

Anticoagulation and Antiplatelet Therapy for Atrial Fibrillation and Stable Coronary Disease

Meta-Analysis of Randomized Trials

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ABSTRACT

BACKGROUND The optimal long-term antithrombotic strategy in patients with atrial fibrillation (AF) and stable coronary artery disease (CAD) remains uncertain. Individual randomized controlled trials (RCTs) had variations in their reported results and were not powered for effectiveness outcomes.

OBJECTIVES This study aimed to pool the results of RCTs comparing the effectiveness and safety of oral anticoagulation (OAC) monotherapy vs OAC plus single antiplatelet therapy (SAPT) in patients with AF and stable CAD.

METHODS We systematically searched PubMed, Embase, and ClinicalTrials.gov until September 09, 2024. The primary effectiveness outcome was a composite of myocardial infarction, ischemic stroke, systemic embolism, or death. The primary safety outcome was major bleeding. We obtained unpublished results from principal investigators of the included RCTs, as needed, to calculate pooled HRs and 95% CIs and to perform prespecified subgroup analyses.

RESULTS Among 690 screened records, 4 RCTs with 4,092 randomized patients were included (2 using edoxaban, 1 using rivaroxaban, and 1 using any oral anticoagulant; mean age 73.9 years, 20.1% women). The median follow-up durations ranged from 12 to 30 months (overall estimated weighted mean follow-up of 21.9 months). There were no statistically significant differences between OAC monotherapy vs OAC plus SAPT in the primary effectiveness outcome (7.3% vs 8.2%; HR: 0.90; 95% CI: 0.72-1.12), myocardial infarction (1.0% vs 0.7%; HR: 1.51; 95% CI: 0.75-3.04), ischemic stroke (1.9% vs 2.1%; HR: 0.89; 95% CI: 0.57-1.37), all-cause death (4.2% vs 5.3%; HR: 0.94; 95% CI: 0.49-1.80), or cardiovascular death (2.4% vs 3.0%; HR: 0.79; 95% CI: 0.54-1.15). OAC monotherapy was associated with a lower risk of major bleeding than OAC plus SAPT (3.3% vs 5.7%; HR: 0.59; 95% CI: 0.44-0.79). Subgroup analyses did not show significant interactions for effectiveness but suggested that the magnitude of bleeding reduction may be greater among men ($P_{\text{interaction}} = 0.03$) and among patients with diabetes mellitus ($P_{\text{interaction}} = 0.04$).

CONCLUSIONS In patients with AF and stable CAD, OAC monotherapy, compared with OAC plus SAPT, was not associated with a statistically significant increased risk of ischemic events but resulted in a significantly reduced risk of bleeding. (JACC. 2025;■:■-■) © 2025 by the American College of Cardiology Foundation.

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ABBREVIATIONS
AND ACRONYMSACS = acute coronary
syndrome

AF = atrial fibrillation

CAD = coronary artery disease

OAC = oral anticoagulation

PCI = percutaneous coronary
interventionRCT = randomized controlled
trialSAPT = single antiplatelet
therapy

Atrial fibrillation (AF) and coronary artery disease (CAD) frequently coexist because they share several risk factors, such as old age, hypertension, diabetes, obesity, renal impairment, and smoking.^{1,2} Prevention of AF-related thromboembolism is typically accomplished by oral anticoagulants (OACs) if indicated.^{3,4} In contrast, secondary prevention in many stable patients with CAD—ie, without recent acute coronary syndrome (ACS) or recent percutaneous coronary intervention (PCI)—is achieved with single antiplatelet therapy (SAPT).^{5,6}

The optimal long-term antithrombotic strategy in patients with AF who also have stable CAD remains uncertain.⁷ Although it is expected that anticoagulant monotherapy, compared with anticoagulation plus SAPT, will result in fewer bleeding events, it is unclear whether the reduction in bleeds offsets an increase in ischemic events. Recent randomized controlled trials (RCTs) have generated critical insights into these tradeoffs⁸⁻¹¹ but produced conflicting results on the risk of ischemic events and were not individually powered for ischemic outcomes.⁸⁻¹¹ It is also unknown whether patient-related potential treatment effects modifiers, such as age, sex, diabetes, or prior revascularization with stenting, are present in this setting, and individual trials had too few events to share meaningful insights. Despite the emergence of some pooled analyses,^{12,13} these studies were limited by lack of prespecified methods, lack of inclusion of all relevant RCTs, and inability to evaluate several outcomes, time-to-first-event estimates, or results within subgroups because of unavailability of data elements from published reports of the existing RCTs. We, therefore, formed a collaborative to pool the results of RCTs comparing the effectiveness and safety of OAC monotherapy vs OAC plus SAPT in patients with AF and stable CAD to obtain estimates for the effects of anticoagulation

monotherapy in the overall investigated population and prespecified potential prognostic subgroups.

METHODS

This systematic review and meta-analysis was conducted based on a prespecified protocol registered in PROSPERO (CRD42024586948) and is reported according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guideline.¹⁴ Institutional Review Board approvals were not required because the study utilized study-level results.

DATA SOURCES AND SEARCH STRATEGY. Systematic searches were conducted in PubMed and Embase to identify RCTs investigating antithrombotic therapy in patients with stable CAD and AF (Supplemental Table 1) (the last search date was September 9, 2024). No restrictions were applied regarding language or publication date. The references of the included RCTs and other relevant studies were manually searched to detect additional studies. Furthermore, we searched ClinicalTrials.gov to identify ongoing RCTs.

ELIGIBILITY CRITERIA AND STUDY SELECTION. Trials that randomized patients with AF and stable CAD to OAC monotherapy vs OAC plus SAPT were sought. Patients with stable CAD were considered as those who were the following: 1) at least 6 months after coronary revascularization with PCI or coronary artery bypass grafting for stable CAD; 2) at least 1 year after coronary revascularization with PCI or coronary artery bypass grafting for ACS; or 3) those with confirmed CAD with $\geq 50\%$ stenosis of a major coronary artery by invasive coronary angiography or coronary computed tomographic angiography not undergoing revascularization.^{8,15} Anticoagulants could be vitamin K antagonists (eg, warfarin) or direct oral anticoagulants (dabigatran, rivaroxaban, apixaban, or edoxaban) according to individual trial choices. Antiplatelet therapy could be achieved by

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The authors attest they are in compliance with human studies committees and animal welfare regulations of the authors' institutions and Food and Drug Administration guidelines, including patient consent where appropriate. For more information, visit the [Author Center](#).

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aspirin or other agents, such as oral P2Y₁₂ inhibitors (clopidogrel, prasugrel, ticagrelor, or ticlopidine).

Nonoriginal publications (reviews, commentaries, or editorials), nonrandomized investigations, and studies evaluating patients with an ACS within <1 year or PCI for stable angina within <6 months were excluded. Two investigators (S.R. and M.K.) independently screened the titles and abstracts and the full text of the selected studies, where needed, against the eligibility criteria for inclusion. Disagreements were resolved by discussion with the senior investigator (B.B.).

OUTCOMES. The primary effectiveness outcome was the composite of myocardial infarction (MI), ischemic stroke, systemic embolism, and all-cause death. Other effectiveness outcomes were individual components of the composite primary effectiveness outcome, cardiovascular mortality, and unplanned coronary revascularization. The primary safety outcome was major bleeding, according to the definition of included RCTs. Another safety outcome of interest was the composite of major and clinically relevant nonmajor bleeding according to the definitions of the trials. The International Society on Thrombosis and Haemostasis (ISTH) definitions for major and clinically relevant nonmajor bleeding were prioritized where available.^{16,17} All outcomes were assessed using the longest reported randomized follow-up from each included RCT. Additionally, we explored the rate of stent thrombosis and fatal bleeding events in the OAC monotherapy and OAC plus SAPT arms of the included trials.

SUBGROUPS. Prespecified subgroup analyses included age (≥ 75 years vs <75 years), sex (women vs men), diabetes mellitus (yes vs no), CHA₂DS₂-VASc score (0-3 vs ≥ 4), prior PCI (yes vs no), and type of antiplatelet agent (aspirin vs other agents such as oral P2Y₁₂ inhibitors). Recognizing that the type of antiplatelet agent could only affect 1 of the 2 arms across the trials (the OAC plus SAPT arm), we specified a priori that this subgroup analysis would be solely hypothesis-generating.

DATA EXTRACTION AND QUALITY ASSESSMENT. Basic characteristics, total number of patients, number of patients with prespecified outcomes within the OAC monotherapy and OAC plus SAPT arms, and summary effect estimates were extracted from each trial. Similar data were extracted for the prespecified subgroups of interest. In case of discrepancies or insufficient reported data in the published papers, the principal investigator of each trial was contacted to acquire additional study-level summary data. For data elements from any given trial that could not be

further clarified, the closest approximation from the available data was used, or that trial was excluded from a given analysis if the consensus was that the data element was not sufficiently representative of the analysis of interest.

The second version of the Cochrane tool for assessing the risk of bias in randomized trials (RoB 2) was used to assess the methodological quality of included RCTs.¹⁸ This tool evaluates RCTs in 5 domains (ie, randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcome, and selective reporting of the results), resulting in an overall risk of bias for each trial.¹⁸ Two investigators (S.R. and M.K.) independently conducted the data collection and quality assessment. All discrepancies were resolved by discussion with the senior investigator (B.B.).

STATISTICAL ANALYSIS. For the outcomes of interest; HRs were the preferred effect measure to consider time-to-first-event. Pooled HRs with 95% CIs were calculated using the inverse variance method. Continuity correction was implemented for trials with 0 events for an outcome,^{19,20} and HRs were estimated using methods described previously.²¹ Pooled risk differences (RDs) were also determined to test the robustness of the findings when at least 1 trial had 0 events.²⁰ Risk ratios (RRs) are reported in supplemental analyses. The Mantel-Haenszel method was used to pool RR and RD. The Cochran's Q test and Higgins' I² statistics were used to estimate heterogeneity among studies,^{22,23} with I² <25% indicating low heterogeneity, 25% to 50% indicating moderate heterogeneity, and >50% indicating high heterogeneity. In case of substantial heterogeneity (ie, I² >50% and P value for Q test <0.05), random-effect models were applied; otherwise, fixed-effect models were implemented in primary analyses. Considering the small number of eligible RCTs and the fact that the I² test may be underpowered to detect heterogeneity, we also explored the pooled HRs using random-effect models. The Grading of Recommendations, Assessment, Development, and Evaluation (GRADE) system was used to report the robustness of generated estimates across trials for each outcome.²⁴ Sensitivity analyses were conducted by excluding 1 trial at a time from the meta-analyses to test each trial's contribution to the pooled estimates. Subgroup analyses with tests for interaction were performed for the prespecified subgroups. The analyses were conducted in Stata version 17.0 (StataCorp LLC) and RevMan version 5.4 (The Cochrane Collaboration), and a P value of <0.05 was considered significant for the primary outcomes. P values for other outcomes were

considered exploratory. For subgroups, we prespecified a P value for interaction <0.1 to indicate potential effect modification to avoid missing possible effect modifiers. Before the analyses, we acknowledged that subgroup analyses can be underpowered and conducted for idea generation.

RESULTS

Among the 690 identified records, 58 were sought for full-text review (Supplemental Figure 1). Ultimately, 5 RCTs were identified as eligible for inclusion, of which 1 is still ongoing (NCT04217447), with expected results in 2028. Therefore, 4 RCTs published between 2019 and 2024 were included.⁸⁻¹¹

These 4 RCTs included a total of 4,092 randomized patients (mean age 73.9 ± 7.6 years, 20.1% women) (Figure 1, Supplemental Tables 2 and 3). Overall, 41.6% of patients had diabetes mellitus, and 73.4% had prior PCI. Two trials used edoxaban,^{10,11} 1 rivaroxaban,⁸ and 1 warfarin or a variety of direct oral anticoagulants.⁹ The antiplatelet agent in the OAC plus SAPT arm was clopidogrel in 1 trial,¹⁰ and was aspirin or other antiplatelet medications, mainly oral P2Y₁₂ inhibitors, in the other 3 trials.^{8,9,11} Overall, among 2,043 patients randomized to OAC plus SAPT, the antiplatelet medications were aspirin (68.3%), clopidogrel (29.2%), prasugrel (0.8%), or other agents (1.7%). The median follow-up durations ranged from 12 to 30 months, with an estimated weighted mean follow-up duration of 21.9 months for the pooled cohort of 4 RCTs.

The included RCTs were open-label but had blinded event adjudication for their prespecified outcomes. All included trials were deemed at low risk of bias regarding the randomization process, deviations from the intended interventions, missing outcome data, measurement of the outcome, and reporting of the results (Supplemental Figure 2, Supplemental Table 4). Overall, all 4 RCTs were considered to have a low risk of bias.

PRIMARY EFFECTIVENESS OUTCOME. There was no significant difference in the primary effectiveness outcome between OAC monotherapy and OAC plus SAPT (7.3% vs 8.2%; HR: 0.90; 95% CI: 0.72-1.12; $P = 0.34$; $I^2 = 45\%$) (Figure 2). Repeating the analyses using pooled RR yielded similar results (RR: 0.89; 95% CI: 0.72-1.10; $P = 0.29$; $I^2 = 41\%$) (Supplemental Figure 3). The results were also consistent using random-effect models (Supplemental Table 5).

OTHER EFFECTIVENESS OUTCOMES. No statistically significant differences were observed between OAC monotherapy and OAC plus SAPT for subsequent risk

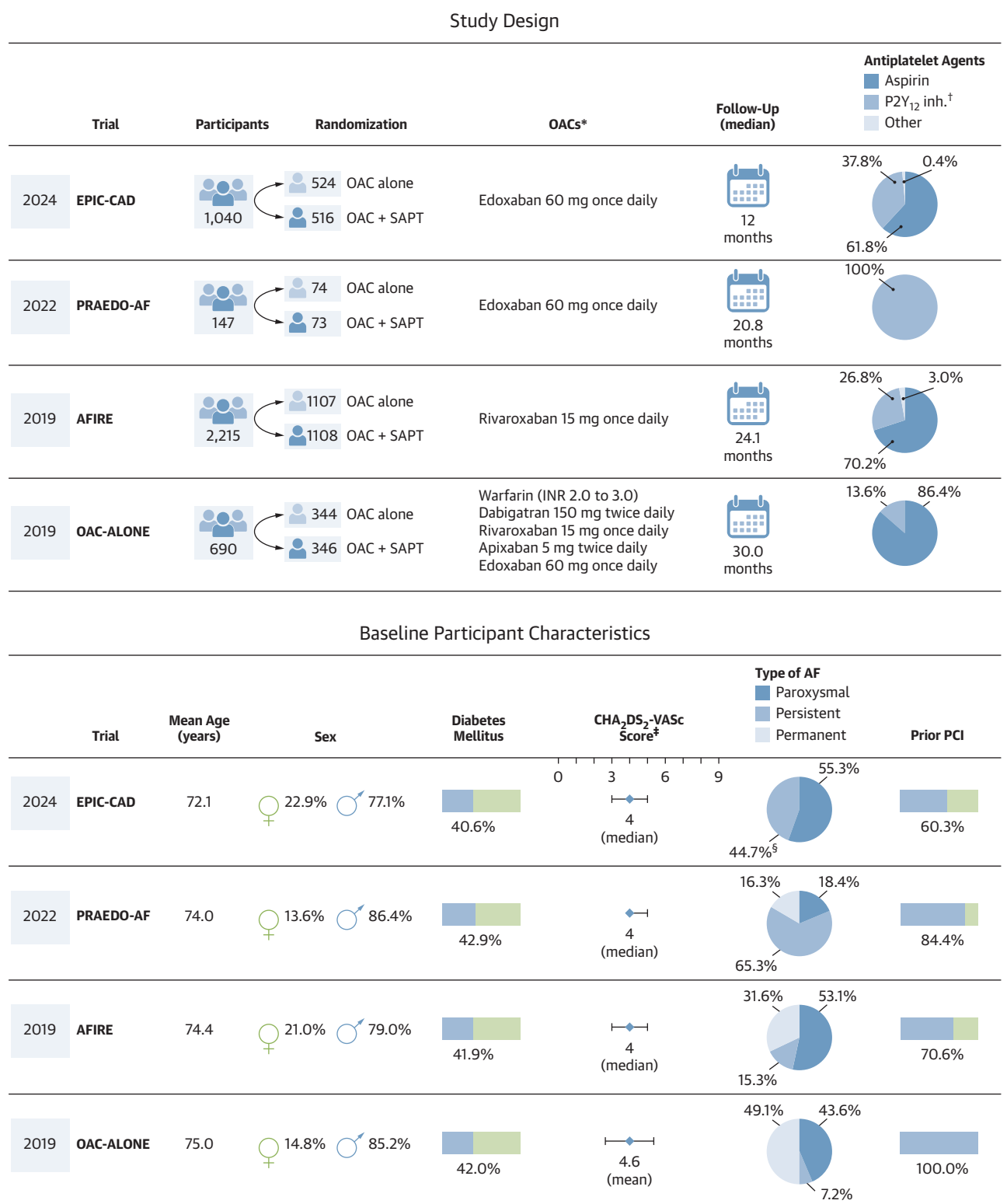
of MI (1.0% vs 0.7%; HR: 1.51; 95% CI: 0.75-3.04; $P = 0.25$; $I^2 = 0\%$), ischemic stroke (1.9% vs 2.1%; HR: 0.89; 95% CI: 0.57-1.37; $P = 0.59$; $I^2 = 0\%$), systemic embolism (0.15% vs 0.15%; HR: 0.94; 95% CI: 0.81-1.09; $P = 0.43$; $I^2 = 0\%$), all-cause death (4.2% vs 5.3%; HR: 0.94; 95% CI: 0.49-1.80; $P = 0.84$; $I^2 = 65\%$), cardiovascular death (2.4% vs 3.0%; HR: 0.79; 95% CI: 0.54-1.15; $P = 0.22$; $I^2 = 22\%$), or unplanned coronary revascularization (1.4% vs 1.4%; HR: 0.98; 95% CI: 0.58-1.64; $P = 0.93$; $I^2 = 0\%$), (Figures 3A to 3F). Results were similar based on pooled RRs and RDs, as well as random-effect models for HRs (Supplemental Table 5, Supplemental Figures 4 and 5). Among patients with coronary stents, stent thrombosis occurred in 2 (0.14%) patients in the OAC monotherapy arm, whereas no patients in the OAC plus SAPT arm experienced stent thrombosis (RD 0.14%; 95% CI: -0.05% to 0.33%; $P = 0.41$; $I^2 = 0\%$) (Supplemental Figure 6).

SAFETY OUTCOMES. All 4 RCTs reported data for major bleeding according to the ISTH definition.⁸⁻¹¹ Except for the OAC-ALONE (Optimizing Antithrombotic Care in Patients With Atrial Fibrillation and Coronary Stent) trial,⁹ the other RCTs also assessed clinically relevant nonmajor bleeding based on the ISTH definition.^{8,10,11} OAC monotherapy compared with OAC plus SAPT was associated with a reduced risk of major bleeding (3.3% vs 5.7%, 4 RCTs; HR: 0.59; 95% CI: 0.44-0.79; $P < 0.001$; $I^2 = 0\%$) and major or clinically relevant nonmajor bleeding (10.0% vs 18.4%, 3 RCTs; HR: 0.53; 95% CI: 0.44-0.63; $P < 0.001$; $I^2 = 58\%$) (Figures 4A and 4B). The results were similar using pooled RRs, RDs, and random-effect models for HRs (Supplemental Table 5, Supplemental Figures 7 and 8). There were a total of 9 (0.4%) fatal bleeding events in the OAC monotherapy arm and 6 (0.3%) in the OAC plus SAPT arm (RD 0.15%; 95% CI: -0.22% to 0.52%; $P = 0.46$; $I^2 = 0\%$) (Supplemental Figure 9).

GRADE CERTAINTY RATINGS. The certainty of pooled estimates according to the GRADE system was deemed to be high for the primary effectiveness outcome, ischemic stroke, systemic embolism, cardiovascular death, unplanned coronary revascularization, and major bleeding and moderate for MI, all-cause death, and major or clinically relevant nonmajor bleeding (Supplemental Table 6).

SENSITIVITY ANALYSES AND SUBGROUP ANALYSES. In sensitivity analyses, which were done by leaving one trial at a time out of the meta-analyses for the outcomes of interest, there was no change in the significance of the pooled estimates (Supplemental Table 7).

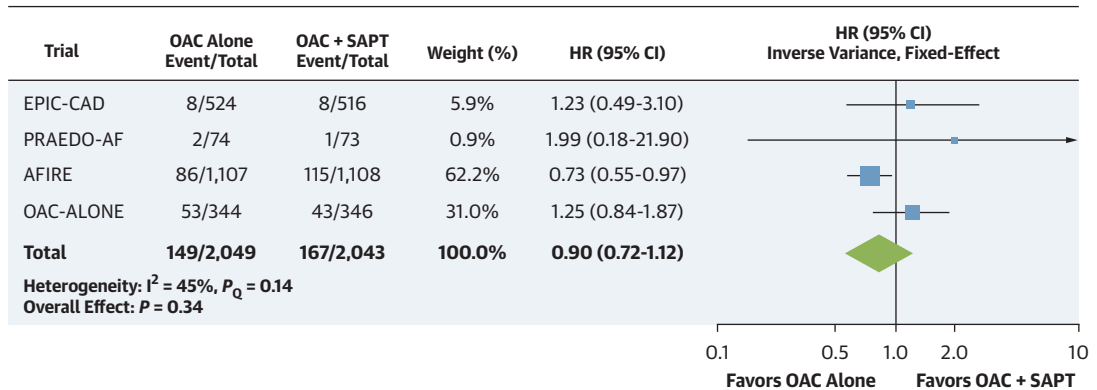
Subgroup analyses for the primary effectiveness outcome did not indicate signals for effect modification in any of the prespecified subgroups (Figure 5A).

FIGURE 1 Characteristics of the Included Randomized Controlled Trials

The figure describes the study design and participant characteristics of the included randomized controlled trials. *See [Supplemental Table 2](#) for dose-reduction criteria for oral anticoagulants (OACs). †P2Y₁₂ inhibitors were clopidogrel in all 4 trials, except for AFIRE, which also included 16 patients receiving prasugrel. ‡Median (IQR) or mean (± SD). §Includes both persistent and permanent atrial fibrillation (AF). AFIRE = Atrial Fibrillation and Ischemic Events with Rivaroxaban in Patients with Stable Coronary Artery Disease; EPIC-CAD = Edoxaban vs Edoxaban with Antiplatelet agent in Patients with Atrial Fibrillation and Chronic Stable Coronary Artery Disease; INR = international normalized ratio; OAC-ALONE = Optimizing Antithrombotic Care in Patients With Atrial Fibrillation and Coronary Stent; PCI = percutaneous coronary intervention; PRAEDO-AF = Prospective Randomized Study of Safety Outcomes Treated with Edoxaban in Patients with Stable Coronary Artery Disease and Atrial Fibrillation; SAPT = single antiplatelet therapy.

FIGURE 2 Primary Effectiveness Outcome

Composite of Myocardial Infarction, Ischemic Stroke, Systemic Embolism, or Death



Pooled HR for the composite of myocardial infarction, ischemic stroke, systemic embolism, or death did not show a significant difference between OAC alone vs OAC SAPT. Abbreviations as in [Figure 1](#).

For the primary safety outcome, pooled results did not show effect modification considering age (≥ 75 years vs < 75 years) ($P_{\text{interaction}} = 0.47$), CHA₂DS₂-VASC score (0-3 vs ≥ 4) ($P_{\text{interaction}} = 0.55$), prior PCI ($P_{\text{interaction}} = 0.51$), or type of antiplatelet agent ($P_{\text{interaction}} = 0.58$). Pooled estimates suggested effect modification based on sex ($P_{\text{interaction}} = 0.03$) and diabetes mellitus ($P_{\text{interaction}} = 0.04$). A more pronounced reduction in the risk of bleeding was indicated with OAC monotherapy compared with OAC plus SAPT in men (HR: 0.46; 95% CI: 0.34-0.62) than in women (HR: 0.92; 95% CI: 0.52-1.63) and in patients with diabetes (HR: 0.44; 95% CI: 0.26-0.73) than in patients without diabetes (HR: 0.86; 95% CI: 0.57-1.30) ([Figure 5B](#)).

DISCUSSION

This systematic review and meta-analysis was conducted based on a prespecified protocol and rigorous statistical methods and incorporated both published and unpublished results of $> 4,000$ patients with AF and stable CAD from 4 completed RCTs. The current study has several strengths compared with prior meta-analyses,^{12,13} including prespecified development of a rigorous protocol and registration, comprehensive review of the literature and inclusion of all existing RCTs, collaboration with the principal investigators of included studies to harmonize data elements and obtain relevant otherwise unpublished information within key subgroups, and enriching the paper with thoughts from a multidisciplinary group of

experts in thromboembolic diseases. It showed that OAC monotherapy, compared with OAC plus SAPT, is associated with a significantly reduced risk of major bleeding (low heterogeneity between RCTs, $I^2 = 0\%$) and major or clinically relevant nonmajor bleeding events (high heterogeneity between RCTs, $I^2 = 58\%$). There was no statistically significant increased risk of the primary composite effectiveness outcome or its components, although the individual studies or the pooled analyses were not powered for individual ischemic outcomes and a small effect cannot be excluded ([Central Illustration](#)). No effect modification was noted for the prespecified clinically relevant subgroups regarding the primary effectiveness outcome, whereas the magnitude of bleeding risk reduction with OAC monotherapy, compared with OAC plus SAPT, seemed to be greater in men and in patients with diabetes.

Selecting optimal antithrombotic therapy in patients with concomitant AF and CAD is a clinical conundrum. It is well known that OACs are superior to antiplatelet therapy in reducing the risk of thromboembolic events in patients with AF²⁵ and confer some protection against other ischemic events, as well.^{26,27} Consequently, OAC is considered an indispensable antithrombotic treatment in patients with AF and CAD. Whether the addition of antiplatelet agents prevents ischemic events and/or enhances bleeding risk in patients with AF and CAD has been debatable. There is emerging evidence suggesting that in patients with CAD (especially in older patients), bleeding events carry greater prognostic

weight than ischemic events, particularly considering non-fatal MI, which still carries a relevant prognostic value but of smaller magnitude in the era of high-sensitivity troponin detection.²⁸⁻³⁰

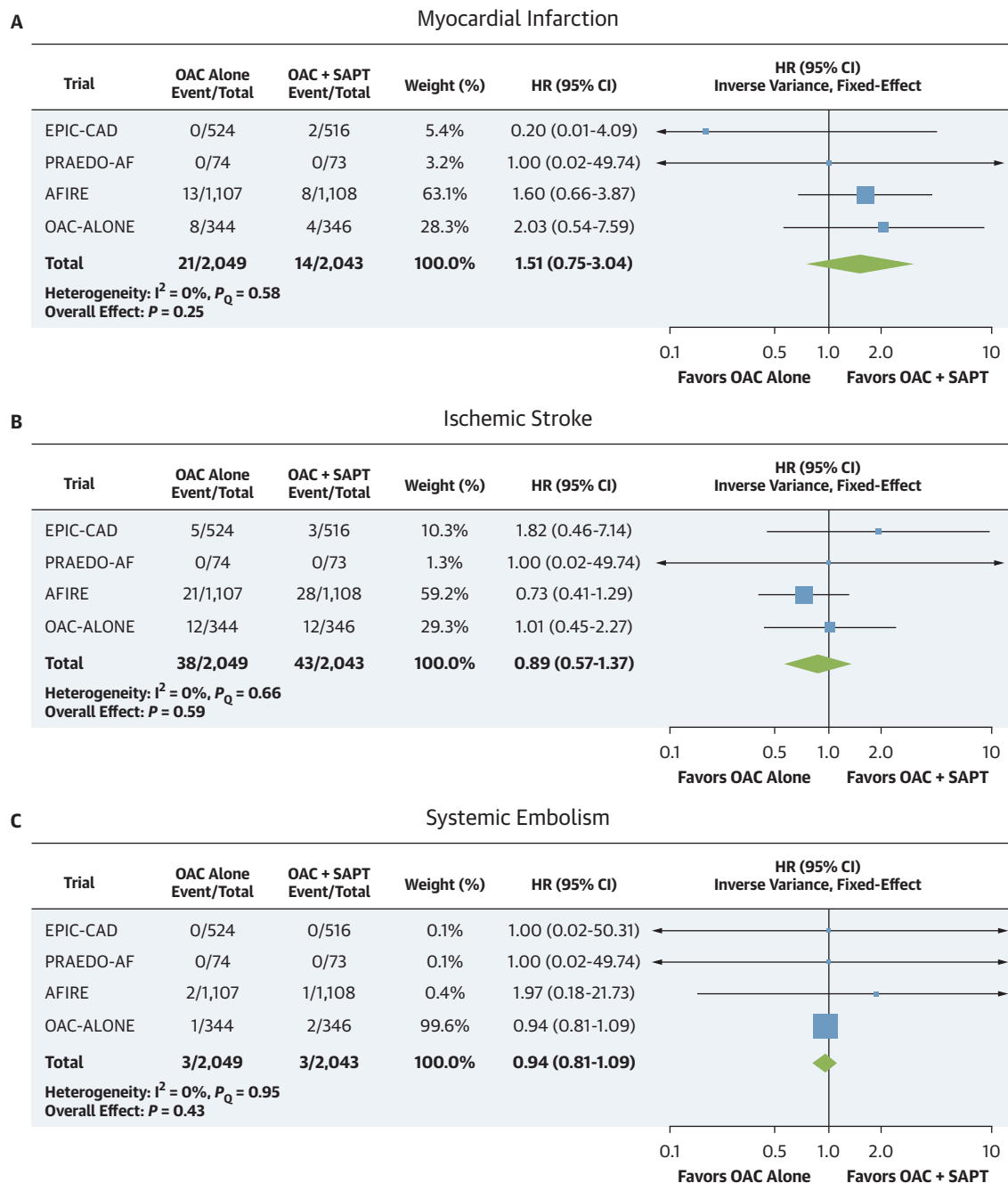
In patients with AF and recent PCI or ACS, several RCTs have demonstrated that de-escalation from triple therapy (anticoagulation plus dual antiplatelet therapy) to dual therapy with anticoagulation plus SAPT for at least 6 to 12 months is safer with respect to bleeding.³¹⁻³⁴ Although these trials were not powered for ischemic events, they did not show a significant increase in ischemic events with anticoagulation plus SAPT when considered individually.³¹⁻³⁴ Some meta-analyses, however, showed that the risk of stent thrombosis was significantly increased with early dual compared with triple antithrombotic therapy.³⁵

Among the population of patients with AF and stable CAD, our analysis did not show a statistically significant increase in the risk of the composite effectiveness outcome or its individual components with OAC monotherapy compared with OAC plus SAPT. However, this pooled analysis may be underpowered to detect small differences in individual ischemic events. For instance, there were numerically higher MI events (1.0% vs 0.7%; HR: 1.51; 95% CI: 0.75-3.04) and stent thrombosis (0.14% vs 0%) in the OAC monotherapy than in the OAC plus SAPT arm. Other effectiveness outcome components (ie, ischemic stroke, systemic embolism, all-cause death, cardiovascular death, and unplanned coronary revascularization), however, occurred equally or less frequently in the OAC monotherapy arm than in the OAC plus SAPT arm. The results from the AFIRE (Atrial Fibrillation and Ischemic Events with Rivaroxaban in Patients with Stable Coronary Artery Disease) trial and the 3 other RCTs were directionally different with respect to ischemic events, such that a significant reduction was observed in AFIRE and a nonsignificant increase in the 3 other trials with OAC monotherapy compared with OAC plus SAPT. However, a pooled analysis of the 3 other trials, excluding AFIRE, did not show a significant increase in the primary effectiveness outcome, and the absolute between-group difference was small (RD 1.1%; 95% CI: -0.9% to 3.3%; $P = 0.27$). The ongoing AQUATIC (Assessment of Quitting Versus Using Aspirin Therapy In Patients Treated With Oral Anticoagulation for Atrial Fibrillation or Other Indication With Stabilized Coronary Artery Disease) trial can bring more certainty to these findings. Future studies are also needed to evaluate whether certain high ischemic-risk subgroups may benefit from OAC plus antiplatelet therapy beyond 1 year after an ACS or

6 months after PCI for stable angina. Therefore, in clinical practice, the findings of this meta-analysis should not be considered akin to stopping SAPT in all patients with AF and stable CAD and rather should be used in the context of their relevant history, symptoms, and biology. Moreover, it should be noted that the prespecified primary effectiveness outcome comprised all-cause death. There may be concerns that higher bleeding events in the OAC plus SAPT arm could have resulted in increased fatal bleeding events and, subsequently, dilution of the effect estimates for the primary effectiveness outcome. However, we showed that the rate of fatal bleeding events was overall low and was even numerically minimally higher in the OAC monotherapy arm than in the OAC plus SAPT arm (0.4% vs 0.3%), refuting this hypothesis. In other words, the primary effectiveness outcome for ischemic events was not disproportionately affected by fatal bleeding events.

Subgroup analyses indicated that men might experience a greater reduction in bleeding risk with OAC monotherapy compared to women. Sex differences in bleeding risk associated with antithrombotic therapy are nuanced, which may be related to variations in patient characteristics and comorbidities, adherence to antiplatelet therapy, or biological differences such as sex hormones.³⁶⁻⁴⁰ We also noted greater risk reduction in bleeding with OAC monotherapy compared with OAC plus SAPT in diabetic than nondiabetic individuals. Prior studies have identified diabetes mellitus as a risk factor for major bleeding events following antiplatelet therapy.³⁸ Therefore, it can be postulated that the exclusion of antiplatelet therapy in diabetic patients with AF and stable CAD can explain, at least in part, the greater decrease in bleeding risk than in nondiabetic patients. Despite the known excess risk of ischemic events with diabetes and acknowledging the fact that subgroup analyses may be underpowered, we did not observe effect modification for elevated thrombotic outcomes in patients with diabetes receiving OAC monotherapy.

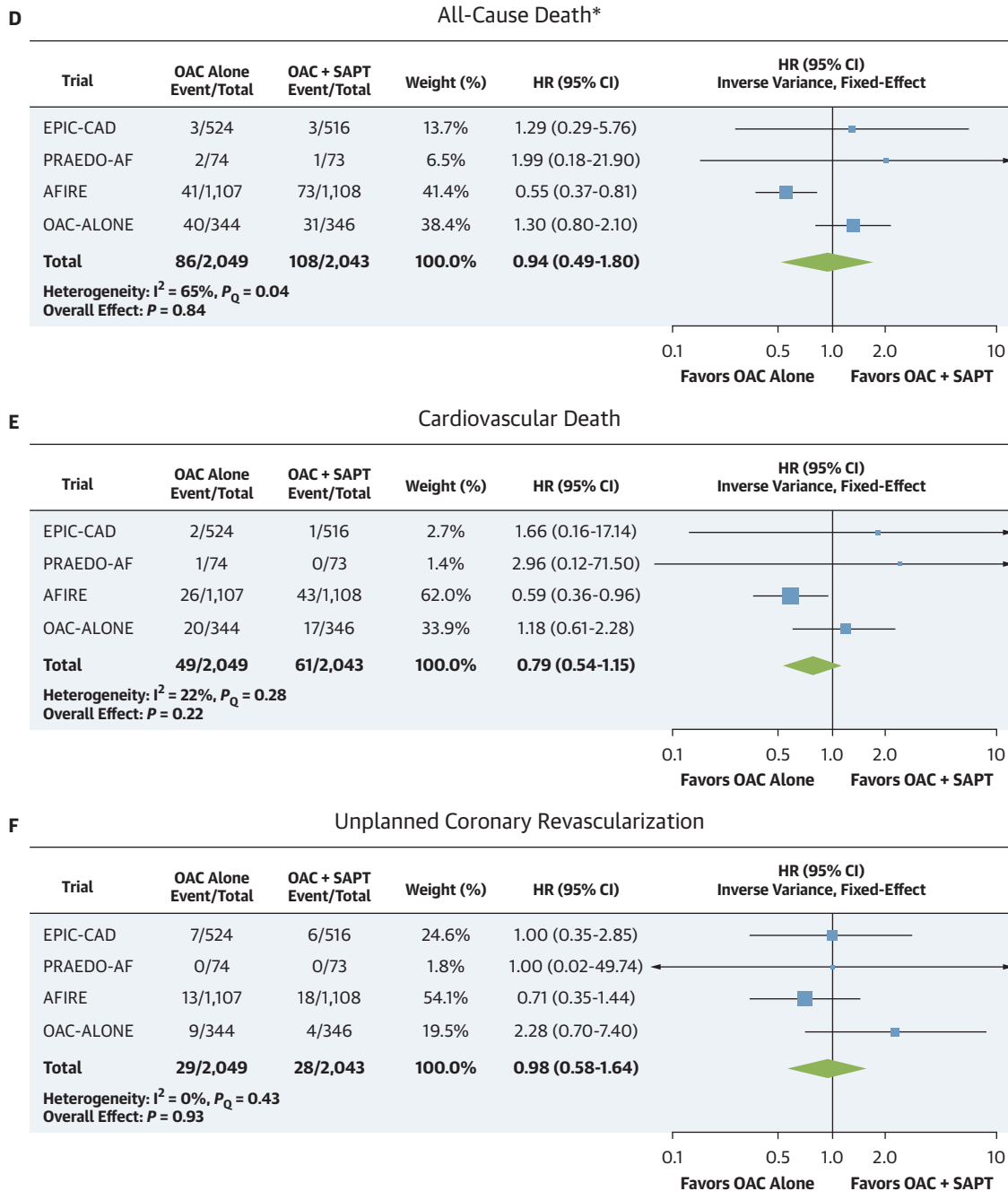
Generalizing these findings to the wide spectrum of patients with AF and stable CAD requires specific considerations. First, all of the completed RCTs were conducted exclusively in East Asia (3 in Japan⁸⁻¹⁰ and 1 in South Korea¹¹), and racial differences in both thromboembolism and bleeding have been reported.^{41,42} Despite racial differences, some prior studies have shown that findings related to antithrombotic therapy from East Asia are directionally reproducible in European/North American cohorts.⁴³⁻⁴⁶ In other populations, an ongoing multicenter, double-blind RCT in France is continuing

FIGURE 3 Secondary Effectiveness Outcomes

Pooled HRs for (A) myocardial infarction, (B) ischemic stroke, (C) systemic embolism, (D) all-cause death, (E) cardiovascular death, and (F) unplanned coronary revascularization did not show statistically significant differences between OAC vs OAC plus SAPT. *A random-effect model was used for all-cause death caused by substantial heterogeneity. Abbreviations as in [Figure 1](#).

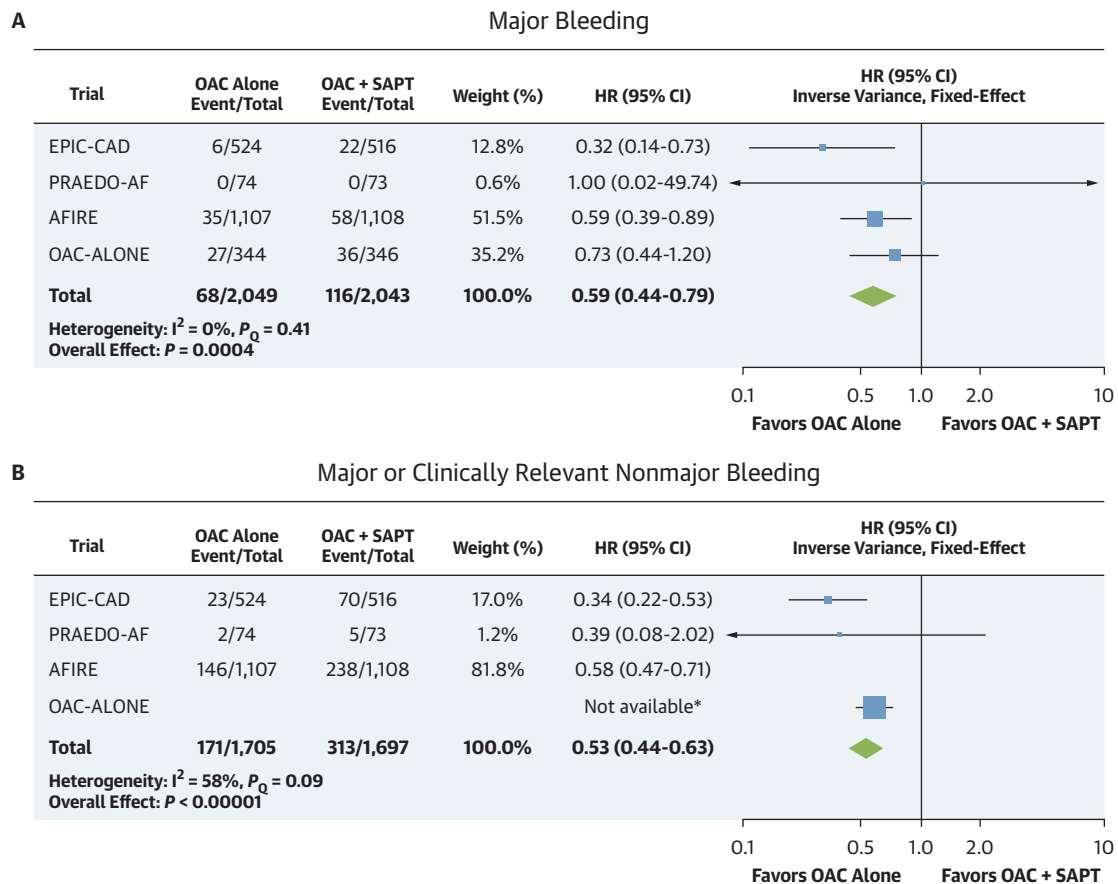
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FIGURE 3 Continued



recruitment to compare the efficacy and safety of OAC plus placebo vs OAC plus aspirin in patients with AF and stable CAD (AQUATIC trial: [NCT04217447](#)). Additionally, the available evidence from nonrandomized studies based on patients from North America and Europe has shown similar findings to this meta-analysis of RCTs (ie, reduced risk of bleeding

without a significantly increased risk of ischemic events with OAC monotherapy than OAC plus antiplatelet therapy).⁴⁷⁻⁵⁰ We plan to update the meta-analysis following the publication of the AQUATIC trial in future years. Therefore, the findings of this meta-analysis should be interpreted considering patient populations of included RCTs, all of which

FIGURE 4 Safety Outcomes

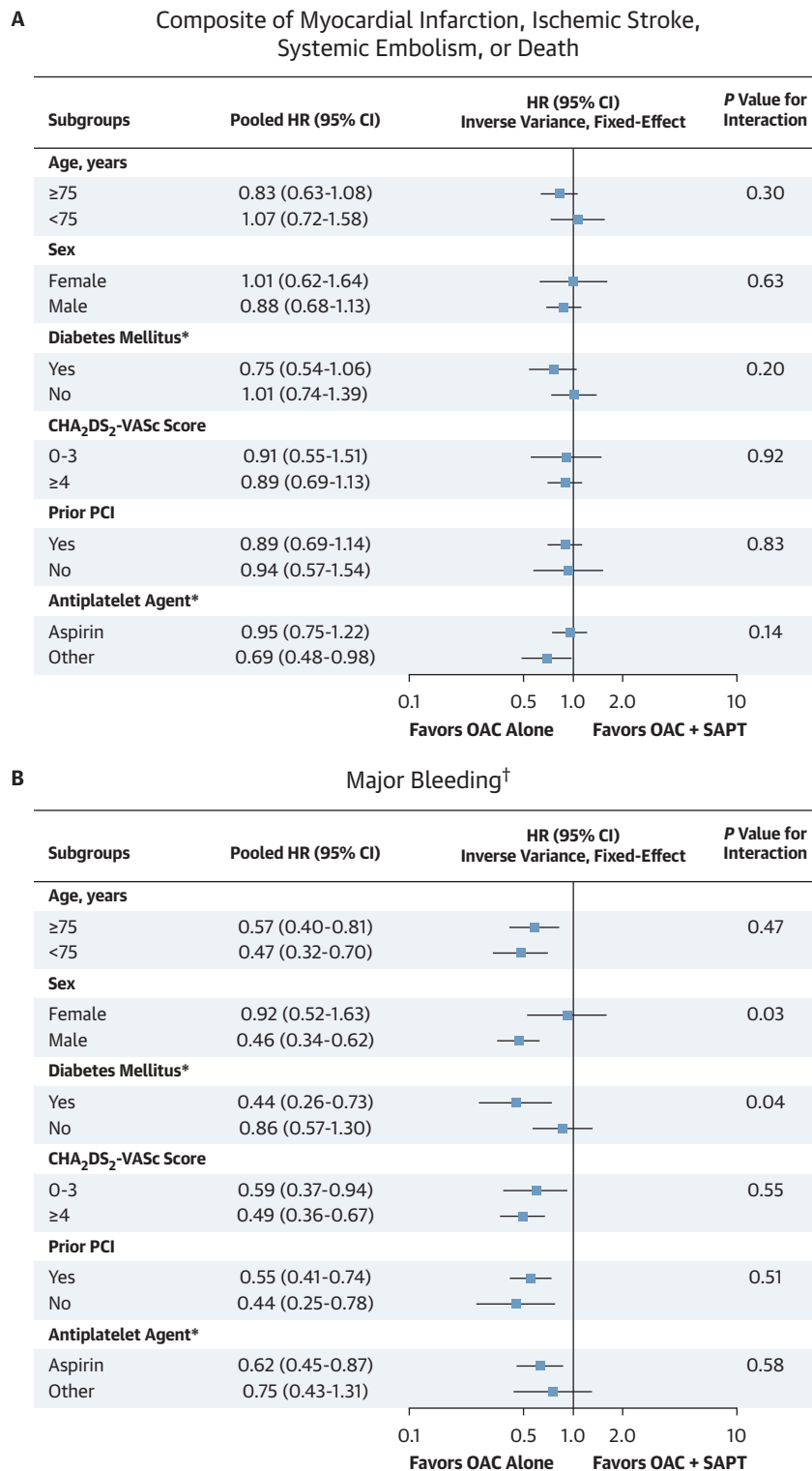
Pooled HRs for (A) major bleeding and (B) major or clinically relevant nonmajor bleeding showed significant reduction with OAC vs OAC plus SAPT. *The data for clinically relevant nonmajor bleeding was unavailable for the OAC-ALONE trial. Abbreviations as in Figure 1.

enrolled patients of Asian descent. The AQUATIC trial will provide complementary information for patients enrolled from Europe. Second, patients scheduled for coronary revascularization were excluded from all included RCTs,⁸⁻¹¹ and some patient subgroups at high risk of ischemic events (such as those with prior stent thrombosis) were not included in some of the trials.^{8,9} Therefore, the results of this meta-analysis may not be applicable to these high-ischemic-risk patients. Apart from AF, other RCTs are assessing the tradeoffs of anticoagulant monotherapy vs dual therapy in patients with acute venous thromboembolism who are on antiplatelet therapy at baseline (NCT05627375).

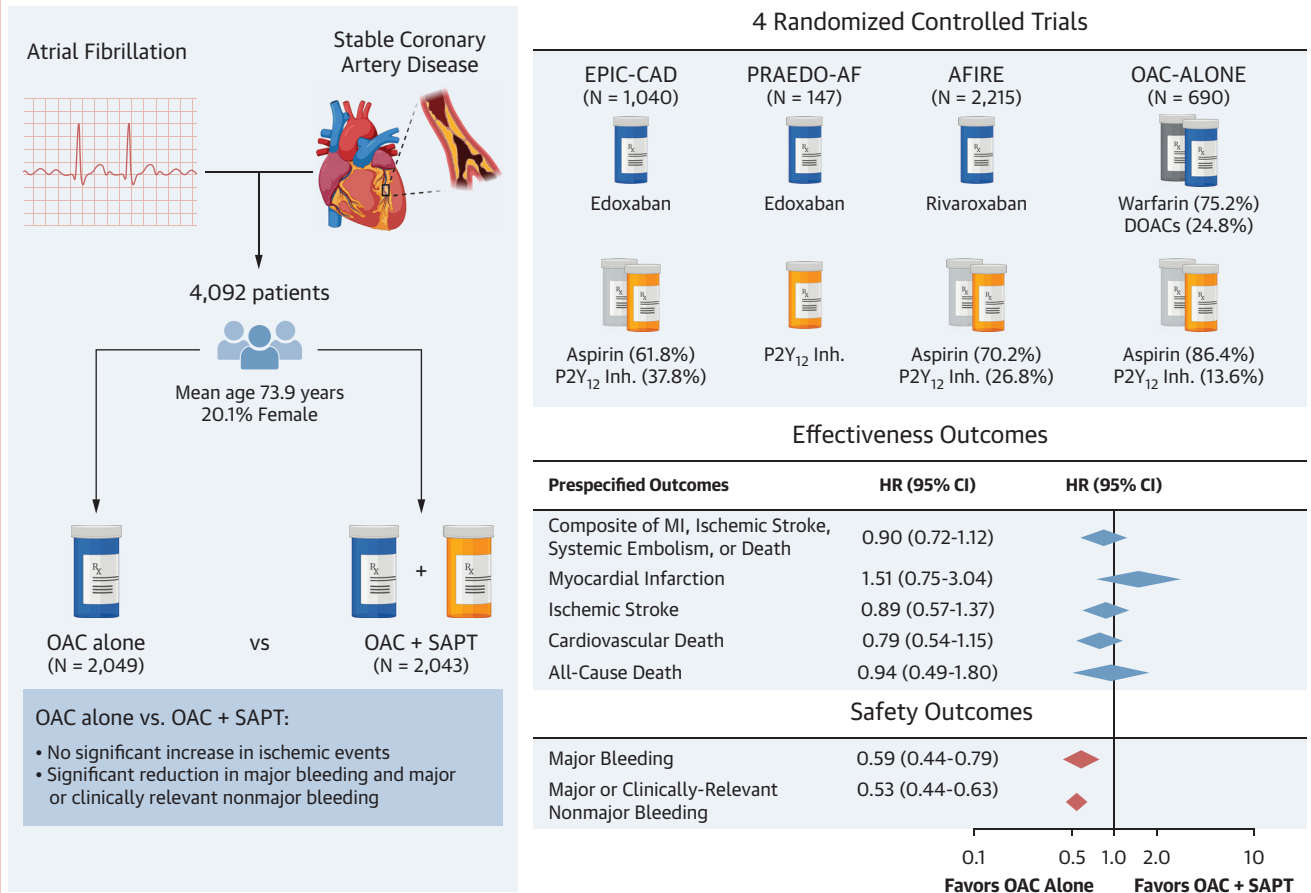
The contemporary American College of Cardiology/American Heart Association guideline for the management of patients with AF has recommended OAC monotherapy for patients with AF and chronic CAD (beyond 1 year after coronary revascularization or CAD

not requiring revascularization) without a history of stent thrombosis.³ Similarly, the 2024 European Society of Cardiology guideline has recommended anticoagulation without antiplatelet therapy for patients with AF and stable CAD not requiring coronary revascularization, 6 months after revascularization for stable chronic CAD, and 1 year after revascularization following ACS.⁵¹ This meta-analysis offers confirmatory support for these recommendations.

STUDY LIMITATIONS. First, men comprised the majority of participants in the included trials (79.9%). Efforts are required to improve the underrepresentation of women, as already ongoing,^{52,53} and additional studies are needed to better understand the detected signal for sex differences in bleeding risk reduction with OAC monotherapy compared with OAC plus SAPT. Furthermore, other subgroup analysis findings should be interpreted cautiously because of the limited number of events.

FIGURE 5 Subgroup Analyses

Pooled HRs for the prespecified subgroups for (A) composite of myocardial infarction, ischemic stroke, systemic embolism, or death, and (B) major bleeding are shown. The results suggested effect modification based on sex and diabetes mellitus for bleeding. *The data for the EPIC-CAD trial were not available for this subgroup. †The subgroup results for the EPIC-CAD trial were available for major or clinically relevant non-major bleeding. As the best available estimate, we incorporated these findings to calculate subgroup-specific results for the safety outcome. Abbreviations as in [Figure 1](#).

CENTRAL ILLUSTRATION Oral Anticoagulant Alone vs Oral Anticoagulant Plus SAPT in Atrial Fibrillation and Stable Coronary Artery Disease

Rashedi S, et al. JACC. 2025;■(■):■-■.

Pooled estimates from 4 randomized controlled trials indicated that oral anticoagulant (OAC) alone, compared with OAC plus single antiplatelet therapy (SAPT), is associated with a significantly reduced risk of bleeding without a statistically significantly increased risk of ischemic events, although a smaller effect cannot be excluded. AFIRE = Atrial Fibrillation and Ischemic Events with Rivaroxaban in Patients with Stable Coronary Artery Disease; DOAC = direct oral anticoagulant; EPIC-CAD = Edoxaban vs Edoxaban with Antiplatelet agent in Patients with Atrial Fibrillation and Chronic Stable Coronary Artery Disease; MI = myocardial infarction; OAC-ALONE = Optimizing Antithrombotic Care in Patients With Atrial Fibrillation and Coronary Stent; PRAEDO-AF = Prospective Randomized Study of Safety Outcomes Treated with Edoxaban in Patients with Stable Coronary Artery Disease and Atrial Fibrillation.

Second, because of limitations with the available data and a small number of events, we did not explore differences based on the type of OAC and certain patient-related factors, such as duration of prior treatment with OAC and SAPT, time since AF diagnosis, time since last coronary event or PCI, type of AF, or history of ACS. Individual participant data meta-analysis of the RCTs can provide additional insights into the choice of anticoagulation and optimal antithrombotic therapy for these patient subsets. Third, despite our efforts to harmonize data from the included trials, some data points (ie, clinically relevant nonmajor bleeding from OAC-ALONE and some

subgroup-specific estimates from EPIC-CAD [Atrial Fibrillation and Ischemic Events with Rivaroxaban in Patients with Stable Coronary Artery Disease]) could not be further clarified. Fourth, the variations in the OACs and antiplatelet agents used in the trials limited us from concluding definitively whether there are differences in effectiveness or safety between these different agents or combinations. Fifth, because of the small number of included studies, the statistical tests of heterogeneity (I^2 and Q test) may have been underpowered. Therefore, we repeated the analyses using random-effect models, which yielded similar results.

CONCLUSIONS

In this meta-analysis of 4 RCTs, OAC monotherapy, compared with OAC plus SAPT, was not associated with a statistically significant increased risk of ischemic events but resulted in a significantly reduced risk of major bleeding and major or clinically relevant nonmajor bleeding. The bleeding risk reduction with OAC monotherapy seemed to be greater in men and patients with diabetes. Further research is needed to confirm these results in a more diverse patient population.

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APPENDIX For supplemental tables and figures, please see the online version of this paper.