Systematic Review/Meta-analysis

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Oral anticoagulant (OAC) monotherapy vs. dual-antithrombotic therapy (DAT) in patients with atrial fibrillation and coronary artery disease; a meta-analysis of four randomized controlled trials

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Background: Dual-antithrombotic therapy (DAT) is recommended for patients with atrial fibrillation (AF) and stable coronary artery disease (CAD) but carries an increased risk of bleeding. Recent trials suggest oral anticoagulant (OAC) monotherapy as a safer alternative, but data remains limited. We conducted a meta-analysis to compare OAC monotherapy with DAT in this population.
Methods: A comprehensive literature search was conducted using PubMed, Embase, and Cochrane Central Library to identify randomized controlled trials (RCTs) that compared OAC monotherapy with DAT in patients with AF and stable CAD. A bivariate random-effects model was used to perform meta-analyses. Statistical analyses were conducted using R Software 4.4.1, with a significance level of $P < 0.05$. Heterogeneity was assessed using I^2 statistics, and the quality of studies was evaluated using the revised Cochrane risk-of-bias tool.
Results: Four RCTs with a total of 4123 patients (20.2% females) were included. The mean age of the participants was 74 years. The results showed a significant reduction in major or clinically relevant nonmajor bleeding (risk ratio [RR]: 0.52; 95% confidence interval [CI]: 0.34–0.80; $P = 0.003$) in the OAC monotherapy group compared to the DAT group. However, net adverse clinical events (NACE) (RR: 0.67; 95% CI: 0.45–1.01; $P = 0.054$), major ischemic events (RR: 0.98; 95% CI: 0.62–1.53; $P = 0.91$) and all-cause mortality (RR: 0.94; 95% CI: 0.49–1.83; $P = 0.87$) were comparable between the two groups.
Conclusions: In patients with AF and stable CAD, OAC monotherapy reduced the risk of major bleeding, with no significant differences in NACE, major ischemic events, or all-cause mortality as compared to DAT.

Keywords: atrial fibrillation (AF), dual-antithrombotic therapy (DAT), oral anticoagulant (OAC) monotherapy, stable coronary artery disease (CAD)

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HIGHLIGHTS

- Study population and treatment groups: The meta-analysis included four randomized controlled trials with a total of 4123 patients, of whom 20.2% were female, and the mean age was 74 years. The study compared two treatment groups: patients receiving OAC monotherapy vs. those on dual-antithrombotic therapy (DAT), which includes a combination of oral anticoagulants and antiplatelet therapy.
- Reduction in major bleeding risk: OAC monotherapy demonstrated a significant reduction in the risk of major or clinically relevant nonmajor bleeding compared to DAT, with a relative risk reduction of 48% (RR: 0.52; 95% CI: 0.34–0.80; $P = 0.003$).
- Comparable efficacy in adverse events: No significant differences were observed between OAC monotherapy and DAT in terms of net adverse clinical events (NACE) (RR: 0.67; 95% CI: 0.45–1.01; $P = 0.054$), major ischemic events (RR: 0.98; 95% CI: 0.62–1.53; $P = 0.91$), or all-cause mortality (RR: 0.94; 95% CI: 0.49–1.83; $P = 0.87$).

Introduction

Atrial fibrillation (AF), where the upper chambers of the heart (the atria) beat irregularly and out of sync with the lower chambers (the ventricles), is the most common cardiac arrhythmia and affects over 33 million people worldwide[1]. It is strongly linked to stroke, heart failure, and other cardiovascular conditions, including valvular heart disease[2]. Coronary artery disease (CAD), a condition where the blood vessels supplying the heart become narrowed or blocked due to plaque buildup, is also common in AF patients, affecting about 25%–35% of this group[3,4]. Managing AF in patients with CAD poses a therapeutic dilemma. The treatment for such patients traditionally involved a combination of anticoagulation (AC) and antiplatelet therapy. While AC is crucial for stroke prevention in AF, antiplatelet therapy is essential for preventing recurrent ischemic events in CAD. As a result, many patients receive DAT, combining anticoagulants and antiplatelets. However, this approach carries a significantly higher bleeding risk; studies indicate that adding a single antiplatelet therapy to an oral anticoagulant (OAC) increases bleeding risk by 20%–60%[3,4].

Current guidelines recommend that after percutaneous coronary intervention (PCI) and coronary artery bypass graft surgery (CABG), dual-antiplatelet therapy (DAPT) along with OAC therapy should be administered for up to 1 week, followed by dual-antithrombotic therapy (DAT) comprising of a P2Y12 inhibitor and an OAC for up to 12 months[5]. However, there is no strong consensus on long-term management beyond the high-risk period for patients who are stable and at low risk for ischemic events. Most recently, the EPIC-CAD trial was published that suggests dabigatran, rivaroxaban, edoxaban, or apixaban (DOAC) monotherapy as a safe alternative to DAT, showing comparable effectiveness while significantly reducing bleeding risks[6]. The 2023 ACC guidelines specifically endorse DOAC monotherapy 1 year after PCI for patients with nonvalvular AF. In such cases, the ACC guidelines suggest that discontinuing antiplatelet therapy and continuing DOAC monotherapy may be reasonable. This recommendation, however, is rated as Class IIb, indicating a need for further evidence[7].

Therefore, the goal of this meta-analysis is to pool all randomized controlled trials (RCTs) conducted to date comparing OAC monotherapy to DAT in stable CAD patients with AF to help inform the latest evidence in the safety and efficacy of these regimens.

Methods

Literature review and search strategy

This systematic review and meta-analysis adhered to the Preferred Reporting Items for Systematic Reviews and Meta-Analysis (PRISMA) guidelines and the Cochrane Handbook for Systematic Reviews of Interventions[8]. The study protocol was registered with the International Prospective Register of Systematic Reviews. The review's methodological quality was ensured by following assessing the methodological quality of systematic reviews guidelines, and the results are reported accordingly.

Three extensive databases PubMed (Ovid), Embase (Ovid), and the Cochrane Central Register of Controlled Trials (via the Cochrane Library) were searched from their inception to September 2024 without any language restrictions using the following keywords: oral anticoagulant monotherapy, OAC, direct oral anticoagulants, DOAC, dual antithrombotic therapy, DAT, atrial fibrillation, and coronary artery disease. Keywords and indexing terms were searched using a combination of Boolean operators, proximity operators, and truncation to ensure comprehensive coverage. Additionally, references of relevant studies were also manually searched to identify any potential studies. Complete search strategy is given in the Supplementary file, http://links.lww.com/MS9/A717.

Eligibility criteria and outcomes

The inclusion criteria for studies in this meta-analysis consisted of studies comparing in patients of AF and stable CAD (P) OAC monotherapy (I) vs. DAT (C). Only RCTs reporting any of the prespecified outcomes of interest were included. The exclusion criteria included studies other than RCTs such as observational studies, case reports, case series, commentaries, editorials, review articles and meta-analyses, and non-peer-reviewed articles. In addition, studies without a comparison group, those not reporting the outcomes of interest and those with overlapping populations were also excluded.

The primary outcomes of interest included major or clinically relevant nonmajor bleeding, net adverse clinical events (NACE), major ischemic events, all-cause mortality, and cardiovascular deaths. Secondary outcomes assessed include any stroke, ischemic stroke, hemorrhagic stroke, and myocardial infarction (MI).

NACE is a composite of death from any cause, MI, stroke, systemic embolism, unplanned urgent revascularization, and major bleeding or clinically relevant nonmajor bleeding, as defined by the International Society on Thrombosis and Haemostasis[9]. Clinically significant bleeding is defined as bleeding that requires medical intervention, such as hospitalization or extended hospitalization, diagnostic tests, imaging, endoscopy, invasive procedures (eg, colonoscopy, cystoscopy, bronchoscopy), or treatments like nasal packing, coil embolization, inotropic therapy, surgery, or changes in AC or other treatments as advised by the patient's physician. Major ischemic events are defined by death from MI, ischemic stroke, or systemic embolism.

Study screening and data extraction

Titles and abstracts identified through the literature search were imported into reference management software (EndNote X9, Clarivate Analytics) for duplicate removal. Two authors independently screened the titles and abstracts for eligibility, followed by a full-text review of the selected articles. Any discrepancies during the screening process were resolved by consensus, with the involvement of a third author when necessary. Additionally, a manual search of the reference lists of the included studies was conducted to identify any further relevant studies. Data from the eligible studies were extracted and cataloged independently by two reviewers using electronic spreadsheets specifically designed on Microsoft Excel (.xlsx format) for this meta-analysis. The data collected included the first author's name, the year of publication, the number of participants, follow-up duration, mean age, sex of participants, inclusion criteria, and reported outcomes.

Statistical analysis

Statistical analyses were performed using R software version 4.4.1 with the "meta" package. Pooled risk ratios (RRs) and 95% confidence intervals (CIs) were calculated for dichotomous outcomes, employing the DerSimonian and Laird random effects model to combine results from the included studies. Forest plots were created to visually display the findings. A *P*-value <0.05 was deemed statistically significant. Heterogeneity across studies was evaluated using the Cochran *Q* test and Higgins I^2 test[10]; *P*-values <0.1 and I^2 > 25% were considered significant for heterogeneity. Sensitivity analyses were conducted using a leave-one-out approach, systematically excluding one study at a time to assess its influence on the overall estimate and explore sources of potential heterogeneity.

Quality assessment

Study quality was independently assessed by two reviewers using the Revised Cochrane risk of bias (RoB-2) tool for RCTs[11]. Studies were scored as low risk of bias, high risk of bias, or some concerns depending on their biases in selection, performance, detection, attrition, and reporting. Any disagreements were resolved by consensus. Due to the limited number of studies (<10), it was not possible to evaluate publication bias.

Results

Search results and study selection

The electronic database search yielded 1922 articles, which were then filtered to remove duplicates (n = 215) and underwent initial screening based on titles and abstracts, resulting in 125 articles for further full-text review. The full-text review led to the exclusion of 75 articles due to observational study design, 25 due to being conference abstracts, 13 articles due to different interventions, 8 due to inadequate outcomes. Finally, four studies met our inclusion criteria, and were included in the meta-analysis[6,12–14]. The detailed steps of our literature search and study selection are given in the PRISMA flow diagram (Fig. 1).

Study characteristics

Our meta-analysis included four RCTs with a total of 4123 patients, out of which 20.2% were female. The mean age of the patients was 74 years, with a range from 60 to 90 years across the studies. Two studies used Edoxaban for the OAC monotherapy group, one study used Rivaroxaban, while one study used either warfarin or DOAC. The CHA2DS2-VASc score ranged from 4 to 4.6, and approximately 14% of patients had a previous history of stroke. The baseline demographics and clinical characteristics of the included studies are summarized in Table 1.

Outcomes and heterogeneity assessment

Primary outcomes

Major or clinically relevant nonmajor bleeding. The risk of major or clinically relevant nonmajor bleeding was significantly lower in the OAC monotherapy group compared to the DAT group (RR: 0.52; 95% CI: 0.34–0.80; *P* = 0.003; Fig. 2). High heterogeneity (I^2 = 58%) was noted, which was reduced to zero after excluding EPIC-CAD[6] (Supplementary Fig. 1, http://links.lww.com/MS9/A717).

NACE. The incidence of NACEs was similar between patients receiving OAC monotherapy and those receiving DAT (RR: 0.67; 95% CI: 0.45–1.01; *P* = 0.054; Fig. 3A). High heterogeneity (I^2 = 76%) was observed between studies, and it did not decrease significantly after performing a leave-one-out analysis (Supplementary Fig. 2, http://links.lww.com/MS9/A717).

Major ischemic events. The outcome of major ischemic events was nonsignificant between the OAC monotherapy and DAT groups (RR: 0.98; 95% CI: 0.62–1.53; *P* = 0.912; Fig. 3B). High heterogeneity (I^2 = 61%) was present, which dropped to zero upon excluding either AFIRE[13] or OAC-ALONE[12] (Supplementary Fig. 3, http://links.lww.com/MS9/A717).

All-cause mortality. All-cause mortality rates were comparable between the OAC monotherapy and DAT treatment arms (RR: 0.94; 95% CI: 0.49–1.83; *P* = 0.867; Fig. 3C). High heterogeneity (I^2 = 68%) was observed, which reduced to zero after excluding AFIRE trial[13] (Supplementary Fig. 3C, http://links.lww.com/MS9/A717).

Cardiovascular death. The risk of cardiovascular death was similar between the two groups (RR: 0.87; 95% CI: 0.52–1.45; *P* = 0.590; Fig. 3D). Moderate heterogeneity (I^2 = 25%) was observed, which dropped to zero when either the AFIRE[13] or OAC-ALONE[12] trials were excluded (Supplementary Fig. 5, http://links.lww.com/MS9/A717).

Secondary outcomes

The secondary outcomes assessed included any stroke, ischemic stroke, hemorrhagic stroke, and MI. When comparing the oral monotherapy group with the DAPT group, the outcome of any stroke yielded nonsignificant results (RR: 0.73; 95% CI: 0.47–1.13; *P* = 0.163; Fig. 4A), with a low heterogeneity (I^2 = 16%). Similarly, the incidence of ischemic stroke was comparable between the two groups (RR: 0.88; 95% CI: 0.57–1.36; *P* = 0.573; Fig. 4B) showing no heterogeneity (I^2 = 0%). The incidence of hemorrhagic stroke also demonstrated nonsignificant differences between the groups (RR: 0.52; 95% CI: 0.23–1.21; *P* = 0.129; Fig. 4C) with no heterogeneity (I^2 = 0%). Finally, the analysis of MI showed no significant difference between the groups (RR: 1.57; 95% CI: 0.79–3.12; *P* = 0.201; Fig. 4D) with no heterogeneity (I = 0%).

Quality assessment

Two of the RCTs (AFIRE and EPIC-CAD) had an overall low risk of bias[6,13], while the OAC-ALONE had some concerns in terms of quality assessment due to the deviations from the intended interventions[12]. PRAEDO-AF trial is a high-risk trial due to concerns regarding the concealment of allocation sequence and unavailability of data regarding blind adjudication[14] (Supplementary Fig. 6, http://links.lww.com/MS9/A717).

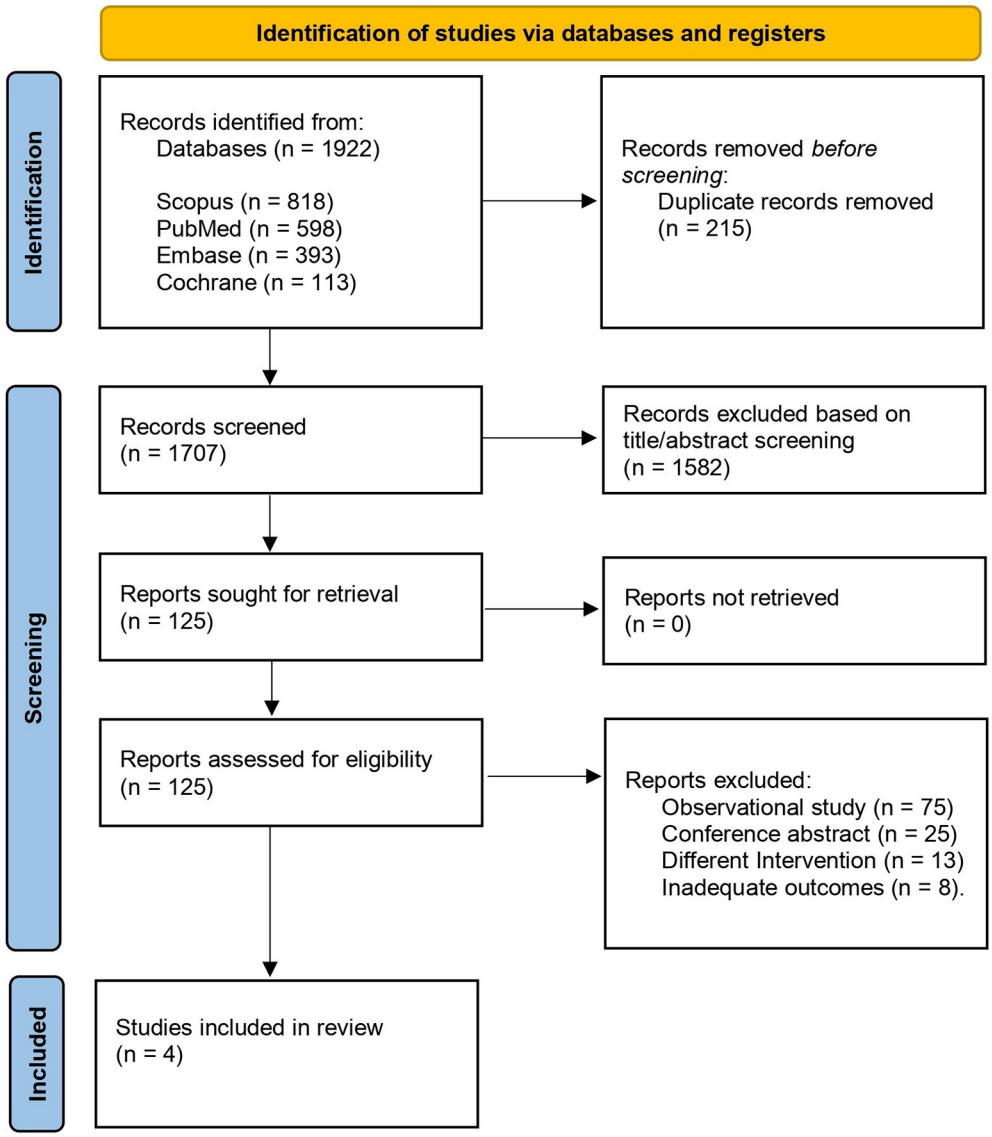


Figure 1. PRISMA flow diagram of the included studies. (From: Page *et al*[8].)

Discussion

Our systematic review and meta-analysis gather evidence from all four RCTs published to date, including the most recent EPIC-CAD trial on this topic, and strongly suggests that OAC monotherapy in patients with stable CAD and AF is a safe strategy with reduced bleeding risk and equivalent reduction in MACE as compared to DAT. The management of antithrombotic therapy in this patient population remains challenging and an area of ongoing research is to find a balanced regimen that provides optimal reduction in major ischemic events while decreasing the bleeding risk. Our meta-analysis demonstrated a significant reduction in major or clinically relevant nonmajor bleeding in the OAC monotherapy group compared to the DAT group. While the other primary outcomes including NACE, major ischemic events, and all-cause mortality were found to be statistically insignificant between the two groups suggesting OAC monotherapy is non-inferior to DAT.

Our meta-analysis expands on previous findings from the meta-analysis by Ahmed *et al.*[15], incorporating additional outcomes including NACE, major ischemic events, cardiovascular death, ischemic stroke, and hemorrhagic stroke as well as a crucial 4th RCT, PRAEDO-AF[14], missed in the last meta-analysis, highlighting its potential methodological limitations, inadequate screening process, and limited outcomes measures.

American College of Cardiology 2023 guidelines give a Level 2 recommendation for OAC monotherapy in patients with stable CAF and AF[5,7]. The increasing amount of evidence from these RCTs and our meta-analysis underscore the need to revisit these guidelines and potentially increase the level of recommendation in favor of OAC monotherapy. Notably, this benefit of OAC monotherapy is observed in RCTs across different DOACs and warfarin and may not be restricted to a specific anticoagulant choice. It is also noteworthy that this benefit is noted across the spectrum of stable CAD including those

Table 1

Baseline characteristics of the included trials

Trial name	Year	Country	Mean Age in years (SD), intervention/ control	No. of patients, n	Female sex, %	Previous Stroke, %	CHA2DS2-VASc score, Intervention/ Control	Intervention group	Control group	Follow-up
AFIRE	2019	Japan	74.3 (8.3)/74.4 (8.2)	2215	21	14.5	4(median) /4 (median)	Rivaroxaban	Rivaroxaban + APT	24.1 months (median)
OAC-ALONE	2019	Japan	74.9 (0.4)/75.2 (0.4)	690	14.8	14.9	4.6 (1.4)/4.6 (1.4)	Warfarin or DOACs	OAC + APT	24 months
EPIC CAD	2024	South Korea	71.7 (8)/72.5 (8.4)	1040	22.9	N/A	4.3 (1.6)/4.4 (1.5)	Edoxaban	Edoxaban + APT	12 months
PRAEDO AF	2022	Japan	74 (7)/74 (9)	147	13.6	14.3	4 (median)/4 (median)	Edoxaban	Edoxaban + APT (clopidogrel)	624 days (median)

SD, standard deviation; CHA2DS2-VASc, congestive heart failure, hypertension, age ≥75 (doubled), diabetes, stroke (doubled), vascular disease, age 65–74 and sex category (female); DOAC, direct oral anti-coagulant; OAC, oral anti-coagulant; APT, antiplatelet therapy.

without prior revascularization and those with revascularization with PCI or CABG more than 12 months ago. The omission of antiplatelet therapy after 12 months did not lead to higher incidence of acute MIs[6,12–14]. It is also to be noted that all trials except OAC-ALONE demonstrated no difference in stent thrombosis between OAC monotherapy and DAT groups[12]. Despite this, Antiplatelet therapy is still continued in common clinical practice along with OAC in these patients[16].

Substantial heterogeneity (>50%) was observed in most primary outcomes, except cardiovascular death (I^2 = 25%). Sensitivity analyses revealed that excluding AFIRE and OAC-ALONE significantly reduced heterogeneity in the majority of primary outcomes. Notably, removing EPIC-CAD eliminated heterogeneity in major or clinically relevant nonmajor bleeding from an I^2 value of 58%–0%[6]. The high heterogeneity associated with AFIRE and EPIC-CAD may be attributed to their premature termination and, in AFIRE's case, the use of non-standard rivaroxaban dosing[13]. In addition to this, included trials lacked clinical and methodological homogeneity. Two out of four trials used edoxaban[6,14], one used rivaroxaban[13], and one used either warfarin or direct OACs as the intervention[12]. Meanwhile, the antiplatelet drug in the control group was clopidogrel in the PRAEDO-AF trial[14], while it was either aspirin or a P2Y12 inhibitor in the remaining three trials[6,12,13]. All trials used standard doses of OACs that is, 60 mg once daily for edoxaban and 15 or 10 mg once daily for rivaroxaban, except AFIRE which used nonstandard dose of rivaroxaban that is 10–15 mg once daily[13].

Our meta-analysis combines results from all the RCTs published on this topic and contributes to the expanding literature that antithrombotic regimen can be simplified to OAC monotherapy in stable CAD and AF patients that leads to a lower bleeding risk. However, while pursuing this strategy individual patient risk factors such as overall bleeding risk, co-morbids, and complexity of coronary anatomy including that of coronary intervention must be taken into consideration for each patient and decisions should then be made accordingly including the choice of OAC.

Limitations

There are a few limitations that underscore the need for future research on this topic. While the benefit of OAC monotherapy appears to be a generalized class effect of AC therapy, the relative comparison of efficacy and safety of individual DOACs cannot be derived from these RCTs and our meta-analysis and can be a target for future research. The existing trials, including EPIC-CAD, lacked sufficient sample sizes to detect significant differences in ischemic events and mortality. Furthermore, two of the four RCTs compared edoxaban monotherapy with DAT and therefore edoxaban appears to have the most robust evidence in comparison to DAT. Similarly, none of the trials exclusively included apixaban and therefore evidence of apixaban monotherapy compared to DAT is scant and requires future investigation. The premature termination of AFIRE and OAC-ALONE trials may have contributed to OAC-ALONE's inability to demonstrate

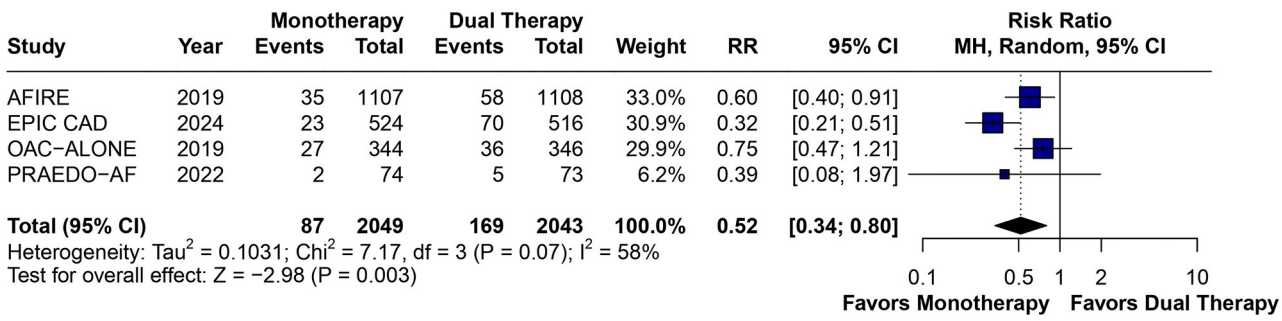
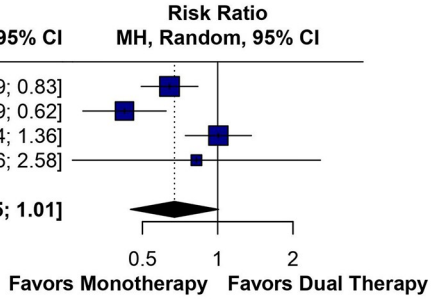


Figure 2. Forest plots of studies comparing OAC monotherapy with DAT in terms of major or clinically relevant nonmajor bleeding.

A Net Adverse Clinical Events (NACE):

Study	Year	Monotherapy Events	Monotherapy Total	Dual Therapy Events	Dual Therapy Total	Weight	RR	95% CI
AFIRE	2019	84	1107	131	1108	32.1%	0.64	[0.49; 0.83]
EPIC CAD	2024	34	524	79	516	27.8%	0.42	[0.29; 0.62]
OAC−ALONE	2019	67	344	67	346	30.7%	1.01	[0.74; 1.36]
PRAEDO−AF	2022	5	74	6	73	9.4%	0.82	[0.26; 2.58]
Total (95% CI)		**190**	**2049**	**283**	**2043**	**100.0%**	**0.67**	**[0.45; 1.01]**

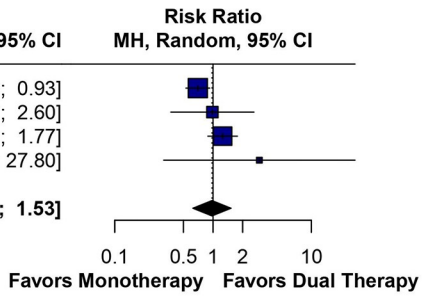
Heterogeneity: $Tau^2 = 0.1154$; $Chi^2 = 12.58$, df = 3 (P < 0.01); $I^2 = 76\%$
Test for overall effect: Z = −1.92 (P = 0.054)



B Major Ischemic Events:

Study	Year	Monotherapy Events	Monotherapy Total	Dual Therapy Events	Dual Therapy Total	Weight	RR	95% CI
AFIRE	2019	77	1107	110	1108	42.4%	0.70	[0.53; 0.93]
EPIC CAD	2024	8	524	8	516	14.9%	0.98	[0.37; 2.60]
OAC−ALONE	2019	61	344	49	346	39.0%	1.25	[0.89; 1.77]
PRAEDO−AF	2022	3	74	1	73	3.7%	2.96	[0.32; 27.80]
Total (95% CI)		**149**	**2049**	**168**	**2043**	**100.0%**	**0.98**	**[0.62; 1.53]**

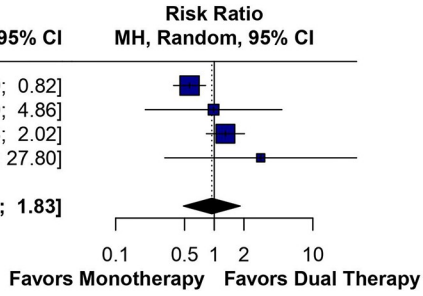
Heterogeneity: $Tau^2 = 0.1028$; $Chi^2 = 7.73$, df = 3 (P = 0.05); $I^2 = 61\%$
Test for overall effect: Z = −0.11 (P = 0.912)



C All-Cause Mortality:

Study	Year	Monotherapy Events	Monotherapy Total	Dual Therapy Events	Dual Therapy Total	Weight	RR	95% CI
AFIRE	2019	41	1107	73	1108	41.0%	0.56	[0.39; 0.82]
EPIC CAD	2024	3	524	3	516	12.6%	0.98	[0.20; 4.86]
OAC−ALONE	2019	40	344	31	346	38.9%	1.30	[0.83; 2.02]
PRAEDO−AF	2022	3	74	1	73	7.4%	2.96	[0.32; 27.80]
Total (95% CI)		**87**	**2049**	**108**	**2043**	**100.0%**	**0.94**	**[0.49; 1.83]**

Heterogeneity: $Tau^2 = 0.2427$; $Chi^2 = 9.34$, df = 3 (P = 0.03); $I^2 = 68\%$
Test for overall effect: Z = −0.17 (P = 0.867)



D Cardiovascular Death:

Study	Year	Monotherapy Events	Monotherapy Total	Dual Therapy Events	Dual Therapy Total	Weight	RR	95% CI
AFIRE	2019	26	1107	43	1108	53.1%	0.61	[0.37; 0.98]
EPIC CAD	2024	2	524	1	516	4.4%	1.97	[0.18; 21.65]
OAC−ALONE	2019	20	344	17	346	39.9%	1.18	[0.63; 2.22]
PRAEDO−AF	2022	1	74	0	73	2.6%	2.96	[0.12; 71.48]
Total (95% CI)		**49**	**2049**	**61**	**2043**	**100.0%**	**0.87**	**[0.52; 1.45]**

Heterogeneity: $Tau^2 = 0.0705$; $Chi^2 = 3.98$, df = 3 (P = 0.26); $I^2 = 25\%$
Test for overall effect: Z = −0.54 (P = 0.590)

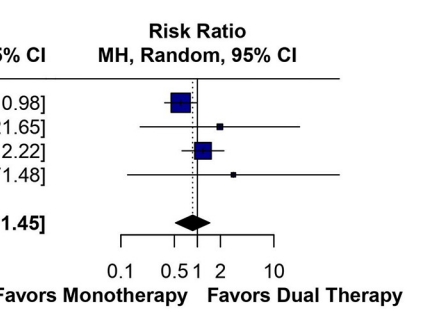
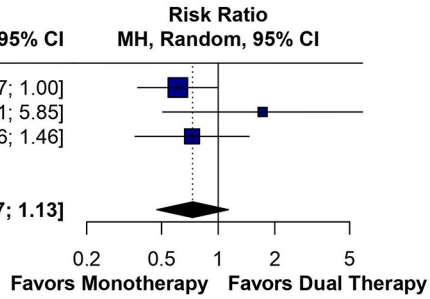


Figure 3. Forest plots of studies comparing OAC monotherapy with DAT in terms of (A) net adverse clinical events (NACE), (C) major ischemic events, (A) all-cause mortality, and (B) cardiovascular death.

A Any Stroke:

Study	Year	Monotherapy Events	Monotherapy Total	Dual Therapy Events	Dual Therapy Total	Weight	RR	95% CI
AFIRE	2019	25	1107	41	1108	55.5%	0.61	[0.37; 1.00]
EPIC CAD	2024	7	524	4	516	12.0%	1.72	[0.51; 5.85]
OAC−ALONE	2019	13	344	18	346	32.5%	0.73	[0.36; 1.46]
PRAEDO−AF	2022	0	74	0	73	0.0%		
Total (95% CI)		**45**	**2049**	**63**	**2043**	**100.0%**	**0.73**	**[0.47; 1.13]**

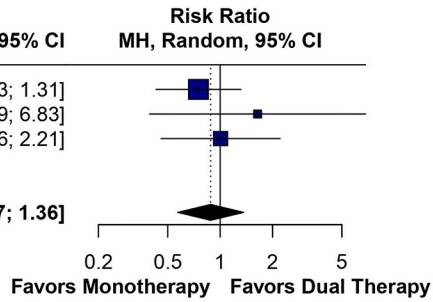
Heterogeneity: $Tau^2 = 0.0276$; $Chi^2 = 2.39$, df = 2 (P = 0.30); $I^2 = 16\%$
Test for overall effect: Z = −1.40 (P = 0.163)



B Ischemic Stroke:

Study	Year	Monotherapy Events	Monotherapy Total	Dual Therapy Events	Dual Therapy Total	Weight	RR	95% CI
AFIRE	2019	21	1107	28	1108	60.2%	0.75	[0.43; 1.31]
EPIC CAD	2024	5	524	3	516	9.3%	1.64	[0.39; 6.83]
OAC−ALONE	2019	12	344	12	346	30.5%	1.01	[0.46; 2.21]
PRAEDO−AF	2022	0	74	0	73	0.0%		
Total (95% CI)		**38**	**2049**	**43**	**2043**	**100.0%**	**0.88**	**[0.57; 1.36]**

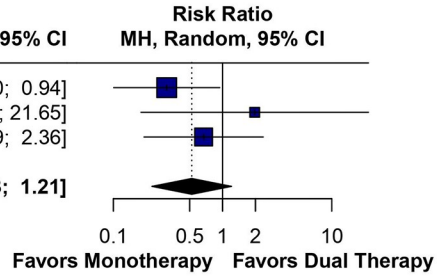
Heterogeneity: $Tau^2 = 0$; $Chi^2 = 1.15$, df = 2 (P = 0.56); $I^2 = 0\%$
Test for overall effect: Z = −0.56 (P = 0.573)



C Hemorrhagic Stroke:

Study	Year	Monotherapy Events	Monotherapy Total	Dual Therapy Events	Dual Therapy Total	Weight	RR	95% CI
AFIRE	2019	4	1107	13	1108	48.6%	0.31	[0.10; 0.94]
EPIC CAD	2024	2	524	1	516	11.8%	1.97	[0.18; 21.65]
OAC−ALONE	2019	4	344	6	346	39.6%	0.67	[0.19; 2.36]
Total (95% CI)		**10**	**1975**	**20**	**1970**	**100.0%**	**0.52**	**[0.23; 1.21]**

Heterogeneity: $Tau^2 = 0.0520$; $Chi^2 = 2.19$, df = 2 (P = 0.33); $I^2 = 9\%$
Test for overall effect: Z = −1.52 (P = 0.129)



D Myocardial Infarction (MI):

Study	Year	Monotherapy Events	Monotherapy Total	Dual Therapy Events	Dual Therapy Total	Weight	RR	95% CI
AFIRE	2019	13	1107	8	1108	61.5%	1.63	[0.68; 3.91]
EPIC CAD	2024	0	524	2	516	5.1%	0.20	[0.01; 4.09]
OAC−ALONE	2019	8	344	4	346	33.3%	2.01	[0.61; 6.62]
PRAEDO−AF	2022	0	74	0	73	0.0%		
Total (95% CI)		**21**	**2049**	**14**	**2043**	**100.0%**	**1.57**	**[0.79; 3.12]**

Heterogeneity: $Tau^2 = 0$; $Chi^2 = 1.99$, df = 2 (P = 0.37); $I^2 = 0\%$
Test for overall effect: Z = 1.28 (P = 0.201)

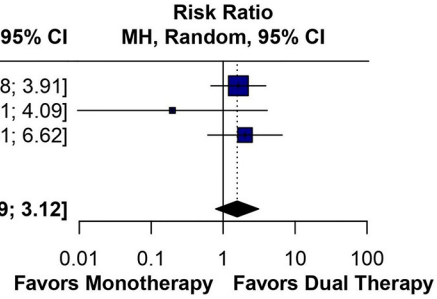


Figure 4. Forest plots of studies comparing OAC monotherapy with DAT in terms of (A) any stroke, (B) ischemic stroke, (C) hemorrhagic stroke, and (D) myocardial infarction (MI).

non-inferiority of OAC monotherapy vs. DAT. This early termination also raises concerns about the generalizability of both trials' results to real-world clinical settings. Females are underrepresented in these RCTs and overall constitute only 20.2% of total patients included in our meta-analysis. The use of gastric protective medications such as proton pump inhibitors influence rates of bleeding and is especially recommended in patients with DAT and are not reported in studies other than EPIC-CAD. Existing trials, including EPIC-CAD, were not designed to detect significant differences in clinically relevant ischemic events and mortality. Our meta-analysis findings have limited generalizability due to a predominantly Asian population in all four RCTs. Ethnic differences in ischemic and bleeding risks between Asian and Western populations underscore the need for additional research in Western populations to confirm our results. Therefore, future studies with diverse ethnic representation are warranted. Lastly, our search did not include Google Scholar or Scopus. Google Scholar was excluded due to its grey literature, which can affect study quality, while Scopus was not used as it overlaps significantly with Embase, offering limited added value. Future studies may consider including these databases for a more exhaustive review.

Conclusion

In conclusion, our meta-analysis suggests that OAC monotherapy offers an equally efficacious and safer alternative to DAT in stable CAD patients while balancing the risk of ischemic events and reducing the risk of overall bleeding.

Ethical approval

Not applicable.

Consent

Not applicable.

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Author's contribution

S.S.: study concept or design, data collection, data extraction, data analysis or interpretation, writing and reviewing the paper; H.S., M.I., A.B., M.Z., U.M.: data extraction, data analysis or interpretation, writing the paper; M.A., A.T.H., H.A.I., Y.A.S.: data extraction, writing, and reviewing the paper; M.S.A., M.A.Z., I.A.C., S.K.: data extraction, supervision, validation, reviewing the paper; N.K.T.: study concept or design, project administration, supervision, validation, writing and reviewing the paper.

Conflicts of interest disclosure

The authors have no conflicts of interest to declare.

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Provenance and peer review

Not applicable.

Data availability statement

Data supporting the findings of this study are available from the corresponding author upon reasonable request.

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References

[1] Kamel H, Okin PM, Elkind MSV, *et al*. Atrial fibrillation and mechanisms of stroke: time for a new model. Stroke 2016;47:895–900.
[2] Batta A, Hatwal J, Batta A, *et al*. Atrial fibrillation and coronary artery disease: an integrative review focusing on therapeutic implications of this relationship. World J Cardiol 2023;15:229–43.
[3] Kumbhani DJ, Cannon CP, Beavers CJ, *et al*. 2020 ACC expert consensus decision pathway for anticoagulant and antiplatelet therapy in patients with atrial fibrillation or venous thromboembolism undergoing percutaneous coronary intervention or with atherosclerotic cardiovascular disease: a report of the American College of Cardiology solution set oversight committee. J Am Coll Cardiol 2021;77:629–58.
[4] Paikin JS, Wright DS, Crowther MA, *et al*. Triple antithrombotic therapy in patients with atrial fibrillation and coronary artery stents. Circulation 2010;121:2067–70.
[5] Writing Committee Members, Joglar JA, Chung MK, Armbruster AL, *et al*. 2023 ACC/AHA/ACCP/HRS guideline for the diagnosis and management of atrial fibrillation: a report of the American College of Cardiology/American Heart Association Joint Committee on clinical practice guidelines. J Am Coll Cardiol 2024;83: 109–279.
[6] Cho MS, Kang DY, Ahn JM, *et al*. Edoxaban antithrombotic therapy for atrial fibrillation and stable coronary artery disease. N Engl J Med 2024;391:2075–86.
[7] Writing Committee Members, Virani SS, Newby LK, Arnold SV, *et al*. 2023 AHA/ACC/ACCP/ASPC/NLA/PCNA guideline for the management of patients with chronic coronary disease: a report of the American Heart Association/American College of Cardiology Joint Committee on clinical practice guidelines. J Am Coll Cardiol 2023;82: 833–955.
[8] Page MJ, McKenzie JE, Bossuyt PM, *et al*. The PRISMA 2020 statement: an updated guideline for reporting systematic reviews. BMJ 2021;372:n71.
[9] Schulman S, Kearon C. Subcommittee on control of anticoagulation of the scientific and standardization committee of the international society on thrombosis and haemostasis. Definition of major bleeding in clinical investigations of antihemostatic medicinal products in non-surgical patients. J Thromb Haemost JTH 2005;3:692–94.
[10] Higgins JPT, Thompson SG, Deeks JJ, *et al*. Measuring inconsistency in meta-analyses. BMJ 2003;327:557–60.
[11] Sterne JAC, Savović J, Page MJ, *et al*. RoB 2: a revised tool for assessing risk of bias in randomised trials. BMJ 2019;366:l4898.
[12] Matsumura-Nakano Y, Shizuta S, Komasa A, *et al*. Open-label randomized trial comparing oral anticoagulation with and without single antiplatelet therapy in patients with atrial fibrillation and stable coronary artery disease

beyond 1 year after coronary stent implantation. Circulation 2019; 139:604–16.
[13] Yasuda S, Kaikita K, Akao M, *et al*. Antithrombotic therapy for atrial fibrillation with stable coronary disease. N Engl J Med 2019;381:1103–13.
[14] Fukamachi D, Okumura Y, Matsumoto N, *et al*. Edoxaban monotherapy in nonvalvular atrial fibrillation patients with coronary artery disease. J Interv Cardiol 2022;2022:5905022.
[15] Ahmed M, Ahsan A, Shafiq A, *et al*. Meta-analysis comparing oral anticoagulant monotherapy versus dual antithrombotic therapy in patients with atrial fibrillation and stable coronary artery disease. Clin Cardiol 2024;47:e70026.
[16] Patail H, Sharma T, Bali AD, *et al*. Dual antiplatelet therapy with concomitant anticoagulation: current perspectives on triple therapy. Arch Med Sci Atheroscler Dis 2023;8:e13–8.