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ORIGINAL RESEARCH

CORONARY

Oral Anticoagulation With or Without Antiplatelet Therapy in Chronic Coronary Syndrome

A Meta-Analysis of Randomized Trials

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ABSTRACT

BACKGROUND The optimal antithrombotic therapy for patients with chronic coronary syndrome (CCS) who also require long-term oral anticoagulation (OAC) remains uncertain.

OBJECTIVES The aim of this study was to evaluate the safety and efficacy of OAC monotherapy compared with OAC plus single antiplatelet therapy (SAPT) in CCS patients with an indication for long-term anticoagulation.

METHODS Randomized trials comparing OAC monotherapy with OAC plus SAPT in patients with CCS and indication for long-term OAC from the PubMed, Cochrane Central, Web of Science, and Scopus databases up to November 10, 2025 were included in this systematic review and meta-analysis. HRs and 95% CIs were estimated through a random-effects meta-analytical framework. The primary efficacy endpoint was trial-defined major adverse cardiovascular events, and the primary safety endpoint was any bleeding.

RESULTS Six trials comprising 5,924 patients were included. The median follow-up duration was 2.3 years (Q1-Q3: 1.3-2.9 years), the median CHA_2DS_2-VASc score was 4.2 (Q1-Q3: 4.0-4.6), and the median time from revascularization to randomization 3.8 years (Q1-Q3: 3.2-4.4 years). Compared with OAC plus SAPT, OAC monotherapy showed similar rates of major adverse cardiovascular events (6.8% vs 8.2%; HR: 0.85; 95% CI: 0.64-1.09; I^2 =23%) and reduced risk of bleeding (8.9% vs 16.1%; HR: 0.49; 95% CI: 0.44-0.55; I^2 =8%). OAC monotherapy also reduced cardiovascular death (HR: 0.69; 95% CI: 0.48-0.97; I^2 =0%), net adverse clinical events (HR: 0.60; 95% CI: 0.47-0.78; I^2 =66%), and major bleeding (HR: 0.46; 95% CI: 0.32-0.66; I^2 =47%) compared with OAC plus SAPT. There were no significant differences in myocardial infarction, stroke, or all-cause mortality.

CONCLUSIONS In patients with CCS requiring long-term OAC, OAC monotherapy was associated with reduced bleeding, cardiovascular death, and net adverse clinical events compared with OAC plus SAPT. (Anticoagulation Alone vs Anticoagulation Plus Antiplatelet Therapy in Atrial Fibrillation With Stable Coronary Disease: A Meta-Analysis of Randomized Trials; CRD420251174643). (JACC Cardiovasc Interv. 2026;19:1294–1306) © 2026 The Authors. Published by Elsevier on behalf of the American College of Cardiology Foundation. This is an open access article under the CC BY license (http://creativecommons.org/licenses/by/4.0/).

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The optimal antithrombotic therapy for patients with chronic coronary syndromes (CCS) who also require long-term oral anticoagulation (OAC), most commonly for stroke prevention in atrial fibrillation (AF), remains a clinical challenge.[1] Single antiplatelet therapy (SAPT), traditionally with aspirin, represents the cornerstone of secondary prevention of atherothrombotic events in CCS and is often prescribed indefinitely.[2] However, although SAPT is effective in reducing both local ischemic events, such as stent thrombosis, as well as systemic atherothrombotic events, it does not adequately prevent cardioembolic stroke in patients with AF, for whom OAC is indicated.[3] Conversely, combining OAC with antiplatelet therapy substantially increases the risk for bleeding, whereas the incremental ischemic benefit in this setting remains uncertain.[3-6] Contemporary guidelines therefore recommend OAC monotherapy for long-term prevention of ischemic events in patients with CCS and concomitant indications for anticoagulation.[7-9] Despite these recommendations, real-world and randomized clinical trial (RCT) evidence indicates that combining OAC and SAPT remains common in clinical practice.[4-6,10] Recent RCTs have broadened the available evidence, addressing limitations of earlier studies such as small sample size, early termination, and the use of nonstandard direct oral anticoagulant dosing regimens (eg, rivaroxaban 10-15 mg/d) or vitamin K antagonists (VKAs).[11,12] Updated and comprehensive meta-analyses including all available RCTs, such as the most recent AQUATIC (Assessment of Quitting Versus Using Aspirin Therapy in Patients With Stabilized Coronary Artery Disease after Stenting Who Require Long-Term Oral Anticoagulation) and ADAPT AF-DES (Appropriate Duration of Antiplatelet and Thrombotic Strategy After 12 Months in Patients With Atrial Fibrillation Treated With Drug-Eluting Stents) trials, are lacking.[10,11,13-15] In this systematic review and meta-analysis, we synthesize contemporary RCT data comparing OAC monotherapy vs OAC plus SAPT in patients with CCS and an indication for long-term anticoagulation.

METHODS

This study was conducted in accordance with the *Cochrane Handbook for Systematic Reviews of Interventions* and reported following the Preferred Reporting Items for Systematic Reviews and Meta-Analyses guidelines (Supplemental Table S1). The study protocol was registered in the International Prospective Register of Systematic Reviews (CRD420251174643). The requirement to obtain approval from the ethics committee was waived because of the nature of this research.

ELIGIBILITY CRITERIA. Studies were considered eligible for inclusion in the meta-analysis if they satisfied the following criteria: 1) inclusion of CCS patients with indications for long-term anticoagulation; 2) comparison of OAC monotherapy vs OAC plus SAPT; and 3) reporting at least 1 of the prespecified endpoints of interest. Exclusion criteria included nonrandomized design and the inclusion of acute coronary syndrome patients. No restrictions were applied regarding language or publication date.

SEARCH DATA EXTRACTION AND QUALITATIVE ASSESSMENT. The specific search strategies for each database are reported in Supplemental Table S2. Information sources included MEDLINE via PubMed, the Cochrane Central Register of Controlled Trials, Web of Science, and Scopus, searched from database inception through November 10, 2025. In addition, the websites of major cardiology societies, relevant

ABBREVIATIONS AND ACRONYMS

AF = atrial fibrillation
CAD = coronary artery disease
CCS = chronic coronary syndrome(s)
GRADE = Grading of Recommendations, Assessment, Development, and Evaluations
MI = myocardial infarction
NACE = net adverse clinical event(s)
NNT = number needed to treat
OAC = oral anticoagulation
PCI = percutaneous coronary intervention
RCT = randomized clinical trial
SAPT = single antiplatelet therapy
VKA = vitamin K antagonist

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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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news outlets, and the reference lists of included studies were manually reviewed to identify additional eligible trials. Three investigators (M.V., C.L., and M.G.) independently screened all retrieved records, with any discrepancies resolved by consensus. Data on study characteristics and outcomes of interest were extracted at the study level and inserted into standardized electronic data sheets. Key trial-level variables, including design, follow-up duration, and endpoint definitions, were systematically summarized. Prior to statistical analysis, 2 reviewers independently evaluated the methodological quality of each trial using the Cochrane Risk of Bias 2 tool, resolving disagreements by consensus. Potential publication bias was examined using contour-enhanced funnel plots and Egger's regression test, with the trim-and-fill method applied when bias was suspected.

STUDY ENDPOINTS. The prespecified primary efficacy and safety endpoints were trial-defined major adverse cardiovascular events and any bleeding. In cases in which multiple definitions of the primary efficacy endpoint were reported, we prioritized those that were more consistent across trials and aligned with the Academic Research Consortium criteria. Secondary endpoints included all-cause death, cardiovascular death, myocardial infarction (MI), stroke, trial-defined net adverse clinical events (NACE), and major bleeding. Major bleeding was defined according to the International Society on Thrombosis and Haemostasis criteria. A detailed description of outcomes definitions across studies is reported in Supplemental Table S3.

STATISTICAL ANALYSIS. To account for both biological variability and different follow-up duration across studies, log HRs were estimated from original time-to-event analysis for each trial with corresponding SEs and pooled by random-effect restricted maximum likelihood meta-analytical model to obtain pooled HRs and 95% CIs for OAC monotherapy vs OAC plus SAPT. Statistical heterogeneity was assessed using τ^2 and I^2 and categorized as low, moderate, or high for I^2 levels of <25%, 25% to 50%, and >50%, respectively.

Post hoc sensitivity analyses included: 1) repeating the analyses using risk ratios; 2) repeating the analyses using fixed-effects models; 3) subgroup and interaction analyses using the Q test according to the OAC regimens allowed (ie, guideline-concordant vs non-guideline-concordant dosing), inclusion of VKAs, and time from revascularization to randomization above vs below the pooled median; and 4) leave-one-out analyses to identify the main sources of heterogeneity. Posterior qualitative assessment of the meta-analysis results was also performed using Grading of Recommendations, Assessment, Development, and Evaluations (GRADE) approach.[16]

Number needed to treat (NNT) and number needed to harm to prevent or cause an adverse event were calculated on the basis of pooled HRs and estimated survival in the control group. Finally, trial sequential analysis was performed for the primary endpoints to assess whether the accumulated evidence was sufficient to draw conclusive results regarding benefit, harm, or neutrality.

All analyses were performed using R version 4.4.2 (R Foundation for Statistical Computing) and Stata version 17.0 (StataCorp).

RESULTS

The study selection process is summarized in Supplemental Figure S1. After screening, 6 RCTs comprising a total of 5,924 patients with a median follow-up duration of 2.3 years (Q1-Q3: 1.3-2.9 years).[10-12,17-19] In all trials, AF was the indication for OAC. In the OAC plus SAPT group, OAC consisted of edoxaban in 2 trials (EPIC-CAD [Edoxaban Versus Edoxaban With Antiplatelet Agent in Patients With Atrial Fibrillation and Chronic Stable Coronary Artery Disease] and PRAEDO-AF [Prospective Randomized Study of Safety Outcomes Treated With Edoxaban in Patients With Stable Coronary Artery Disease and Atrial Fibrillation]), rivaroxaban 10-15 mg in 1 trial (AFIRE [Atrial Fibrillation and Ischemic Events With Rivaroxaban in Patients With Stable Coronary Artery Disease Study]), mostly VKAs in 1 trial (OAC-ALONE [Optimizing Antithrombotic Care in Patients With Atrial Fibrillation and Coronary Stent]), and a mix of different DOACs in 2 trials (AQUATIC and ADAPT AF-DES). All but 2 trials—PRAEDO-AF and ADAPT AF-DES, in which all patients received clopidogrel—primarily used aspirin in the OAC plus SAPT arm. All studies included patients with prior percutaneous coronary intervention (PCI), except AFIRE and EPIC-CAD, which also enrolled coronary artery disease (CAD) patients managed without PCI. The median time from revascularization to randomization was 3.8 years (Q1-Q3: 3.2-4.4 years), ranging from 2.7 years in ADAPT AF-DES to 4.6 years in the EPIC-CAD trial, and the median CHA_2DS_2-VASc score was 4.2 (Q1-Q3: 4.0-4.6). Women and East Asians accounted for 19.6% and 85.3% of the study population, respectively. The key characteristics of the included studies are summarized in **Figure 1** and Supplemental Table S4. Only 1 RCT showed some

FIGURE 1 Main Characteristics of Included Randomized Controlled Trials

Trial (Year)	Population	Mean Patient Characteristics	N Total	Randomization	Median Time From Revascularization To Randomization	OAC and SAPT Regimen	Primary Endpoint	Follow-Up
AFIRE (2019)	 AF, CAD	Mean age = 74 ± 8 Female = 21% CHA_2DS_2-VASc = 4.1 ± 1.4 DM = 39% PCI = 70% Enrolled in East Asia = 100%	2, 215	**OAC alone (n = 1,108)** **OAC + SAPT (n = 1,107)**	3.9 y	Rivaroxaban 15 mg daily (10 mg in patients with eGFR 15-49 mL/min) Rivaroxaban 15 mg daily, aspirin (81-100 mg daily), or clopidogrel (50-75 mg daily) or prasugrel (2.5-3.75 mg daily)	**MACE**	24 mo
OAC-ALONE (2019)	 AF, CAD	Mean age = 74 ± 8 Female = 20% CHA_2DS_2-VASc = 4.0 ± 1.2 DM = 35% PCI = 100% Enrolled in East Asia = 100%	690	**OAC alone (n = 346)** **OAC + SAPT (n = 344)**	4.5 y	VKA ~75% (target INR 2.0-3.0 in patients <70 y of age or 1.6-2.6 in elderly), DOAC ~25% (dabigatran 110-150 mg twice daily, rivaroxaban 10-15 mg daily, apixaban 2.5-5 mg twice daily, edoxaban 30-60 mg daily) VKA ~75% (target INR 2.0-3.0 in patients <70 years of age, or 1.6-2.6 in elderly) or DOAC ~25% (dabigatran 110-150 mg twice daily, or rivaroxaban 10-15 mg daily, or apixaban 2.5-5 mg twice daily, or edoxaban 30-60 mg daily) + aspirin (81-324 mg daily) or clopidogrel (75 mg daily).	**MACE**	30 mo
PRAEDO-AF (2022)	 AF, CAD	Mean age = 74 ± 9 Female = 26% CHA_2DS_2-VASc = 4.3 ± 1.6 DM = 32% PCI = 100% Enrolled in East Asia = 100%	147	**OAC alone (n = 73)** **OAC + SAPT (n = 74)**	3.7 y	Edoxaban 60 mg daily (30 mg if CrCl < 50 mL/min or weight < 60 kg) Edoxaban 60 mg daily (30 mg if CrCl < 50 mL/min or weight < 60 kg) + clopidogrel (dose not reported)	**Bleeding (ISTH)**	20 mo
EPIC-CAD (2024)	 AF, CAD	Mean age = 72 ± 9 Female = 23% CHA_2DS_2-VASc = 4.3 ± 1.3 DM = 40% PCI = 81% Enrolled in East Asia = 100%	1,040	**OAC alone (n = 516)** **OAC + SAPT (n = 524)**	4.6 y	Edoxaban 60 mg daily (30 mg if CrCl < 50 mL/min or weight < 60 kg or use of Pgp inhibitors) Edoxaban 60 mg daily (30 mg if CrCl < 50 mL/min or weight < 60 kg or use of Pgp inhibitors) + SAPT (62% aspirin, 38% clopidogrel, dosages not reported)	**NACE**	12 mo
AQUATIC (2025)	 AF, CAD	Mean age = 73 ± 8 Female = 22% CHA_2DS_2-VASc = 4.2 ± 1.4 DM = 37% PCI = 92% Enrolled in East Asia = 0%	872	**OAC alone (n = 433)** **OAC + SAPT (n = 439)**	3 y	Any OAC with dosing regimens according to current guidelines (apixaban 62%, rivaroxaban 24%, edoxaban 3%, VKA 11%) Any OAC with dosing regimens according to current guidelines (apixaban 62%, rivaroxaban 24%, edoxaban 3%, VKA 11%). + aspirin 100 mg daily.	**MACE**	26 mo
ADAPT AF-DES (2025	 AF, CAD	Mean age = 71 ± 8 Female = 21% CHA_2DS_2-VASc = 4.1 ± 1.4 DM = 38% PCI = 100% Enrolled in East Asia = 100%	960	**OAC alone (n = 482)** **OAC + SAPT (n = 478)**	2.7 y	Apixaban 5 mg twice daily (2.5 mg in patients with 80 y, body weight < 60 kg, or serum creatinine 1.5 mg/mL) or rivaroxaban 30 mg daily (15 mg in patients with CrCl < 51 mL/min), with apixaban in 61% of patients, rivaroxaban 34%, edoxaban 4%, and VKA 1% Apixaban 5 mg twice daily (2.5 mg in patients with 80 y, body weight < 60 kg, or serum creatinine 1.5 mg/mL) or rivaroxaban 15 mg daily (10 mg in patients with CrCl < 51 mL/min), with apixaban in 61% of patients, rivaroxaban 34%, edoxaban 4%, and VKA 1% + clopidogrel 75 mg	**NACE**	12 mo

Continued on the next page

concern for bias (Supplemental Figure S2). Visual inspection of funnel plots did not highlight signs of publication bias, as being mostly well balanced between the sides of the panel, and all Egger's regression tests had P values >0.180 (Supplemental Figure S3).

PRIMARY ENDPOINTS. Compared with OAC plus SAPT, OAC monotherapy showed no difference in the primary efficacy outcome (6.8% vs 8.2%; HR: 0.85; 95% CI: 0.66-1.09; I^2 = 23%; τ^2 = 0.0252) while significantly reducing the risk for the primary safety outcome (8.9% vs 16.1%; HR: 0.49; 95% CI: 0.44-0.55; I^2 = 8%; τ^2 = 0.0047) (**Figure 2**). The NNT for the primary efficacy endpoint was 83 (95% CI: 37-4,111), whereas the NNT for the primary safety endpoint was 13 (95% CI: 11-23). The certainty of evidence, as assessed using GRADE, was rated moderate for the primary efficacy endpoint and high for the primary safety endpoint. Trial sequential analysis indicated that sufficient power was achieved to establish conclusiveness for benefit in the primary safety endpoint and conclusiveness for neutrality in the primary efficacy endpoint (**Figure 3**).

SECONDARY ENDPOINTS. OAC monotherapy significantly reduced cardiovascular death (HR: 0.69; 95% CI: 0.48-0.97; I^2 = 0%; τ^2 = 0.0291; NNT = 91 [95% CI: 55-1,097]), trial-defined NACE (HR: 0.60; 95% CI: 0.47-0.78; I^2 = 66%; τ^2 = 0.0578; NNT = 16 [95% CI: 12-30]), and major bleeding (HR: 0.46; 95% CI: 0.32-0.66; I^2 = 47%; τ^2 = 0.0820; NNT = 30 [95% CI: 23-48]) compared with OAC plus SAPT (**Figure 4**). There were no differences between groups in all-cause death (HR: 0.77; 95% CI: 0.53-1.13; I^2 = 52%; τ^2 = 0.1057), MI (HR: 1.05; 95% CI: 0.59-1.89; I^2 = 22%; τ^2 = 0.0882), and stroke (HR: 0.92; 95% CI: 0.63-1.33; I^2 =0%; τ^2 = 0) (**Figure 5**). GRADE and NNT or number needed to harm for each secondary outcome are reported in Supplemental Tables S5 and Table S6, respectively.

SENSITIVITY ANALYSES. Secondary analyses generally yielded results consistent with the main analyses (Supplemental Tables S7 and S8). Subgroup analyses showed significant interaction by the OAC regimen administered for major bleeding (P = 0.008 for interaction), with a greater reduction in major bleeding observed when OAC monotherapy was administered at guideline-recommended doses (Supplemental Table S8). Leave-one-out analysis also highlighted that OAC-ALONE was the major contributor to heterogeneity, and repeat analysis after its exclusion reported reduced mortality and major adverse cardiovascular events with OAC alone compared with OAC plus SAPT (Supplemental Table S9).

DISCUSSION

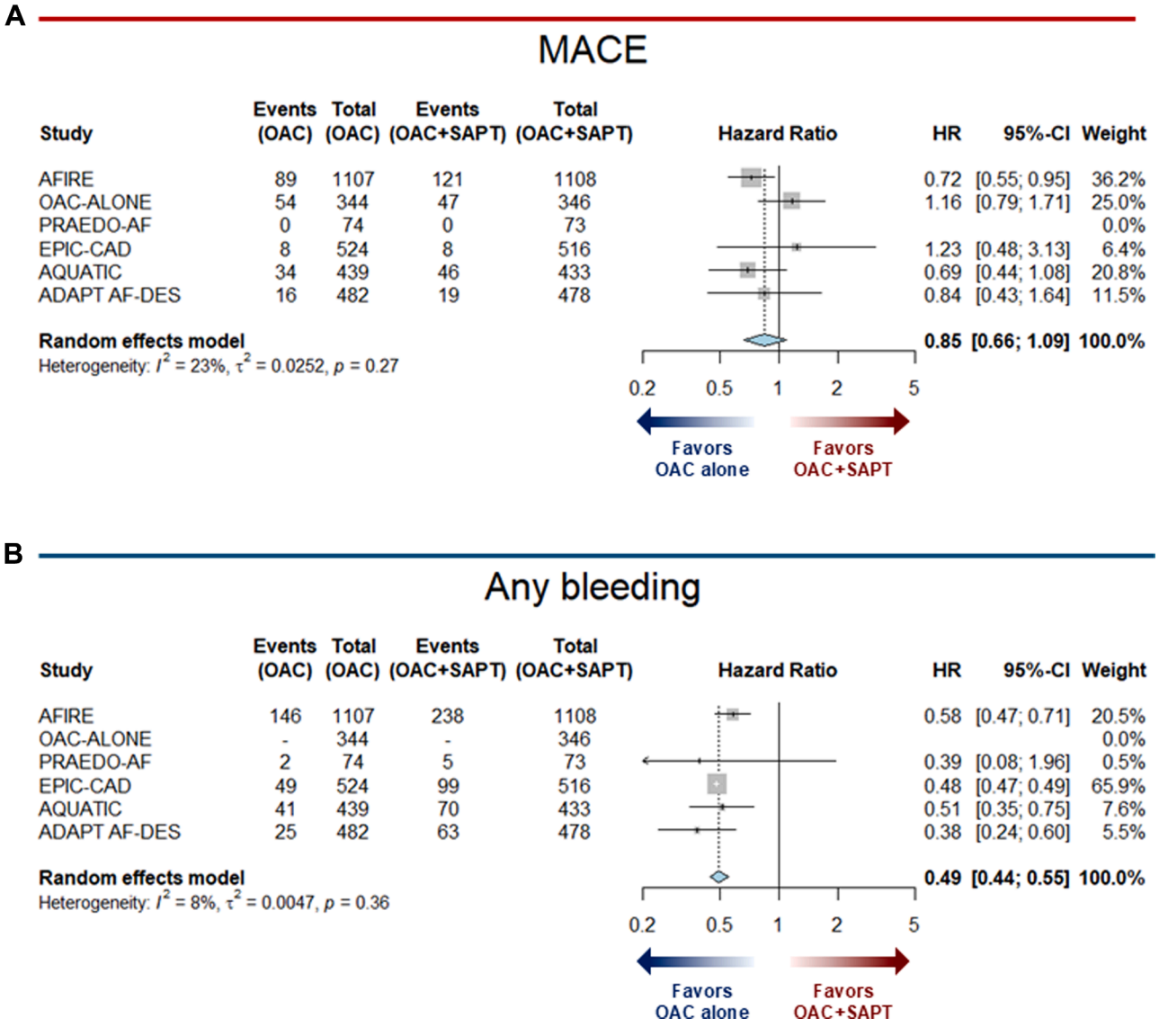
The results of the present meta-analysis, integrating evidence from all available RCTs comparing OAC monotherapy with OAC plus SAPT in CCS patients with AF and including almost 6,000 patients, demonstrate that OAC monotherapy is associated with a substantially lower risk for any bleeding, major bleeding, cardiovascular death, and NACE, without evidence of an increased risk in composite or individual ischemic events compared with OAC plus SAPT (**Central Illustration**). These results corroborate and further strengthen the evidence from previous trials and meta-analyses.[10,11,13-15,17-21]

AF and CAD are distinct yet closely interrelated conditions that share common risk factors and an underlying prothrombotic milieu.[22] However, their pathophysiological mechanisms leading to thrombosis differ substantially. Thrombogenesis in AF is driven predominantly by blood stasis within the atria, leading to activation of the coagulation cascade, while CAD is characterized by high-shear arterial thrombosis, mediated primarily by platelet activation.[22] Therefore, OAC represents the cornerstone of thromboembolic prevention in AF, whereas antiplatelet agents are the mainstay of secondary prevention in CAD.[2,23] However, combining OAC with antiplatelet therapy substantially increases the risk for bleeding, which carries important prognostic

FIGURE 1 Continued

AF = atrial fibrillation; ADAPT AF-DES = Appropriate Duration of Antiplatelet and Thrombotic Strategy After 12 Months in Patients With Atrial Fibrillation Treated With Drug-Eluting Stents; AFIRE = Atrial Fibrillation and Ischemic Events With Rivaroxaban in Patients With Stable Coronary Artery Disease Study; AQUATIC = Assessment of Quitting Versus Using Aspirin Therapy in Patients With Stabilized Coronary Artery Disease after Stenting Who Require Long-Term Oral Anticoagulation; CAD = coronary artery disease; CrCl = creatinine clearance; DM = diabetes mellitus; DOAC = direct oral anticoagulant agent; eGFR = estimated glomerular filtration rate; EPIC-CAD = Edoxaban Versus Edoxaban With Antiplatelet Agent in Patients With Atrial Fibrillation and Chronic Stable Coronary Artery Disease; INR = international normalized ratio; ISTH = International Society on Thrombosis and Haemostasis; MACE = major adverse cardiovascular event(s); NACE = net adverse clinical event(s); NR = not reported; OAC = oral anticoagulation; OAC-ALONE = Optimizing Antithrombotic Care in Patients With Atrial Fibrillation and Coronary Stent; PCI = percutaneous coronary intervention; Pgp = P-glycoprotein; 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; VKA = vitamin K antagonist.

FIGURE 2 Forest Plot for the Primary Efficacy and Safety Endpoints



(A) Primary efficacy and (B) safety endpoints. Abbreviations as in Figure 1.

implications that may outweigh the potential ischemic benefits of combined OAC and SAPT.[24-26] Therefore, contemporary guidelines recommend OAC monotherapy for the long-term prevention of ischemic events in patients with CCS and concomitant indications for anticoagulation.[7-9]

Despite these recommendations, real-world and RCT evidence indicates that combining OAC and SAPT remains common in clinical practice.[4-6,10] The rationale for combining SAPT with OAC is based on the presumed need for additional protection against local coronary thrombotic events, such as stent thrombosis, particularly in patients with prior PCI.[27] However, increasing evidence shows that this limitation applies mostly to patients at high thrombotic risk during the early post-PCI period and/or acute coronary syndrome, whereas the incremental ischemic benefit in CCS remains uncertain.[4-6] Data from contemporary trials suggest that premature aspirin withdrawal in this early phase may increase the risk for stent thrombosis and MI, particularly among patients with high platelet reactivity or

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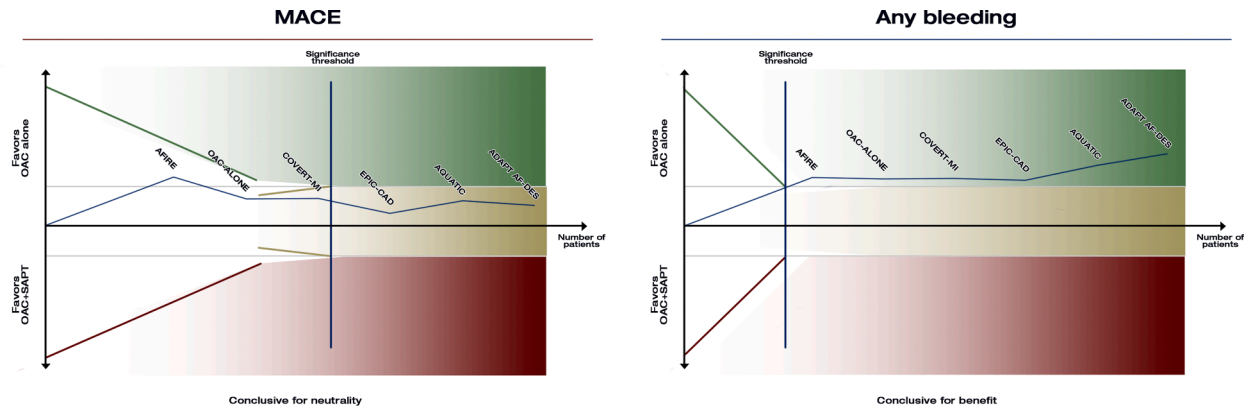
FIGURE 3 Trial Sequential Analysis for the Primary Endpoints



The plots illustrate the trial sequential analysis for the primary endpoints. For each endpoint, the blue horizontal line represents the cumulative estimate of the treatment effect as patient numbers increase, while the vertical blue line indicates the required sample size threshold to achieve conclusiveness for benefit (green zone), neutrality (orange zone), or harm (red zone). When the cumulative line crosses the vertical lines and lands into one of these zones, the result can be considered conclusive on the basis of statistical power calculations. Abbreviations as in Figure 1.

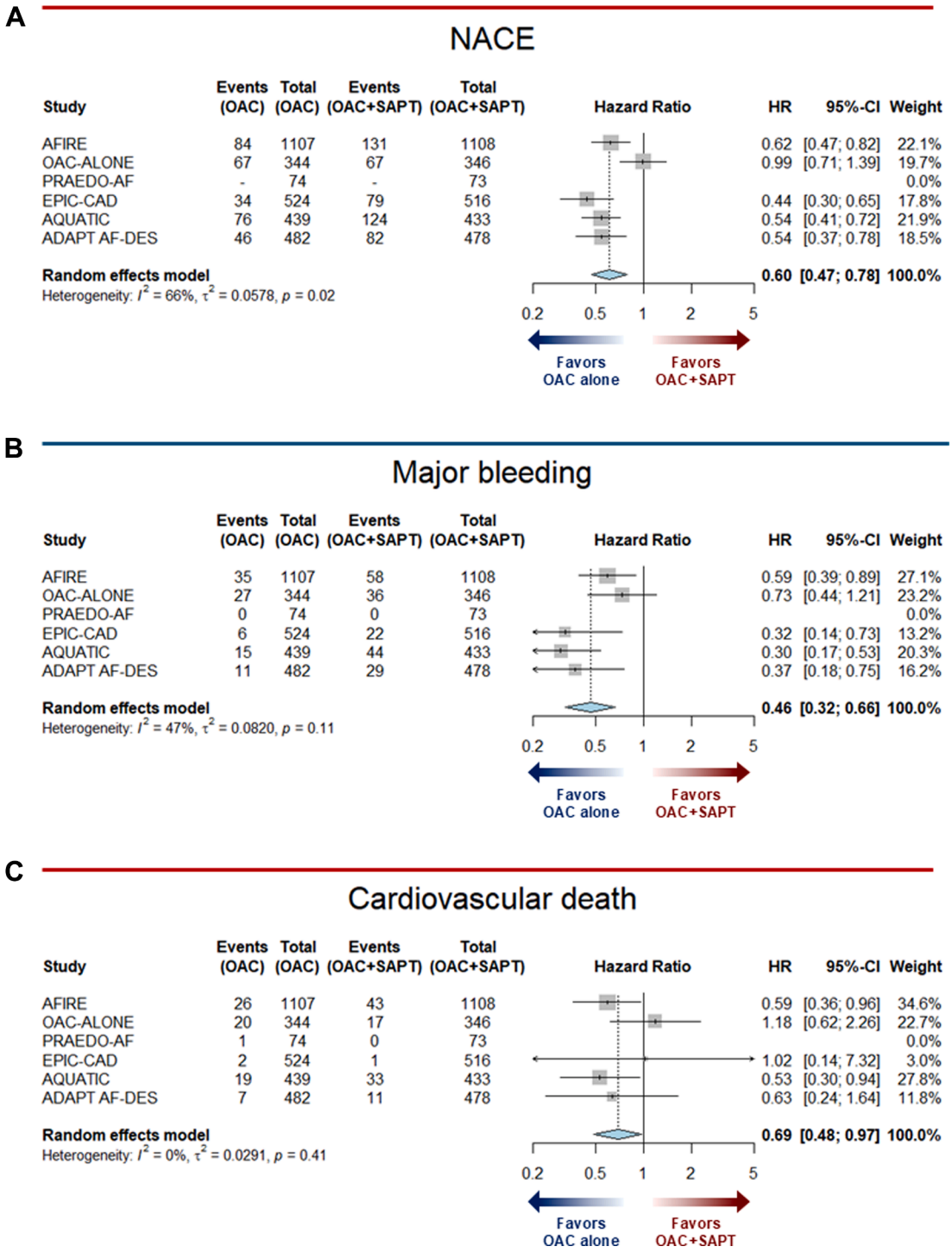
suboptimal response to clopidogrel.[1,28-30] Indeed, up to 80% of definite stent thrombosis events in these studies occurred within 30 days of PCI, underscoring the potential vulnerability of this period.[31] Beyond the early post-PCI phase, once endothelialization is largely complete and the risk for stent thrombosis becomes minimal, the ischemic advantage of continuing SAPT diminishes, while the bleeding risk remains substantial.[23,32] This evolving balance between bleeding and ischemic risks provides a strong biological and clinical rationale for discontinuing SAPT and continuing OAC monotherapy for long-term management.[24]

To address this clinical conundrum, several RCTs have been published in recent years.[10,11,13,14] However, their clinical impact has been limited by factors such as small sample size, early termination, and the use of OAC regimens not recommended by current guidelines, including low-dose direct oral anticoagulant agents (eg, rivaroxaban 10-15 mg/d) or VKAs.[11,13,14] Even the more recent AQUATIC and ADAPT AF-DES trials had limited statistical power for hard clinical endpoints, as the first was terminated prematurely due to an excess of all-cause mortality in the SAPT plus OAC group, and the latter encountered lower than anticipated event rates in the context of a noninferiority design.[10,11]

This systematic review and meta-analysis of RCTs expands upon previous contributions that did not include the AQUATIC and ADAPT AF-DES trials, enhancing statistical power to assess both composite and individual hard endpoints and strengthening the evidence base supporting OAC monotherapy over combination therapy.[10,11,13-15] In addition, the present analysis also offers important statistical and methodological advances that add robustness to the existing literature,[13-15] including more recent meta-analyses that included the same trials.[20,21] Specifically, the use of HRs ensured an optimal estimation of effect sizes across trials with different follow-up durations. Moreover, we implemented a thorough exploration of heterogeneity, as well as evaluation of the quality of evidence and calculation of NNT, finding consistent results with the main analysis after excluding trials that used anticoagulant agents or doses not recommended in current guidelines, further supporting the clinical applicability of these results. The NNTs for any and major bleeding were 13 and 30, respectively, while the NNT for NACE was 16, underscoring the substantial clinical benefit of avoiding combination therapy with OAC plus SAPT in this population.

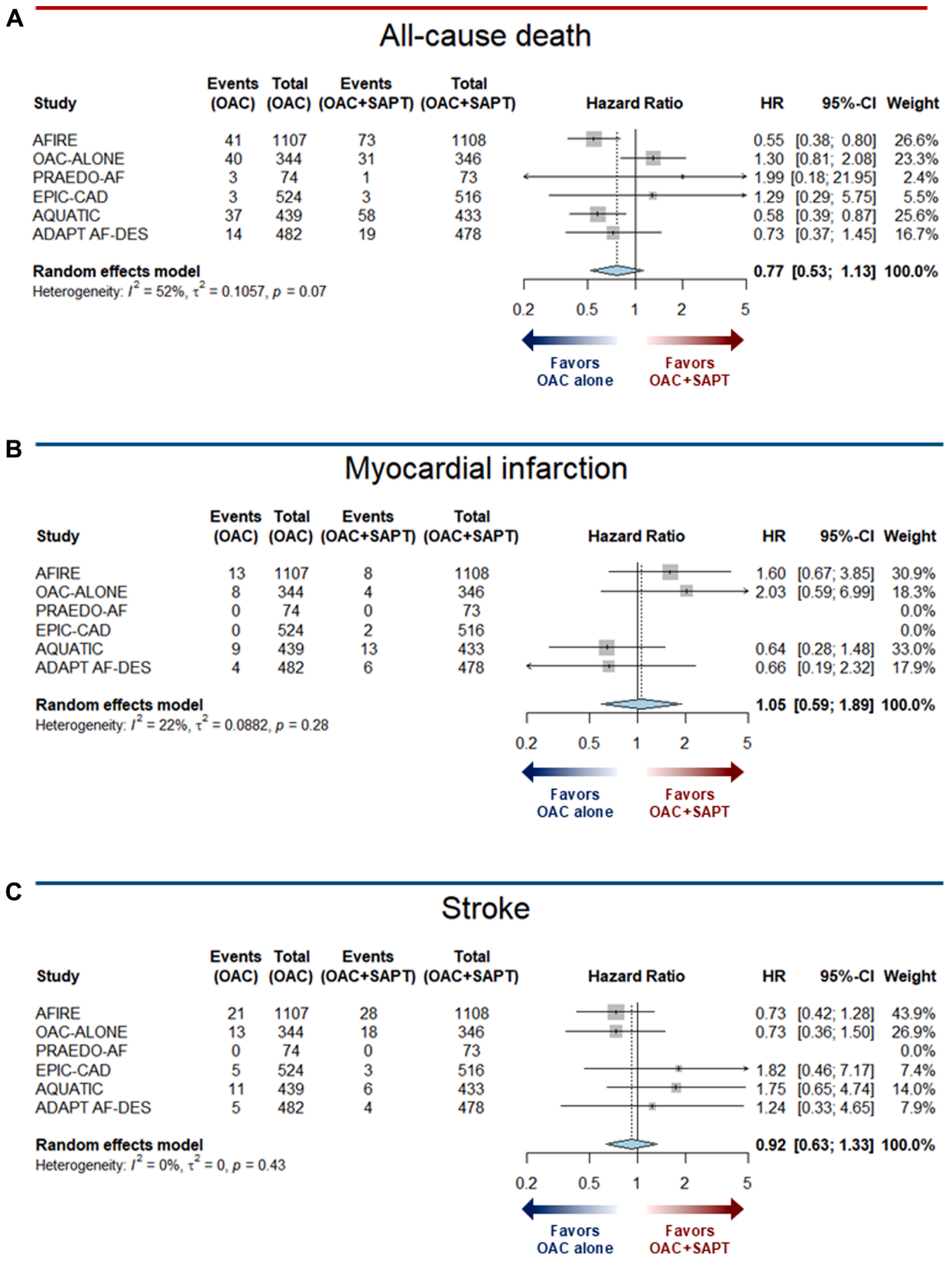
Our analysis is also the first to demonstrate a significant mortality advantage with OAC monotherapy. Specifically, compared with OAC plus SAPT, OAC monotherapy reduced cardiovascular mortality by 31% (NNT = 91) and was associated with lower all-cause mortality when trials not aligned with

FIGURE 4 Forest Plot for NACE, Major Bleeding, and Cardiovascular Death



(A) NACE. (B) Major bleeding. (C) Cardiovascular death. Abbreviations as in Figure 1.

FIGURE 5 Forest Plot for All-Cause Death, Myocardial Infarction, and Stroke

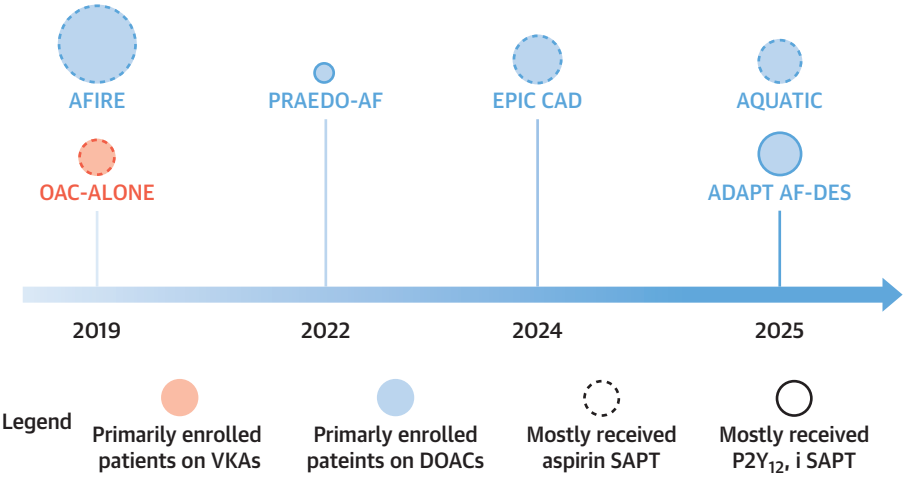


(A) All-cause death. (B) Myocardial infarction. (C) Stroke. Abbreviations as in Figure 1.

CENTRAL ILLUSTRATION **Pooled Data of Long-Term Antithrombotic Therapy for CCS**

Oral Anticoagulation With or Without Antiplatelet Therapy in Chronic Coronary Syndrome

Included Randomized Controlled Trials



Pooled Baseline Characteristics

5,924 patients with indication for long-term OAC

5,273 (89%) patients on long-term DOAC

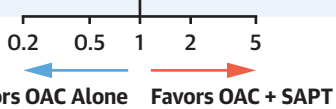
5,049 (85%) patients with previous revascularization

Median time from index event to randomization: 3.8 (3.2-4.4) years

Co-primary endpoints: MACE any bleeding

Main Results

Endpoint	HR (95% CI)	NNT (95% CI)
MACE	0.85 (0.66-1.09)	83 (37-4,111)
Any bleeding	0.49 (0.44-0.55)	13 (11-23)
All-cause death	0.77 (0.53-1.13)	73 (38-159)
Cardiovascular death	0.69 (0.48-0.97)	91 (55-1,097)
NACE	0.60 (0.47-0.78)	16 (12-30)
Myocardial infarction	1.05 (0.59-1.89)	1,640 (101-Infinite)
Stroke	0.92 (0.63-1.33)	131 (28-infinite)
Major bleeding	0.46 (0.32-0.66)	30 (23-48)



- Among patients with stable CAD requiring long-term OAC, OAC alone resulted in a significant 51% reduction in any bleeding and 54% reduction in major bleeding, without increasing ischemic events.
- These benefits translated to a 40% reduction in NACE and 31% reduction in cardiovascular death, with an NNT/NNH ratio ranging between 0.16 and 0.36.
- In aggregate, the present analysis supports the use of OAC alone compared to OAC+SAPT among patients with stable CAD as the strategy offering the most favorable risk/benefit ratio.

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guideline-recommended regimens were excluded. Finally, the presence of moderate- to high-quality evidence and conclusive results for the primary endpoints further reinforces the clinical relevance and reliability of our findings.

Overall, although our findings support the advantages of OAC monotherapy over combination therapy, these results apply primarily to patients with characteristics similar to those enrolled in the analyzed trials, predominantly East Asian male patients at high ischemic risk with AF and CCS, most of whom had undergone PCI approximately 5 years before enrollment. Moreover, between-trial differences in design, antithrombotic regimens, and patient risk profiles underscore the need for further research, particularly in patients at higher ischemic risk or with reduced responsiveness to $P2Y_{12}$ inhibition. Ongoing trials, including ADONIS-PCI (Dual Antithrombotic Therapy With Dabigatran and Ticagrelor in Patients With ACS and Non-Valvular AF Undergoing PCI; NCT04695106) and WOEST-3 (What is the Optimal Antithrombotic Strategy in Patients With Atrial Fibrillation Undergoing PCI?; NCT04436978), will help refine patient selection and define optimal regimens in AF patients undergoing PCI by evaluating intensified early strategies and alternative sequencing of antithrombotic therapy.

Taken together, these findings reinforce current guideline recommendations supporting OAC monotherapy as the preferred long-term antithrombotic strategy for patients with AF and stable CAD, providing comparable protection against ischemic events while significantly reducing bleeding and mortality.[7,8] Nevertheless, treatment decisions should remain individualized, taking into consideration patient-specific clinical and procedural characteristics, time elapsed since PCI, and the presence of residual high-risk features. Ongoing and future studies, particularly patient-level meta-analyses or trials enrolling more diverse populations, will be crucial to validate these results and to identify high thrombotic risk patient subgroups that may still derive benefit from extended combination therapy.

STUDY LIMITATIONS. First, the absence of individual patient-level data precluded a more granular assessment of the impact of key covariates—such as prior coronary artery bypass grafting, sex, ethnicity, the use of clopidogrel vs aspirin, and the clinical management of CAD vs PCI—on treatment effect estimates. Moreover, some clinical heterogeneity was observed, driven largely by differences in the OAC regimens used across trials. Interaction analyses indicated that the bleeding and mortality benefits of OAC monotherapy were more pronounced in studies using guideline-recommended OAC dosing, whereas effects were attenuated in trials using reduced OAC doses. Notably, a reduced dosing regimen is not supported by current evidence and may increase the risk for stroke in this population. Second, moderate to significant statistical heterogeneity was observed for certain endpoints, highlighting the difference in time from PCI to randomization and antithrombotic regimen administered across trials. Leave-one-out analyses identified OAC-ALONE as the main contributor to heterogeneity. OAC-ALONE included the highest proportion of warfarin-treated patients (75.2%), and more than one-half of patients receiving direct oral anticoagulant agents were treated with off-label reduced doses; moreover, participants had higher CHA_2DS_2-VASc scores than in other trials.

Third, the applicability of these results to specific high-risk or underrepresented populations—such as older adults, women, non-East Asian populations, and patients undergoing complex PCI—remains uncertain. This remains a limitation, given the distinct response to antithrombotic agents that these populations may exhibit compared with those included in our study.[33-36]

Fourth, as most trials did not limit the use of a specific $P2Y_{12}$ inhibitor, it remains uncertain whether our findings were influenced by the specific SAPT

CENTRAL ILLUSTRATION Continued

The plot illustrates the main results of the meta-analysis, including main characteristics of included studies (top), baseline characteristics of the patients enrolled across studies and primary outcomes (middle), and results for long-term outcomes (bottom). In the top panel, circles are proportional to the number of patients enrolled in each trial, while colors and lines represent specific antithrombotic therapies, detailed in the legend. For long-term outcomes, significant results are highlighted by colors. ADAPT AF-DES = Appropriate Duration of Antiplatelet and Thrombotic Strategy After 12 Months in Patients With Atrial Fibrillation Treated With Drug-Eluting Stents; AFIRE = Atrial Fibrillation and Ischemic Events With Rivaroxaban in Patients With Stable Coronary Artery Disease Study; AQUATIC = Assessment of Quitting Versus Using Aspirin Therapy in Patients With Stabilized Coronary Artery Disease after Stenting Who Require Long-Term Oral Anticoagulation; CAD = coronary artery disease; DOAC = direct oral anticoagulant agent; EPIC-CAD = Edoxaban Versus Edoxaban With Antiplatelet Agent in Patients With Atrial Fibrillation and Chronic Stable Coronary Artery Disease; MACE = major adverse cardiovascular event(s); NACE = net adverse clinical event(s); NNH = number needed to harm; NNT = number needed to treat; OAC = oral anticoagulation; OAC-ALONE = Optimizing Antithrombotic Care in Patients With Atrial Fibrillation and Coronary Stent; $P2Y_{12}$i = $P2Y_{12}$ inhibitor; 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; VKA = vitamin K antagonist.

administered. Adequately powered RCTs are warranted to address this question, ideally incorporating assessments of interindividual variability in clopidogrel response.[30]

CONCLUSIONS

In this updated meta-analysis of RCTs, we found conclusive evidence that OAC monotherapy is associated with a substantially lower risk for any bleeding, major bleeding, cardiovascular mortality, and NACE, without an increased risk for ischemic events compared with OAC plus SAPT in CCS patients with AF. These findings reinforce current guideline recommendations supporting OAC monotherapy as the preferred long-term antithrombotic strategy for patients with AF and stable CAD. Ongoing and future studies will be crucial to validate these results and to identify subgroups that may still derive benefit from extended combination therapy.

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PERSPECTIVES

WHAT IS KNOWN? Antiplatelet therapy is central to the prevention of thrombotic events in CAD, whereas OAC is indicated for stroke prevention in AF. However, a substantial proportion of patients suffer from both conditions, and the optimal antithrombotic management in this setting remains challenging: combination therapy may lower ischemic risk but at the cost of increased bleeding. Prior trials assessing long-term antithrombotic strategies in this population have produced inconsistent results, largely because of limited sample sizes and the use of anticoagulant regimens no longer endorsed in current guidelines.

WHAT IS NEW? In this pairwise meta-analysis of 6 randomized controlled trials including 5,924 patients with AF and stable CAD, OAC alone, compared with OAC plus SAPT, was associated with a 51% reduction in any bleeding and a 54% reduction in major bleeding, without an increase in major adverse cardiovascular events. Notably, OAC monotherapy was also associated with a 31% reduction in cardiovascular death and a 40% reduction in NACE.

WHAT IS NEXT? Data from this updated and comprehensive meta-analysis may inform clinical practice and future guideline development in the management of patients with stable CAD and AF, supporting OAC monotherapy as the strategy offering the most favorable balance between ischemic protection and bleeding risk in this high-risk population. These findings also highlight the need for further research to better identify patient subgroups that may benefit from combination therapy and to determine the optimal timing for antiplatelet discontinuation during long-term OAC treatment.

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KEY WORDS atrial fibrillation, chronic coronary syndrome, coronary artery disease, oral anticoagulant, single antiplatelet therapy

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