2018	June 2016	3 February 2018
Study completion date	30 June 2020	December 2018	31 December 2021
Population	Coronary artery disease NVAF	ACS AF Coronary artery disease	ACS NVAF
Intervention	TAT (dabigatran etexilate, 110 mg twice daily; aspirin, 100 mg/d; clopidogrel, 75 mg/d for 1 mo, followed by dabigatran, 110 mg/d; clopidogrel, 75 mg/d for ≥5 mo) TAT (warfarin; aspirin, 100 mg/d; clopidogrel, 75 mg/d for 1 mo, followed by warfarin + clopidogrel, 75 mg/d for ≥5 mo)	DAT (apixaban, 5 mg/d [or in reduced dosing of 2.5 mg/d based on age, renal function, and body weight]; clopidogrel, 75 mg/d) TAT (HAS-BLED score <3: phenprocoumon [INR, 2.0–2.5]; clopidogrel, 75 mg/d; and aspirin, 100 mg/d for 6 mo. HAS-BLED score ≥3: phenprocoumon [INR, 2.0–2.5]; clopidogrel, 75 mg/d; and aspirin, 100 mg/d for 1 mo, followed by phenprocoumon [INR, 2.0–3.0] and clopidogrel, 75 mg/d for 5 mo.)	TAT (warfarin; aspirin, 100 mg/d; clopidogrel, 75 mg/d) DAT (dabigatran, 110 mg twice daily, + ticagrelor, 90 mg twice daily, or clopidogrel, 75 mg/d)
Allocation	Randomized	Randomized	Randomized
Intervention model	Parallel assignment	Parallel assignment	Parallel assignment
Masking	Single (outcomes assessor)	None (open label)	None (open label)
Inclusion criteria	Age ≥18 y Patients with nonsecondary (e.g., pericarditis, hyperthyroidism, recent surgery) NVAF requiring long-term anticoagulant treatment Patients who have PCI indications and coronary heart disease that was successfully treated with a DES	Age ≥18 y Patients with NVAF who require oral anticoagulation and underwent PCI for ACS Women of childbearing potential must have a negative result on a serum or urine pregnancy test ≤24 h before start of study drug therapy Women of childbearing potential must not be breastfeeding	Age ≥18 y Patients with ACS and concomitant NVAF who underwent PCI and new-generation DES implantation CHA_2DS_2-VASc score ≥2 and in need of oral anticoagulation Low to moderate risk for bleeding (HAS-BLED score <3)
Exclusion criteria	Mechanical or biological heart valve prosthesis Patients proposed to undergo left atrial appendage occlusion or AF radiofrequency ablation Cardiogenic shock during current hospitalization Patients who have used fibrinolytic agents within 24 h of randomization Stroke ≤1 mo before screening visit Major surgery ≤1 mo before screening Patient has received or is on a waiting list for an organ transplant History of intraocular, spinal, retroperitoneal, or traumatic intra-articular bleeding Gastrointestinal bleeding ≤1 mo before screening; major or life-threatening bleeding episode Hemorrhagic disorder or bleeding diathesis Anemia or thrombocytopenia, including heparin-induced thrombocytopenia Severe renal impairment Active liver disease Need for continued treatment with systemic ketoconazole, itraconazole, posaconazole, cyclosporine, tacrolimus, dronedarone, rifampicin, phenytoin, carbamazepine, or any cancer therapy Patients requiring continuous treatment with nonsteroidal anti-inflammatory drugs Known allergy to dabigatran etexilate or warfarin Patients with a contraindication to clopidogrel or aspirin Pregnant (present, suspected, or planned) or lactating woman or premenopausal women	Age <18 y History of intracranial bleeding, active bleeding, TIMI major bleeding, and/or type ≥3b BARC criteria in the past 6 mo History of peptic ulcer in the past 6 mo History of a complicated or prolonged cardiogenic shock in the past 2 wk Planned major surgery during the study course with planned discontinuation of antithrombotic therapy Conditions with life expectancy <1 y Mechanical valve replacement Valvular AF Severe renal insufficiency Severe liver insufficiency Known or persistent abuse of medication, drugs, or alcohol reliable by the investigator in individual cases Known contraindications to apixaban, phenprocoumon, clopidogrel, or aspirin treatment Relevant hematologic deviations; current or planned pregnancy or breastfeeding women	Implantation of other types of stent during this PCI DES implantation in the left main stem Cardiogenic shock or Killip class III or IV Patients who have ST-segment elevation MI and malignant arrhythmias, underwent electrode fibrillation or cardiopulmonary resuscitation, or have cardiac mechanical complications (e.g., heart rupture, ventricular septal perforation, or nipple muscle fracture) History of severe gastrointestinal or intracranial hemorrhage; active bleeding, recent trauma, or major surgery in the past month; or suspected or diagnosed aortic dissection Known allergy or intolerance to the study medications: warfarin, clopidogrel, aspirin, dabigatran, ticagrelor, and heparin Previous enrollment in other trials without achieving primary end point Planned major surgery within the next 12 mo with the need to discontinue antiplatelet therapy Planned radiofrequency catheter ablation or left atrial appendage occlusion within the next 12 mo Abnormal liver or kidney function History of blood system disease or bleeding tendency Cancer or other comorbid conditions with life expectancy <1 y Pregnant (present, suspected, or planned) or lactating woman Patients in need of drugs that affect the efficacy of clopidogrel

Continued on following page

Appendix Table 4–Continued

Characteristic	COACH-AF-PCI	APPROACH-ACS-AF	OPTIMAL*
Primary outcome	Clinically relevant bleeding: BARC-defined (grade 2–5) clinically relevant bleeding	The combined end point of moderate or major bleeding complications during the initial hospitalization and follow-up (BARC type ≥2 bleeding)	Primary end point of OPTIMAL-1: a composite efficacy outcome of death (cardiac death or sudden death), thrombotic events (nonfatal MI, ischemic stroke, or systemic thromboembolism), or unplanned revascularization Primary end point of OPTIMAL-2: major bleeding or clinically relevant nonmajor bleeding assessed by the ISTH definition
Follow-up	24 mo	6 mo	12 mo
Sponsors and collaborators	Shenyang Northern Hospital Beijing Anzhen Hospital Second Affiliated Hospital of Third Military Medical University	Klinikum der Universität München Deutsches Zentrum für Herz-Kreislauf-Forschung (DZHK) Technische Universität München Helmholtz Zentrum München University of Göttingen University of München University Medicine Greifswald	The First Affiliated Hospital with Nanjing Medical University

ACS = acute coronary syndrome; AF = atrial fibrillation; BARC = Bleeding Academic Research Consortium; DAT = dual antithrombotic therapy (oral anticoagulant plus P2Y12 inhibitor); DES = drug-eluting stent; INR = international normalized ratio; ISTH = International Society on Thrombosis and Haemostasis; MI = myocardial infarction; NVAF = nonvalvular AF; PCI = percutaneous coronary intervention; TAT = triple antithrombotic therapy (oral anticoagulant plus dual antiplatelet therapy); TIMI = Thrombolysis in Myocardial Infarction.
* This prospective, multicenter, randomized clinical trial contains 2 substudies: OPTIMAL-1 and OPTIMAL-2.

Appendix Table 5. Risk-of-Bias Assessment

Study	Similar Groups	Sequence Generation	Selective Outcome Reporting	Intention-to-Treat Analysis	Incomplete Outcome Data	Allocation Concealment	Blinding of Participants and Personnel	Blinding of Outcome Assessors	Loss to Follow-up
PIONEER AF-PCI	Low	Low	Intermediate	High	Low	Low	High	Low	Low
RE-DUAL PCI	Low	Low	Low	Low	Low	Low	High	Low	Low
AUGUSTUS	Low	Low	Low	Low	Low	Low	High	Low	Low
ENTRUST-AF PCI	Low	Low	Low	Low	Low	Low	High	Low	Low

AUGUSTUS = Open-Label, 2 × 2 Factorial, Randomized Controlled, Clinical Trial to Evaluate the Safety of Apixaban vs. Vitamin K Antagonist and Aspirin vs. Aspirin Placebo in Patients With Atrial Fibrillation and Acute Coronary Syndrome or Percutaneous Coronary Intervention; ENTRUST-AF PCI = Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention; PIONEER AF-PCI = Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention; RE-DUAL PCI = Randomized Evaluation of Dual Antithrombotic Therapy With Dabigatran vs. Triple Therapy With Warfarin in Patients With Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention.

Appendix Table 6. GRADE (Certainty of Evidence) for Dual Antibiotic Therapy Compared With Triple Antibiotic Therapy for Bleeding and Cardiovascular Outcomes

Outcome	Median Follow-up, *y*	Risk Difference (95% CI)	Trials, *n*	Certainty of the Evidence (GRADE)
Primary analysis*				
All-cause mortality	1	0.004 (−0.010 to 0.017)	4 RCTs	⊕⊕◯◯ Low†
Cardiovascular mortality	1	0.001 (−0.011 to 0.013)	4 RCTs	⊕⊕◯◯ Low†
MI	1	0.003 (−0.010 to 0.017)	4 RCTs	⊕⊕◯◯ Low†
Stroke	1	0.003 (−0.010 to 0.005)	4 RCTs	⊕⊕◯◯ Low†
Stent thrombosis	1	0.003 (−0.005 to 0.010)	4 RCTs	⊕⊕◯◯ Low†
TIMI major bleeding	1	−0.013 (−0.025 to −0.002)	4 RCTs	⊕⊕⊕⊕ High
TIMI major and minor bleeding	1	−0.031 (−0.049 to −0.012)	4 RCTs	⊕⊕⊕⊕ High
Trial-defined bleeding	1	−0.072 (−0.129 to −0.015)	4 RCTs	⊕⊕⊕⊕ High
MACE	1	0.003 (−0.016 to 0.023)	4 RCTs	⊕⊕◯◯ Low†
Intracerebral hemorrhage	1	−0.004 (−0.009 to 0.000)	4 RCTs	⊕⊕⊕◯ Moderate†
Sensitivity analysis‡				
All-cause mortality	1	0.006 (−0.008 to 0.020)	4 RCTs	⊕⊕◯◯ Low†
Cardiovascular mortality	1	0.004 (−0.008 to 0.016)	4 RCTs	⊕⊕◯◯ Low†
MI	1	0.006 (−0.007 to 0.019)	4 RCTs	⊕⊕◯◯ Low†
Stroke	1	−0.003 (−0.011 to 0.006)	4 RCTs	⊕⊕◯◯ Low†
Stent thrombosis	1	0.005 (−0.003 to 0.012)	4 RCTs	⊕⊕◯◯ Low†
TIMI major bleeding	1	−0.015 (−0.026 to −0.004)	4 RCTs	⊕⊕⊕⊕ High
TIMI major and minor bleeding	1	−0.034 (−0.054 to −0.015)	4 RCTs	⊕⊕⊕⊕ High
Trial-defined bleeding	1	−0.087 (−0.150 to −0.023)	4 RCTs	⊕⊕⊕⊕ High
MACE	1	0.018 (−0.026 to 0.062)	4 RCTs	⊕⊕◯◯ Low†
Intracerebral hemorrhage	1	−0.004 (−0.009 to 0.001)	4 RCTs	⊕⊕⊕◯ Moderate†

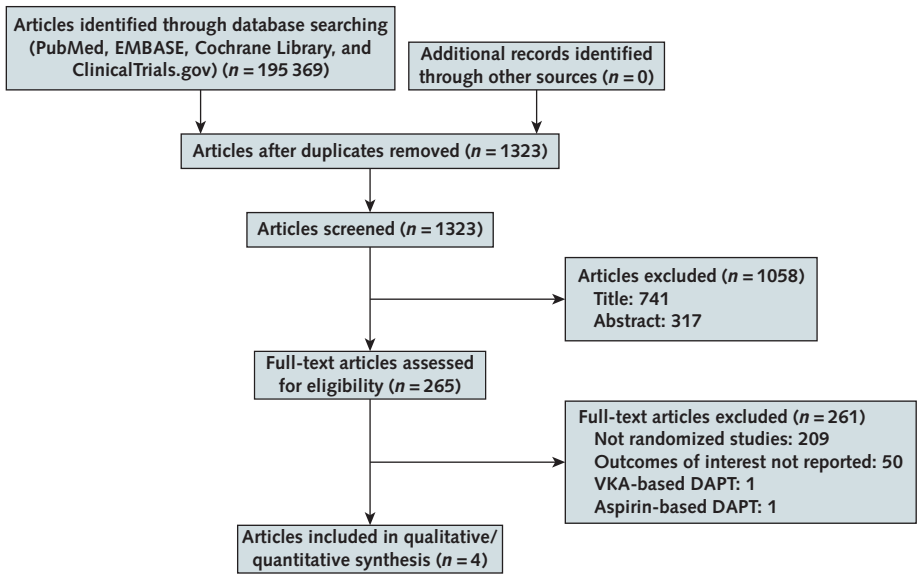
GRADE = Grading of Recommendations Assessment, Development and Evaluation; MACE = major adverse cardiovascular events; MI = myocardial infarction; RCT = randomized controlled trial; TIMI = Thrombolysis in Myocardial Infarction.

* By pooling dosages of dabigatran, 150 mg twice daily, from RE-DUAL PCI (Randomized Evaluation of Dual Antithrombotic Therapy With Dabigatran vs. Triple Therapy With Warfarin in Patients With Nonvalvular AF Undergoing PCI). Patient or population: atrial fibrillation and percutaneous coronary intervention. Intervention: dual antithrombotic therapy. Comparison: triple antithrombotic therapy.

† Serious imprecision was considered if the 95% CIs overlap with the minimally important difference for clinical benefit or harm. Very serious imprecision was considered if the 95% CIs include both clinically important benefit and harm.

‡ By pooling dosages of dabigatran, 110 mg twice daily, from RE-DUAL PCI.

Appendix Figure 1. Evidence search and selection.



DAPT = dual antiplatelet therapy; VKA = vitamin K antagonist.

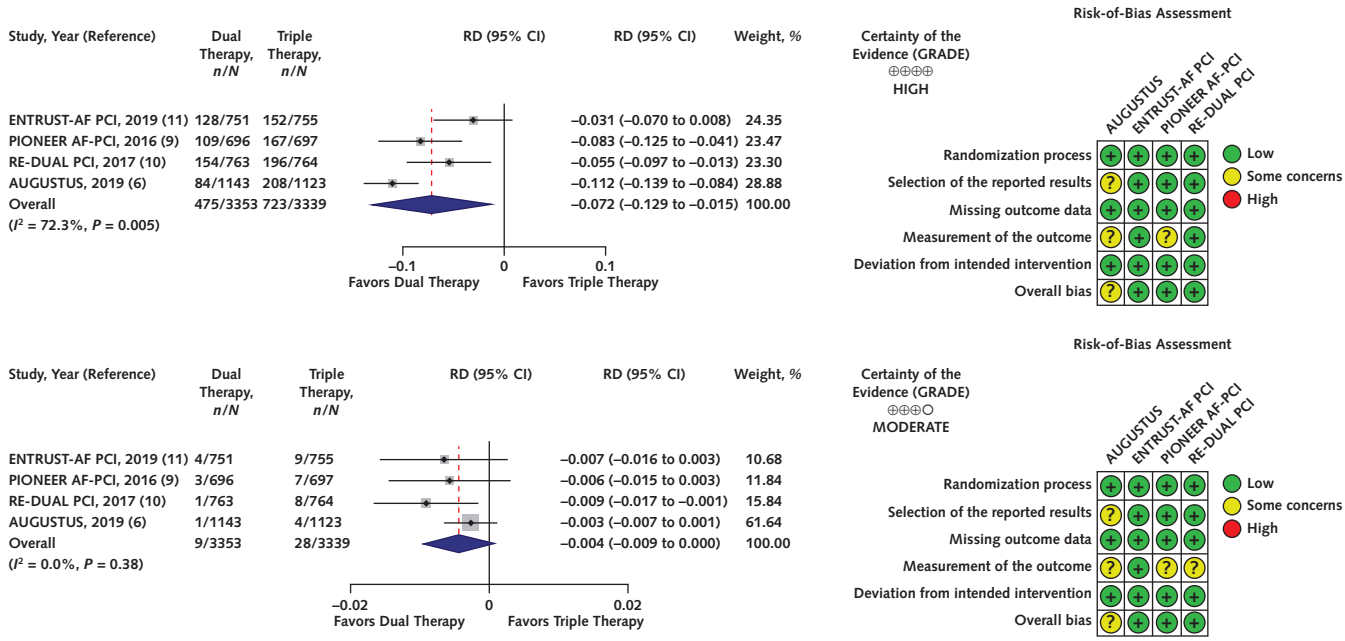
Appendix Table 7. Baseline Characteristics of Trials and Participants*

Characteristic	PIONEER AF-PCI (9)		RE-DUAL PCI (10)			AUGUSTUS (6)		ENTRUST-AF PCI (11)	
	Rivaroxaban + P2Y12 Inhibitor	VKA + DAPT	Dabigatran (110 mg) + P2Y12 Inhibitor	Dabigatran (150 mg) + P2Y12 Inhibitor	VKA + DAPT	Apixaban + P2Y12 Inhibitor	VKA + DAPT	Edoxaban + P2Y12 Inhibitor	VKA + DAPT
Participants at randomization, *n*	709	706	981	763	981	1153	1154	751	755
Mean or median age as reported by trial, *y*	70.4	69.9	71.5	68.6	71.7	69.8	70.5	69	70
Male sex	528 (74.4)	518 (73.3)	728 (74.2)	529 (69.3)	750 (76.4)	840 (72.9)	815 (70.6)	557 (74)	563 (75)
Diabetes	204 (28.8)	221 (31.3)	362 (36.9)	260 (34.1)	371 (37.9)	414 (35.9)	414 (35.9)	259 (34)	258 (34)
Hypertension	520 (73.3)	532 (75.4)	–	–	–	1024 (88.8)	1013 (87.8)	674 (90)	687 (91)
History of MI	140 (19.7)	157 (22.2)	237 (24.2)	194 (25.4)	268 (27.3)	–	–	188 (25)	177 (23)
History of heart failure	180 (25.4)	175 (24.8)	–	–	–	483 (41.9)	490 (42.5)	418 (56)	408 (54)
History of stroke	–	–	74 (7.5)	52 (6.8)	100 (10.2)	171 (14.9)	142 (12.4)	97 (13)	92 (12)
History of PCI	–	–	326 (33.2)	239 (31.3)	347 (35.4)	–	–	–	195 (26)
History of coronary artery bypass grafting	–	–	97 (9.9)	79 (10.4)	111 (11.3)	–	–	–	49 (6)
Type of P2Y12 inhibitor						–	–	–	
Clopidogrel	660 (93.1)	680 (96.3)	848 (86.4)	663 (86.9)	886 (90.3)	–	–	–	695 (92)
Prasugrel	12 (1.7)	5 (0.7)	0	0	0	–	–	–	3 (<1)
Ticagrelor	37 (5.2)	21 (3.0)	124 (12.6)	92 (12.1)	77 (7.8)	–	–	–	57 (8)
CHA_2DS_2-VASc score									
≤2	189 (26.7)	147 (20.8)	230 (23.4)	247 (32.4)	193 (19.7)	248 (21.5)	240 (20.8)	174 (23.2)	141 (18.7)
≥3	520 (73.3)	559 (79.2)	751 (76.6)	516 (67.6)	788 (80.3)	905 (78.5)	914 (79.2)	577 (76.8)	614 (81.3)
HAS-BLED score									
≤2	196 (27.6)	208 (29.5)	326 (33.2)	309 (40.5)	288 (29.4)	570 (51.7)	559 (50.9)	255 (33.9)	218 (28.9)
≥3	513 (72.3)	498 (70.5)	655 (66.8)	454 (59.5)	693 (70.6)	533 (48.3)	540 (49.1)	496 (66.1)	537 (71.1)
Bare-metal stent	231 (32.6)	224 (31.8)	148 (15.2)	123 (16.1)	133 (13.6)	–	–	83 (11.1)	101 (13.4)
Drug-eluting stent	464 (65.4)	468 (66.5)	804 (82.1)	621 (81.5)	829 (84.6)	–	–	647 (86.2)	628 (83.2)
Bare-metal and drug-eluting stent	14 (2.0)	12 (1.7)	19 (1.9)	10 (1.3)	12 (1.2)	–	–	12 (1.6)	10 (1.3)
Other stent	–	–	8 (0.8)	8 (1.0)	5 (0.5)	–	–	8 (1.1)	15 (2.0)
Mean creatinine clearance (SD), *mL/min/1.73 m²*	78.3 (31.3)	80.7 (30.0)	76.3 (28.9)	83.7 (31.0)	75.4 (29.1)	79.4 (31.7)	78.7 (30.2)	71.8	71.7
Index event	–	–	–	–	–	–	–	388 (52)	389 (52)
Non-STEMI	130 (18.5)	123 (17.8)	203 (20.7)	179 (23.5)	206 (21.0)	–	–	–	–
STEMI	86 (12.3)	74 (10.7)	144 (14.7)	114 (14.9)	143 (14.6)	–	–	–	–
Unstable angina	145 (20.7)	164 (23.7)	195 (19.9)	126 (16.5)	166 (16.9)	–	–	–	–
Type of AF									
Persistent	146 (20.7)	149 (21.1)	174 (17.7)	132 (17.3)	178 (18.2)	–	–	140 (19)	146 (19)
Permanent	262 (37.4)	243 (34.5)	320 (32.6)	250 (32.8)	318 (32.4)	–	–	209 (28)	250 (33)
Paroxysmal	300 (42.8)	313 (44.4)	487 (49.6)	380 (49.8)	484 (49.4)	–	–	402 (54)	358 (47)

AF = atrial fibrillation; AUGUSTUS = Open-Label, 2 × 2 Factorial, Randomized Controlled, Clinical Trial to Evaluate the Safety of Apixaban vs. VKA and Aspirin vs. Aspirin Placebo in Patients With AF and Acute Coronary Syndrome or PCI; DAPT = dual antiplatelet therapy (P2Y12 inhibitor + aspirin); ENTRUST-AF PCI = Edoxaban Treatment Versus VKA in Patients With AF Undergoing PCI; MI = myocardial infarction; PCI = percutaneous coronary intervention; PIONEER AF-PCI = Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral VKA Treatment Strategy in Subjects With AF Who Undergo PCI; RE-DUAL PCI = Randomized Evaluation of Dual Antithrombotic Therapy With Dabigatran vs. Triple Therapy With Warfarin in Patients With Nonvalvular AF Undergoing PCI; STEMI = ST-segment elevation MI; VKA = vitamin K antagonist.

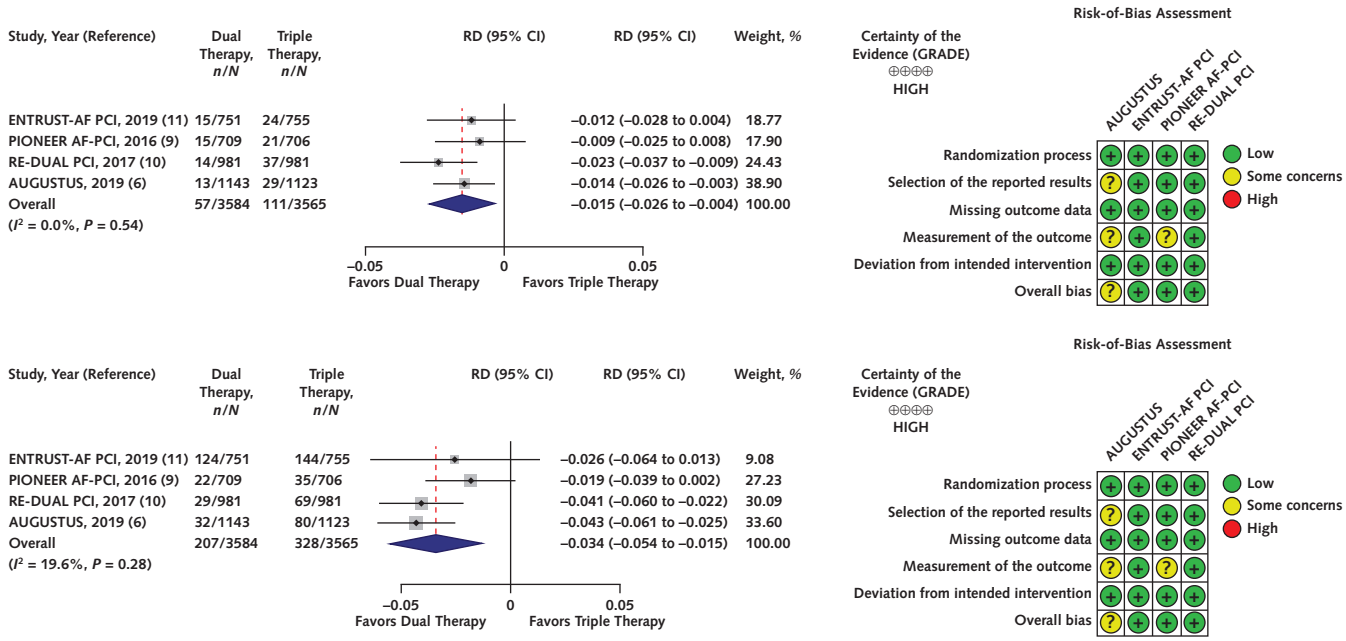
* Values are numbers (percentages) unless otherwise indicated.

Appendix Figure 2. Trial-defined bleeding (*top*) and intracerebral hemorrhage (*bottom*) after pooling data about dabigatran, 150 mg twice daily, from RE-DUAL PCI.



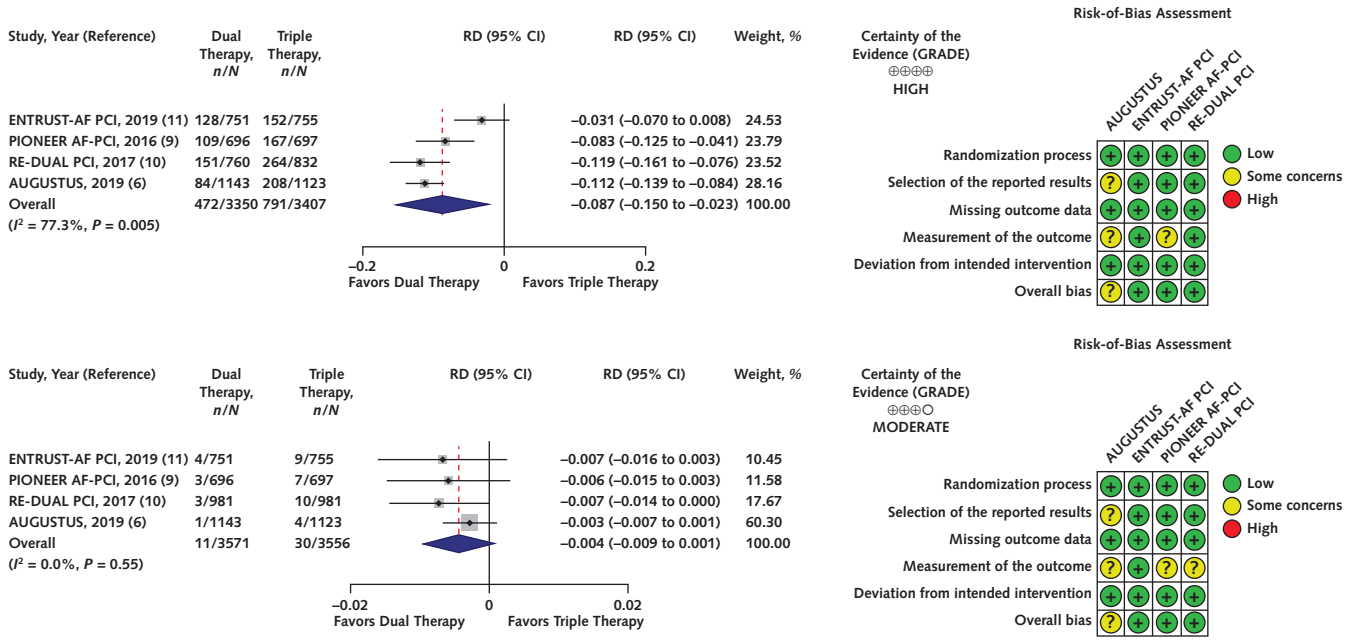
AUGUSTUS = Open-Label, 2 × 2 Factorial, Randomized Controlled, Clinical Trial to Evaluate the Safety of Apixaban vs. Vitamin K Antagonist and Aspirin vs. Aspirin Placebo in Patients With Atrial Fibrillation and Acute Coronary Syndrome or Percutaneous Coronary Intervention; ENTRUST-AF PCI = Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention; GRADE = Grading of Recommendations Assessment, Development and Evaluation; PIONEER AF-PCI = Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention; RD = risk difference; RE-DUAL PCI = Randomized Evaluation of Dual Antithrombotic Therapy With Dabigatran vs. Triple Therapy With Warfarin in Patients With Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention.

Appendix Figure 3. TIMI major bleeding (*top*) and TIMI major and minor bleeding (*bottom*) after pooling data about dabigatran, 110 mg twice daily, from RE-DUAL PCI.



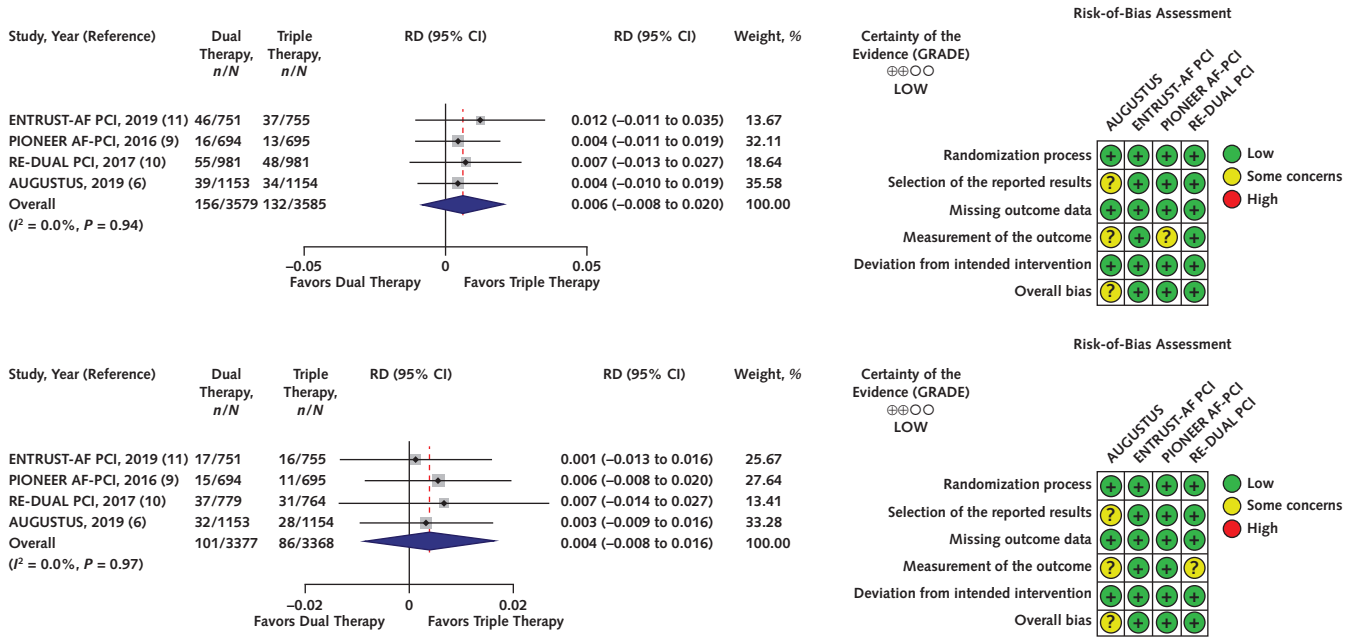
AUGUSTUS = Open-Label, 2 × 2 Factorial, Randomized Controlled, Clinical Trial to Evaluate the Safety of Apixaban vs. Vitamin K Antagonist and Aspirin vs. Aspirin Placebo in Patients With Atrial Fibrillation and Acute Coronary Syndrome or Percutaneous Coronary Intervention; ENTRUST-AF PCI = Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention; GRADE = Grading of Recommendations Assessment, Development and Evaluation; PIONEER AF-PCI = Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention; RD = risk difference; RE-DUAL PCI = Randomized Evaluation of Dual Antithrombotic Therapy With Dabigatran vs. Triple Therapy With Warfarin in Patients With Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention.

Appendix Figure 4. Trial-defined bleeding (*top*) and intracerebral hemorrhage (*bottom*) after pooling data about dabigatran, 110 mg twice daily, from RE-DUAL PCI.



AUGUSTUS = Open-Label, 2 × 2 Factorial, Randomized Controlled, Clinical Trial to Evaluate the Safety of Apixaban vs. Vitamin K Antagonist and Aspirin vs. Aspirin Placebo in Patients With Atrial Fibrillation and Acute Coronary Syndrome or Percutaneous Coronary Intervention; ENTRUST-AF PCI = Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention; GRADE = Grading of Recommendations Assessment, Development and Evaluation; PIONEER AF-PCI = Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention; RD = risk difference; RE-DUAL PCI = Randomized Evaluation of Dual Antithrombotic Therapy With Dabigatran vs. Triple Therapy With Warfarin in Patients With Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention.

Appendix Figure 5. All-cause mortality (*top*) and cardiovascular mortality (*bottom*) after pooling data about dabigatran, 110 mg twice daily, from RE-DUAL PCI.



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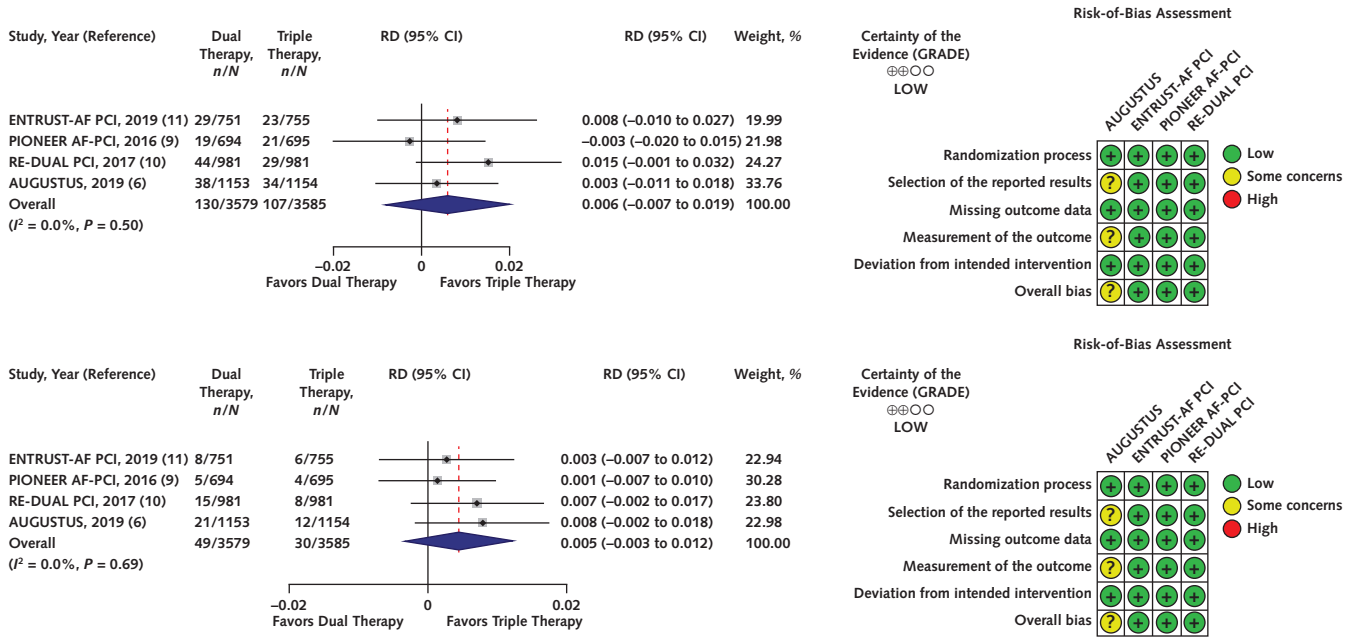
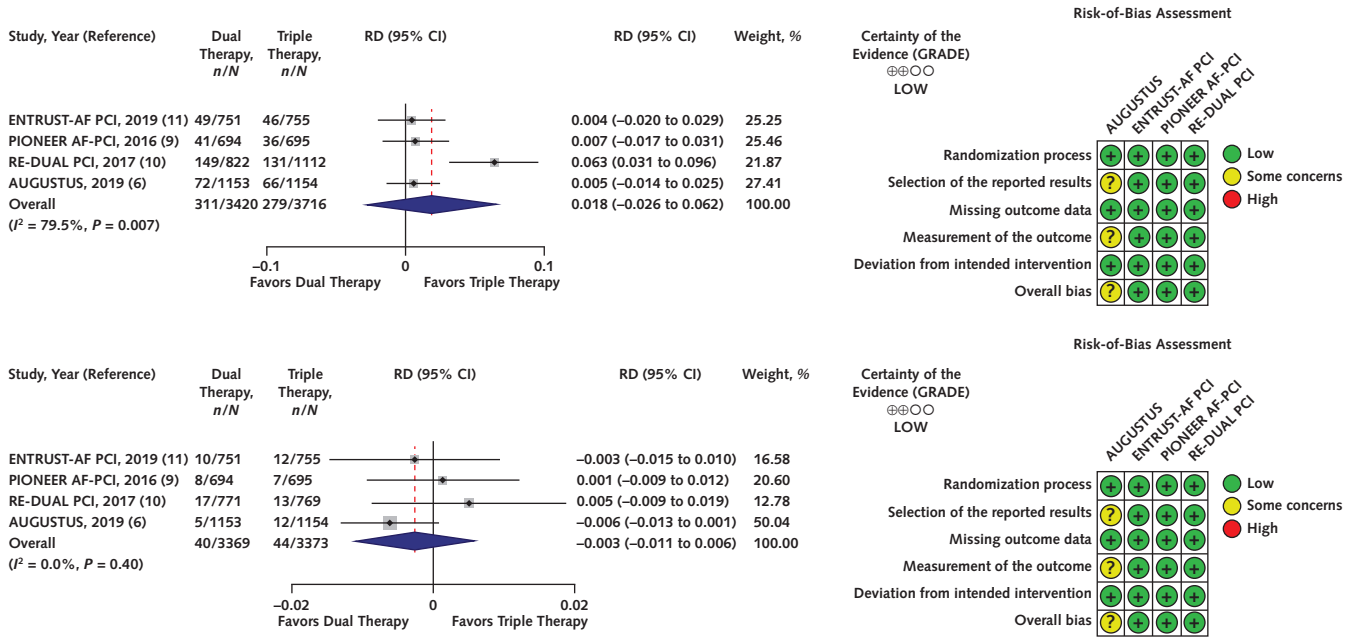
Appendix Figure 6. Myocardial infarction (*top*) and stent thrombosis (*bottom*) after pooling data about dabigatran, 110 mg twice daily, from RE-DUAL PCI.



AUGUSTUS = Open-Label, 2 × 2 Factorial, Randomized Controlled, Clinical Trial to Evaluate the Safety of Apixaban vs. Vitamin K Antagonist and Aspirin vs. Aspirin Placebo in Patients With Atrial Fibrillation and Acute Coronary Syndrome or Percutaneous Coronary Intervention; ENTRUST-AF PCI = Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention; GRADE = Grading of Recommendations Assessment, Development and Evaluation; PIONEER AF-PCI = Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention; RD = risk difference; RE-DUAL PCI = Randomized Evaluation of Dual Antithrombotic Therapy With Dabigatran vs. Triple Therapy With Warfarin in Patients With Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention.

Appendix Figure 7. Major adverse cardiovascular events (*top*) and stroke (*bottom*) after pooling data about dabigatran, 110 mg twice daily, from RE-DUAL PCI.



AUGUSTUS = Open-Label, 2 × 2 Factorial, Randomized Controlled, Clinical Trial to Evaluate the Safety of Apixaban vs. Vitamin K Antagonist and Aspirin vs. Aspirin Placebo in Patients With Atrial Fibrillation and Acute Coronary Syndrome or Percutaneous Coronary Intervention; ENTRUST-AF PCI = Edoxaban Treatment Versus Vitamin K Antagonist in Patients With Atrial Fibrillation Undergoing Percutaneous Coronary Intervention; GRADE = Grading of Recommendations Assessment, Development and Evaluation; PIONEER AF-PCI = Open-Label, Randomized, Controlled, Multicenter Study Exploring Two Treatment Strategies of Rivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention; RD = risk difference; RE-DUAL PCI = Randomized Evaluation of Dual Antithrombotic Therapy With Dabigatran vs. Triple Therapy With Warfarin in Patients With Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention.