How does the addition of antiplatelet therapy to antithrombotic therapy in patients with atrial fibrillation and stable coronary artery disease affect outcomes? A meta-analysis of randomized controlled trials

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Atrial fibrillation (AF) and stable coronary artery disease (CAD) often coexist, creating a significant burden. The efficacy of adding antiplatelet therapy to oral anticoagulant (OAC) therapy in treating these patients remains unclear, prompting this meta-analysis. A comprehensive search across databases was conducted for relevant studies. Outcomes of interest included net adverse clinical event (NACE), all-cause mortality, cardiovascular disease (CVD) mortality, major bleeding, any bleeding, hemorrhagic stroke, and ischemic stroke. A hazard ratio (HR) with 95% confidence intervals (CI) was pooled. Three randomized controlled trials (3945 patients) were analyzed. OAC monotherapy (MT) significantly reduced major bleeding (HR: 0.57; 95% CI: 0.40–0.83; $P = 0.003$) and any bleeding (HR: 0.55; 95% CI: 0.46–0.65; $P < 0.0001$) compared to combination therapy. No significant findings were observed for NACE, all-cause mortality, CVD mortality, hemorrhagic and ischemic strokes. Our meta-analysis revealed that OAC MT significantly reduced bleeding events while the number of stroke events and mortality remained similar compared to combination therapy in patients with AF and stable CAD. ***Cardiovasc Endocrinol Metab*** **14: 1–5**

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Introduction

Coronary artery disease (CAD) and atrial fibrillation (AF) are closely interconnected conditions that frequently coexist. Approximately 20–30% of patients with CAD also have AF [1]. In AF, anticoagulation is more effective than antiplatelet therapy for preventing thromboembolic events, while dual antiplatelet therapy remains the standard treatment for CAD. However, managing comorbid AF and stable CAD presents a therapeutic challenge as it requires carefully balancing the antithrombotic and antiplatelet strategies. This complexity is reflected in the Canadian Cardiovascular Society and the European Society of Cardiology guidelines which suggest limiting the use of triple therapy [dual antiplatelet therapy with aspirin and a P2Y12 inhibitor, plus an oral anticoagulant (OAC)] to a short duration of 4–6 weeks, followed by dual therapy (P2Y12 inhibitor plus an OAC) for up to 12 months in patients with AF undergoing percutaneous coronary intervention [2,3]. Despite these recommendations, the shift to OAC monotherapy (MT) after 12 months remains uncertain, further complicating the treatment approach for patients with both AF and stable CAD. Several previous meta-analyses have attempted to reduce this uncertainty. However, most relied on observational studies, which are prone to bias or yielded inconclusive results due to the limited number of randomized controlled trials (RCTs) available [4,5].

The Edoxaban vs. Edoxaban With antiPlatelet Agent In Patients With A and Chronic Stable CAD (EPIC-CAD) clinical trial recently provided new evidence, demonstrating that Edoxaban MT significantly reduced the incidence of primary outcome events at 12 months compared to dual antithrombotic therapy [6]. Notably, the rates of major ischemic events were similar between the

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two groups, while the risk of major or clinically relevant nonmajor bleeding was lower in the Edoxaban group. We aimed to provide definitive evidence to understand the effects of adding antiplatelet therapy to anticoagulant therapy in patients with both AF and CAD, using data from all trials published to date.

Methods

Our meta-analysis followed the preferred reporting items for systematic review and meta-analysis guidelines. Two independent reviewers (M.I.S and A.R.S) searched PubMed/MEDLINE, Scopus, CINAHL, Cochrane CENTRAL, and EMBASE databases from inception till October 2024 without any language or time restrictions. The articles that satisfied the eligibility criteria were compiled in EndNote and carefully assessed by two independent reviewers (M.I.S and A.R.S), with any conflicts resolved by a third author (A.S). Studies were eligible for inclusion if they met the following eligibility criteria: The population, intervention, control, outcomes format for systematic reviews was used for our inclusion criteria, where P represents patients with AF and stable CAD, I represents patients receiving MT with anticoagulants, C represents patients receiving combination therapy with anticoagulants and antiplatelet therapy, and O represents net adverse clinical events (NACE), all-cause mortality, cardiovascular mortality, hemorrhagic stroke, ischemic stroke, major bleeding, and any bleeding. Our analysis only included RCTs.

Two investigators (N.D. and M.T.K.) independently extracted data from selected studies (baseline characteristics, primary and secondary outcomes, and the number of events). In addition, the modified Cochrane Collaboration's risk of bias tool 2.0 for RCTs was used to assess the quality of included studies by two independent authors. All statistical analyses were performed using Review Manager (version 5.4; Copenhagen). The results were pooled using hazard ratios (HRs) with 95% confidence intervals (CI) using the Mantel-Haenszel random effects model. Higgins I2 statistic was used to assess heterogeneity among the studies, with an I^2 of more than 50% considered significant heterogeneity.

Results

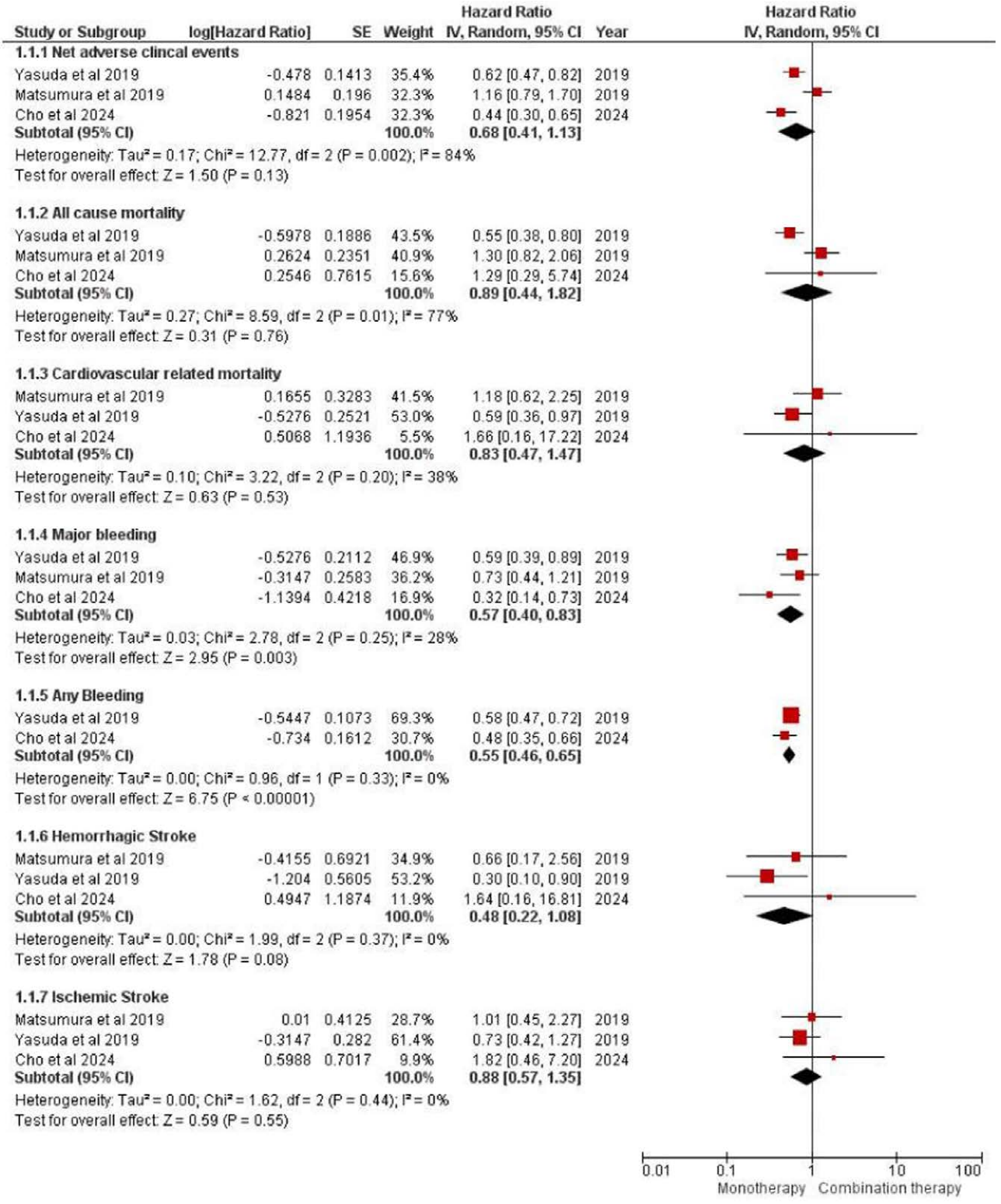
The initial search identified 447 articles from inception to 30 September 2024. Following the removal of duplicate articles, 181 articles remained. After employing a comprehensive screening strategy on the remaining articles, three articles were eligible for inclusion in this meta-analysis. 3945 patients were pooled (1975 OAC MT: 1970 combined therapy) [6–8]. The study and baseline characteristics of the included trials are available in Table 1. The included studies demonstrated a score of low to some concerns as per the modified Cochrane Collaboration's risk of bias tool. The complete risk of bias assessment is available in Supplementary Figure 1, Supplemental Digital Content 1, *http://links.lww.com/CAEN/A69*. Our analysis showed no significant differences in NACE (HR: 0.68; 95% CI: 0.41–1.13; $P = 0.13$; $I^2 = 84\%$) between OAC MT when compared with combination therapy. Additionally, no significant differences were exhibited among the groups for all-cause mortality (HR: 0.89; 95% CI: 0.44–1.82; $P = 0.76$; $I^2 = 77\%$), cardiovascular-related mortality (HR: 0.83; 95% CI: 0.47–1.47; $P = 0.53$; $I^2 = 38\%$), hemorrhagic stroke (HR: 0.48; 95% CI: 0.22–1.08; $P = 0.08$; $I^2 = 0\%$), and ischemic stroke (HR: 0.88; 95% CI: 0.57–1.35; $P = 0.55$; $I^2 = 0\%$). On the contrary, significant declines were observed in major bleeding (HR: 0.57; 95% CI: 0.40–0.83; $P = 0.003$; $I^2 = 28\%$) and any bleeding (HR: 0.55; 95% CI: 0.46–0.65; $P < 0.0001$; $I^2 = 0\%$) when comparing OAC MT to dual therapy (Fig. 1).

Table 1 **Study and patient characteristics of the included studies**

Study name	Yasuda *et al.*	Cho *et al.*	Matsumura *et al.*
Year of study	2019	2024	2019
Study type	Multicenter, open-label, randomized control trial	Multicenter, open-label, adjudicator-masked, randomized trial	Multicenter, open-label, noninferiority trial
Median follow up	24.1 months	12 months	30 months
Monotherapy (MT) type	Rivaroxaban	Edoxaban	Oral anticoagulant
Combined therapy (CT) type	Rivaroxaban + aspirin or P2Y12 inhibitor	Edoxaban + single antiplatelet agent (either aspirin or a P2Y12 inhibitor)	Oral anticoagulant + antiplatelet therapy
Sample size MT	$N = 1107$	$N = 524$	$N = 344$
Sample size CT	$N = 1108$	$N = 516$	$N = 346$
Mean age MT	74.3 ± 8.3	71.7 ± 8.0	74.9 ± 0.4
Mean age CT	74.4 ± 8.2	72.5 ± 8.4	75.2 ± 0.4
Male MT *N*(%)	875 (79.0)	396 (75.6)	294 (85.5)
Male CT *N*(%)	876 (79.1)	406 (78.7)	294 (85.0)
BMI MT	24.5 ± 3.7	25.3 ± 3.3	24.3 ± 3.4
BMI CT	24.5 ± 3.7	25.4 ± 3.4	24.4 ± 3.4
Diabetes MT- *N*(%)	461 (41.6)	224 (42.7)	152 (44.2)
Diabetes CT- *N*(%)	466 (42.1)	197 (38.2)	138 (39.9)
Previous PCI MT- *N*(%)	781 (70.6)	308 (58.8)	241 (71.7)
Previous PCI CT- *N*(%)	783 (70.7)	318 (61.6)	240 (70.6)

PCI, percutaneous coronary intervention.

Fig. 1



Forest plot comparing monotherapy vs. combination therapy with the outcomes.

Discussion

Our meta-analysis, including 3945 patients with AF and stable CAD, suggests no significant difference between OAC MT and combination therapy in reducing NACE, all-cause and cardiovascular mortality, and ischemic and hemorrhagic stroke. However, OAC MT was associated with significantly reduced bleeding events. The results of our meta-analysis align with prior RCTs in demonstrating the safety benefit of MT though discrepancies remain regarding its efficacy in cardiovascular outcomes [6–8]. The OAC in Patients with Atrial Fibrillation and Coronary Stent trial which included 690 patients, was unable to establish the noninferiority of OAC MT vs. combination therapy in this patient population 1 year beyond stenting due to early termination of enrollment and insufficient power [8]. Similarly, the AF and ischemic events with rivaroxaban in patients with stable coronary artery disease trial (n = 2215), which was terminated prematurely owing to increased mortality observed in the combination therapy group, demonstrated that rivaroxaban MT, as compared with combination therapy with rivaroxaban plus antiplatelet therapy was superior in reducing major bleeding events and noninferior for composite of cardiovascular events or death from any cause [7]. In the EPIC-CAD trial (n = 1040), edoxaban MT was associated with a lower risk of major bleeding and a reduced composite outcome of mortality, MI, stroke, embolism, and revascularization, while major ischemic events occurred at similar rates in both groups [6]. Our findings are congruent with previous meta-analyses, which have also shown that MT reduces bleeding risk while cardiovascular outcomes remain comparable between the two groups [4,5]. Notably, in contrast to previous meta-analyses, which incorporated observational studies, our analysis exclusively included RCTs to overcome the inherent bias associated with observational studies. Moreover, our study had low heterogeneity among most of the outcomes included.

Several previous studies have explored the role of OAC and antiplatelet therapy in patients with AF [9–11]; however, in patients with concomitant stable CAD, further considerations are needed. A plausible explanation for the lack of difference in mortality between the two groups is that the benefit of antiplatelet therapy is most pronounced in individuals with CAD during the first year following an index acute coronary syndrome. After 1 year, when they are classified as having stable CAD, the likelihood of further ischemic events decreases [12]. Therefore, OAC MT may be sufficient to protect against both recurrent ischemic incidents and thromboembolic complications.

This is particularly important in elderly patients who are at high risk of bleeding due to an increased risk for falls and polypharmacy [13], and in those with bleeding disorders, making them more susceptible to life-threatening bleeding episodes, which may make OAC MT a preferable alternative. However, in patients with a high risk of thrombosis, combination therapy with OAC could be considered, with shared decision-making.

Limitations

Our primary limitation is the limited number of studies, which suggests that the insignificant results for outcomes may be due to the underpowered nature of the studies. Additionally, the high heterogeneity in some outcomes is likely attributable to different baseline comorbidities and variable patient characteristics; this possibility cannot be ruled out. Finally, this meta-analysis is geographically limited, with studies primarily from regions in South Korea and Japan, which may impact the overall generalizability of the results.

Conclusion

Our results highlight the comparability of outcomes between the two groups, showing no notable benefit from adding antiplatelet therapy. Notably, OAC MT was associated with fewer bleeding events, thereby possibly minimizing complications. However, no statistical significance was achieved for all-cause mortality, cardiovascular-related mortality, or strokes. Future research with large-scale RCTs is necessary for a well-powered meta-analysis.

Acknowledgements

The data that support the findings of this study are available upon request from the corresponding author.

No ethical approval was required for this study design, as all data were obtained from publicly available, deidentified sources.

Conflicts of interest

There are no conflicts of interest.

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