CJC Open 6 (2024) 708–720

Systematic Review/Meta-analysis

Antithrombotic Therapy in Patients With Atrial Fibrillation and Coronary Artery Disease With Recent or Remote Events: Systematic Review and Meta-analysis

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ABSTRACT

Background: Ongoing debate remains regarding optimal antithrombotic therapy in patients with atrial fibrillation (AF) and coronary artery disease.

Methods: We performed a systematic review and meta-analysis to synthesize randomized controlled trials (RCTs) comparing the following: (i) dual-pathway therapy (DPT; oral anticoagulant [OAC] plus antiplatelet) vs triple therapy (OAC and dual-antiplatelet therapy) after percutaneous coronary intervention (PCI) or acute coronary syndrome (ACS), and (iii) OAC monotherapy vs DPT at least 1 year after PCI or

RÉSUMÉ

Contexte : La question du traitement antithrombotique optimal chez les personnes présentant une fibrillation auriculaire (FA) et une coronaropathie demeure controversée.

Méthodologie : Nous avons réalisé une revue systématique et une méta-analyse pour synthétiser les essais contrôlés randomisés ayant comparé i) la bithérapie (anticoagulant oral et antiplaquettaire) et la trithérapie (anticoagulant oral et bithérapie antiplaquettaire) après une intervention coronarienne percutanée (ICP) ou un syndrome coronarien aigu (SCA), et ii) un anticoagulant oral en monothérapie et la

Coronary artery disease (CAD) and atrial fibrillation (AF) are disease states that are pathophysiologically linked and often coexist in a patient.[1] In AF, anticoagulation is more efficacious than antiplatelet therapy in preventing thromboembolic events,[2,3] whereas dual-antiplatelet therapy is the preferred treatment for CAD, based on trials conducted in the early era of coronary stenting.[4,5] This difference poses a management dilemma, as finding the optimal balance in patients with concomitant indications for different antithrombotic agents remains a conundrum. Based on randomized controlled trials (RCTs), European and North American guidelines have been aligned in several respects regarding the management of patients with concomitant AF and CAD. These include favouring direct oral anticoagulants over vitamin K antagonists (VKAs), favouring clopidogrel over potent $P2Y_{12}$ inhibitors (ticagrelor and prasugrel), and omitting acetylsalicylic acid (ASA) in long-term treatment.[6-11] However, these studies were heterogeneous, and they were insufficiently powered for thrombotic events. To address this, meta-analyses have been carried out that show a decrease in bleeding with dual-pathway therapy (DPT) consisting of an oral anticoagulant (OAC) and single-antiplatelet vs triple-antithrombotic therapy with dual-antiplatelet therapy plus OAC.[12,13] However, these meta-analyses were methodologically classified as being of low quality according to the **A M**ea**s**urement **T**ool to **A**ssess Systematic **R**eviews (AMSTAR) 2 criteria. Additionally, recent evidence has emerged, challenging the practice of combining antiplatelet therapy and OAC beyond 1 year for patients with AF and percutaneous coronary intervention (PCI) or acute coronary syndrome (ACS).[14,15]

We aimed to synthesize evidence from RCTs in patients with AF and either of the following: (i) recent PCI or ACS, with a particular emphasis on addressing pertinent and specific management issues; or (ii) chronic CAD without recent PCI or ACS. The goal was to provide evidence-based guidance for the management of antithrombotic agents in patients with concomitant AF and CAD, throughout their journey.

Received for publication September 21, 2023. Accepted January 6, 2024.

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See page 718 for disclosure information.

https://doi.org/10.1016/j.cjco.2024.01.001

ACS. Following a 2-stage process, we identified systematic reviews published between 2019 and 2022 on these 2 clinical questions, and we updated the most comprehensive search for additional RCTs published up to October 2022. Outcomes of interest were major adverse cardiovascular events (MACE), death, stent thrombosis, and major bleeding. We estimated risk ratios (RRs) and 95% confidence intervals (CIs) using a random-effects model.

Results: Based on 6 RCTs (n = 10,435), DPT reduced major bleeding (RR 0.62, 95% CI 0.52-0.73) and increased stent thrombosis (RR 1.55, 95% CI 1.02-2.36), vs triple therapy after PCI or medically-managed ACS, with no significant differences in MACE and death. In 2 RCTs (n = 2905), OAC monotherapy reduced major bleeding (RR 0.66, 95% CI 0.49-0.91) vs DPT in AF patients with remote PCI or ACS, with no significant differences in MACE or death.

Conclusions: In patients with AF and coronary artery disease, using less-aggressive antithrombotic treatment (DPT after PCI or ACS, and OAC alone after remote PCI or ACS) reduced major bleeding, with an increase in stent thrombosis with recent PCI. These results support a minimalist yet personalized antithrombotic strategy for these patients.

bithérapie au moins 1 an après une ICP ou un SCA. Nous avons procédé en 2 temps, d'abord en répertoriant les revues systématiques publiées entre 2019 et 2022 sur ces 2 questions cliniques, puis en effectuant la recherche la plus exhaustive possible pour trouver d'autres essais contrôlés randomisés publiés jusqu'en octobre 2022. Les paramètres qui nous intéressaient étaient les événements cardiovasculaires indésirables majeurs (ECIM), le décès, la thrombose de l'endoprothèse et l'hémorragie majeure. Nous avons estimé les rapports de risques (RR) et les intervalles de confiance (IC) à 95 % à l'aide d'un modèle à effets aléatoires.

Résultats : D'après 6 essais contrôlés randomisés (n = 10 435), la bithérapie a réduit les hémorragies majeures (RR : 0,62; IC à 95 % : 0,52 à 0,73) et augmenté les thromboses de l'endoprothèse (RR : 1,55; IC à 95 % : 1,02 à 2,36), comparativement à la trithérapie après une ICP ou un SCA ayant fait l'objet d'une prise en charge médicale, tandis qu'aucune différence significative n'a été observée quant aux ECIM et aux décès. Dans 2 essais contrôlés randomisés (n = 2 905), un anticoagulant oral en monothérapie a réduit les hémorragies majeures (RR : 0,66; IC à 95 % : 0,49 à 0,91) comparativement à la bithérapie chez des patients présentant une FA après une ICP ou un SCA plus lointain, sans différence significative quant aux ECIM et aux décès.

Conclusions : Chez les patients présentant une FA et une coronaropathie, l'utilisation d'un traitement antithrombotique moins agressif (bithérapie après un ICP ou un SCA, et anticoagulant oral en monothérapie après une ICP ou un SCA plus lointain) réduit les hémorragies majeures, mais s'accompagne d'une augmentation des thromboses de l'endoprothèse en cas d'ICP récente. Ces résultats plaident en faveur d'une stratégie antithrombotique minimaliste, mais personnalisée chez ces patients.

Methods

We conducted a systematic review and meta-analysis to support the development of recommendations for the 2023 Canadian Cardiovascular Society /Canadian Association of Interventional Cardiology focused update of the guidelines for the use of antiplatelet therapy. We followed a 2-stage process, as follows. First, we searched for all recent systematic reviews that addressed any of the predefined clinical questions for this topic (outlined below) and extracted all relevant RCTs from these systematic reviews. We rated all identified systematic reviews using the AMSTAR 2 criteria.[16] We subsequently identified and updated the most-comprehensive search strategies from available systematic reviews. Two of the current authors (B.J.M. and R.D.T.) re-extracted all data from the original RCT articles. This report follows the 2020 **P**referred **R**eporting **I**tems for **S**ystematic Reviews and **M**eta-**A**nalyses (PRISMA) statement.[17]

Search strategies and data source

To identify relevant systematic reviews, we searched PubMed (for the period January 1, 2019 to October 1, 2022). We selected 2019 to ensure that identified systematic reviews would include the most-recent large studies addressing these clinical questions— **E**doxaba**n** **Tr**eatment Vers**us** Vitamin K Antagonist in Pa**t**ients With **A**trial **F**ibrillation Undergoing **P**ercutaneous **C**oronary **I**ntervention (ENTRUST-AF-PCI) and **A**trial **F**ibrillation and **I**schemic Events With **R**ivaroxaban in Patients With Stabl**e** Coronary Artery Disease (AFIRE)—which were both published in 2019. We then refined and updated (using minor optimizations to increase search specificity) the most comprehensive search among these meta-analyses, for each clinical question, and we updated these searches in PubMed, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL), to identify subsequent RCTs. Supplemental Appendix S1 describes the full search strategies.

We included parallel RCTs that evaluated the following clinical issues, and reported on at least one of the outcomes of interest (listed in Outcomes section below): (i) DPT (direct oral anticoagulant [DOAC] and $P2Y_{12}$ inhibitor) vs triple-antithrombotic therapy (ASA, $P2Y_{12}$ inhibitor, and a VKA or DOAC) in patients with AF and PCI (for ACS or stable CAD) or medically-managed ACS; and (ii) comparison of OAC monotherapy (DOAC or VKA) to DPT (OAC plus one antiplatelet agent) in patients with AF and CAD with remote (> 1 year) ACS and/or PCI.

One reviewer (B.J.M.) performed all database searches and imported the records into Covidence. Using Covidence, 2 reviewers (B.J.M. and R.D.T.) independently screened article titles and abstracts, and reviewed full-text articles for inclusion. One reviewer (B.J.M.) extracted data using a standardized data collection form, with replication of the data extraction by a second reviewer (R.D.T.).

Assessment of risk of bias (RoB) and certainty of evidence

Two reviewers (B.J.M. and R.D.T.) independently evaluated trial-level RoB using the Cochrane RoB 2 tool.[18] The

same reviewers then rated outcome-level certainty of evidence using the Grading Recommendations Assessment, Development and Evaluation (GRADE) framework, which incorporates the risk of bias, imprecision, inconsistency, indirectness, and publication bias.[19] No discrepancies between the reviewers occurred.

Outcomes

The outcomes of interest were as follows: (i) major adverse cardiovascular events (MACE; composite of death from any cause, myocardial infarction [MI], or stroke—when this composite was not available, we used the composite of cardiovascular death, MI, or stroke, or a broader composite that encompasses additional components, as reported); (ii) all-cause death; (iii) stent thrombosis (definite or probable based on original Academic Research Consortium (ARC) or ARC-2 definition)[20,21]; and (iv) major bleed (Bleeding ARC [BARC] 3 or 5 bleed[22]; when information using this classification was not available, we preferentially reported bleeding based on the International Society on Thrombosis and Haemostasis definition, followed by the Thrombolysis in Myocardial Infarction [TIMI] definition, as used in the respective trials).

Statistical analysis

We pooled dichotomous outcomes as risk ratios (RRs) with 95% confidence intervals (CIs) using a DerSimonian-Laird inverse variance random-effects model for all outcomes. We evaluated statistical heterogeneity with visual inspection of the forest plot, and quantified the percentage of variability due to heterogeneity between trials using the I^2 statistic.

We prespecified the following subgroups of interest for the comparison of DPT vs triple-antithrombotic therapy in recent PCI: choice of $P2Y_{12}$ inhibitor; and early vs late effect (with respect to the duration of ASA). We did not conduct any subgroup analyses for the comparison of OAC monotherapy to DPT in AF with remote PCI and/or ACS.

We conducted all analyses using Review Manager version 5.4 (Cochrane, Copenhagen, Denmark).

Results

The initial search strategy identified 30 recent meta-analyses (with or without systematic reviews) addressing comparisons of interest (Fig. 1).[12,13,23-49] All meta-analyses except for one Cochrane review[26] were ranked as having low or critically low quality levels according to the AMSTAR 2 criteria (Supplemental Table S1). The high-quality Cochrane review compared DOACs to VKAs post-PCI, which was not a focus for this review. Consequently, the reviews of next-highest quality level were selected instead.

DPT vs triple-antithrombotic therapy in AF after PCI or medically-managed ACS

Characteristics of included studies. We selected the highest-quality systematic review for this question and updated their searches to extend them to October 2022.[13] From 1536 records screened, we identified 2 additional RCTs,[50,51] for a total of 6 RCTs (n = 11,156). Table 1 describes key study and participant characteristics. In brief, across all trials, the weighted mean age was 70 years; 41% of participants were women; the median CHA_2DS_2-VASc (**C**ongestive Heart Failure, **H**ypertension, **A**ge [≥ 75 years] [doubled], **D**iabetes Mellitus, **S**troke/Transient Ischemic Attack [doubled], **V**ascular Disease, **A**ge [65-74] Years, **S**ex **C**ategory [female]) score was 4; and clopidogrel was the predominant $P2Y_{12}$ inhibitor (91%). Time from PCI to randomization ranged from a mean of 1.9 days (ENTRUST-AF-PCI) to 6 days (Apixaban Versus Warfarin in Patients With AF and ACS or PCI [AUGUSTUS]). In the AUGUSTUS trial,[9] 1097 patients (23.9% of the total population) had medically-managed ACS, and 1714 (37.3%) had ACS managed with PCI.

RoB and certainty of evidence. We rated 4 trials at a low risk of bias, and 2 trials at a high risk of bias (Fig. 2). AUGUSTUS employed a 2-by-2 factorial design to compare the use of ASA vs placebo (double-blind), as well as apixaban vs VKA (open-label); all other trials were open-label. Notably, we rated the open-label comparisons within AUGUSTUS, ENTRUST-AF, Exploration of Two Treatment Strategies of **R**ivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects With **A**trial **F**ibrillation Who Undergo a **P**ercutaneous **C**oronary **I**ntervention (PIONEER-AF PCI), and **R**andomized **E**valuation of **Dual** Therapy With Dabigatran vs Triple Therapy With Warfarin in Patients With AF That Undergo a **PCI** With Stenting (RE-DUAL PCI) as having a low RoB, given the limited evidence of trial protocol deviations, and the use of relatively bias-proof outcomes combined with blinded outcome adjudication.

We rated the certainty of evidence as moderate for MACE, death, and stent thrombosis, due to serious imprecision, whereas we rated the certainty of evidence as high for major bleeding. GRADE certainty of evidence ratings, along with relative and absolute estimates of effect, are provided in Table 2.

Outcomes and subgroup analyses. All 6 trials reported on all outcomes of interest. The differences in MACE (RR 1.12, 95% CI 0.97-1.28, $I^2 = 0\%$; Fig. 3A) and death (RR 1.07, 95% CI 0.88-1.30, $I^2 = 0\%$; Fig. 3B) between DPT and triple-antithrombotic therapy were not statistically significant. DPT increased the risk of stent thrombosis, compared with triple-antithrombotic therapy (RR 1.55, 95% CI 1.02-2.36, $I^2 = 0\%$; Fig. 3C), translating to a 0.4% absolute risk increase. Conversely, DPT reduced the risk of major bleeding, compared with triple-antithrombotic therapy (RR 0.62, 95% CI 0.52-0.73, $I^2 = 0\%$; Fig. 3D), translating to a 2.1% absolute risk reduction.

No statistical heterogeneity and no significant subgroup interaction was present in the results for any outcome between patients managed with PCI (elective PCI or ACS treated with PCI) or medically-managed ACS in the AUGUSTUS trial.[9]

Exploration of the timing of treatment effects regarding ASA duration was variably reported and could not be meta-analyzed, so this is reported separately. In a *post hoc* landmark analysis of AUGUSTUS,[52] ASA was compared to placebo (ie, DPT vs triple-antithrombotic therapy) in the first 30 days after randomization, and days 30-180 after randomization. Within

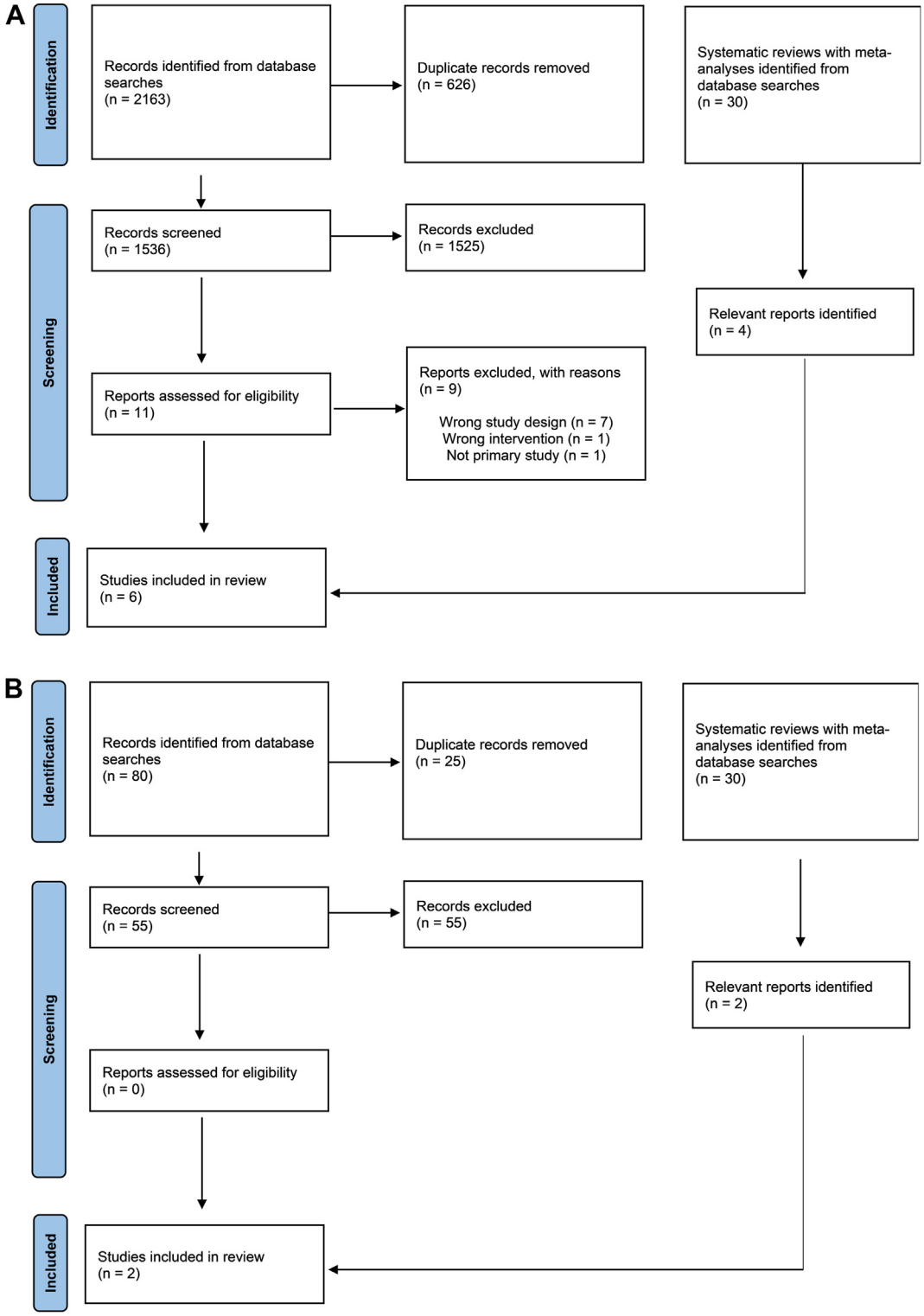

Figure 1. Study flow diagram for comparing the following: (**A**) dual-pathway therapy vs triple-antithrombotic therapy; and (**B**) oral anticoagulant monotherapy vs dual-pathway therapy.

30 days, ASA increased bleeding events (fatal, intracranial, and major) by an absolute 0.97% (95% CI 0.23%-1.70%), and reduced thrombotic events (cardiovascular death, MI, stroke, and stent thrombosis) by 0.91% (-1.74% to -0.08%). After day 30, an increase in bleeding occurred with ASA (1.25%, 95% CI 0.23%-2.27%) and no significant reduction occurred in thrombotic events (-0.17%, 95% CI -1.33%-0.98%). In a similar analysis in RE-DUAL PCI,[53] a consistent reduction

Table 1. Patient's characteristics across all included studies in atrial fibrillation after PCI or medically-managed ACS

	AUGUSTUS (PCI subgroup, n = 3498)	AUGUSTUS (n = 1097, medically managed subgroup)	ENTRUST-AF-PCI (n = 1506)	PIONEER-AF PCI (n = 2124)	RE-DUAL PCI (n = 2725)	Bai et al.[50] (2022) (n = 100)	Liu et al.[51] (2021) (n = 106)
Age, mean, y	70.7	69.6	70	70.2	70.8	58.0	78.5
Female, %	25.8	39.0	25.6	26.1	24.0	37.0	40.6
$CHAD_2DS_2VASc$, mean	3.9	4.1	4	4	3.6	3	4.7
HAS-BLED, mean	2.6	2.5	3	3	2.7	2	3.9
ACS, %	50.0	100	51.6	51	50.5	100	58.5
NSTE-ACS/STEMI, %	—	—	—	39.2/11.5	39.5/14.8	—	—
DES, %	—	0	—	67.7	84.1	100	100
Days from index event to randomization	**< 14 (mean 6.0)**	**< 14 (mean 8.5)**	**≤ 5 (mean 1.9)**	**≤ 3**	**≤ 5**	—	**≤ 3**
$P2Y_{12}$i at baseline							
Clopidogrel, %	**91.0**	97.7	**92.4**	**94.7**	**88.0**	—	—
Prasugrel/ticagrelor, %	1.5/7.5	0.2/2.1	0/7	1.2/4.1	-/10.7	—	—
Dual therapy							
OAC	Apixaban 5 mg BID or warfarin (INR 2-3)		Edoxaban 60 mg daily	Rivaroxaban 15 mg daily	Dabigatran 110 mg or 150 mg BID	Rivaroxaban 15 mg daily	Rivaroxaban 15 mg daily
$P2Y_{12}$i	Clopidogrel or ticagrelor or prasugrel		Clopidogrel or ticagrelor or prasugrel	Clopidogrel or ticagrelor or prasugrel	Clopidogrel or ticagrelor	Clopidogrel	Ticagrelor
Triple therapy							
OAC	Apixaban 5 mg BID or warfarin (INR 2-3)		Warfarin (INR 2-3)	Warfarin (INR 2-3)	Warfarin (INR 2-3)	Warfarin (INR 2-3)	Warfarin (INR 1.6-2.5)
$P2Y_{12}$i	Clopidogrel or ticagrelor or prasugrel		Clopidogrel or ticagrelor or prasugrel	Clopidogrel or ticagrelor or prasugrel	Clopidogrel or ticagrelor	Clopidogrel	Clopidogrel
Outcome definitions							
MACE	Death, MI, stroke, stent thrombosis (definite or probable), or urgent revascularization		Death, MI, stroke, stent thrombosis (definite), or systemic embolism	CV death, MI, or stroke	Death, MI, stroke, systemic embolism	Death, MI, stroke, stent thrombosis, unplanned revascularization	CV death, MI, stroke, or stent thrombosis
Major bleeding	ISTH		BARC (3 or 5)	ISTH	ISTH	TIMI	TIMI
Stent thrombosis	Reported: Definite/probable		Reported: Definite/probable	Reported	Reported: Definite	Reported	Reported
Follow-up duration, mo	6		12	12	14	12	12

ACS, acute coronary syndrome; AUGUSTUS, Apixaban Versus Warfarin in Patients With AF and ACS or PCI; BARC, Bleeding Academic Research Consortium; BID, twice a day; CHA_2DS_2-VASc, **C**ongestive Heart Failure, **H**ypertension, **A**ge [≥ 75 years] [doubled], **D**iabetes Mellitus, **S**troke/Transient Ischemic Attack [doubled], **V**ascular Disease, **A**ge [65-74] Years, **S**ex **C**ategory [female]); CV, cardiovascular; DES, drug-eluting stent; ENTRUST-AF-PCI, **E**doxaba**n** **T**reatment Vers**us** Vitamin K Antagonist in Pa**t**ients With **A**trial **F**ibrillation Undergoing **P**ercutaneous **C**oronary **I**ntervention; HAS-BLED, **H**ypertension, **A**bnormal Renal/Liver Function, **S**troke, **B**leeding History or Predisposition, **L**abile INR, **E**lderly (> 65 Years), **D**rugs/Alcohol Concomitantly; INR, international normalized ratio; MACE, major adverse cardiovascular events; OAC, oral anticoagulant; MI, myocardial infarction; ISTH, International Society on Thrombosis and Haemostasis; NSTE-ACS, non-ST-elevation ACS; PCI, percutaneous coronary intervention; PIONEER-AF PCI, Exp**l**orat**i**on of Tw**o** Treatme**n**t Strat**e**g**i**es of **R**ivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects With **A**trial **F**ibrillation Who Undergo a **PCI**; $P2Y_{12}$i, $P2Y_{12}$ inhibitor; RE-DUAL PCI, **R**andomized **E**valuation of **Dual** Therapy With Dabigatran vs Triple Therapy With Warfarin in Patients With AF That Undergo a **PCI** With Stenting; STEMI, ST-elevation myocardial infarction; TIMI, thrombolysis in myocardial infarction.

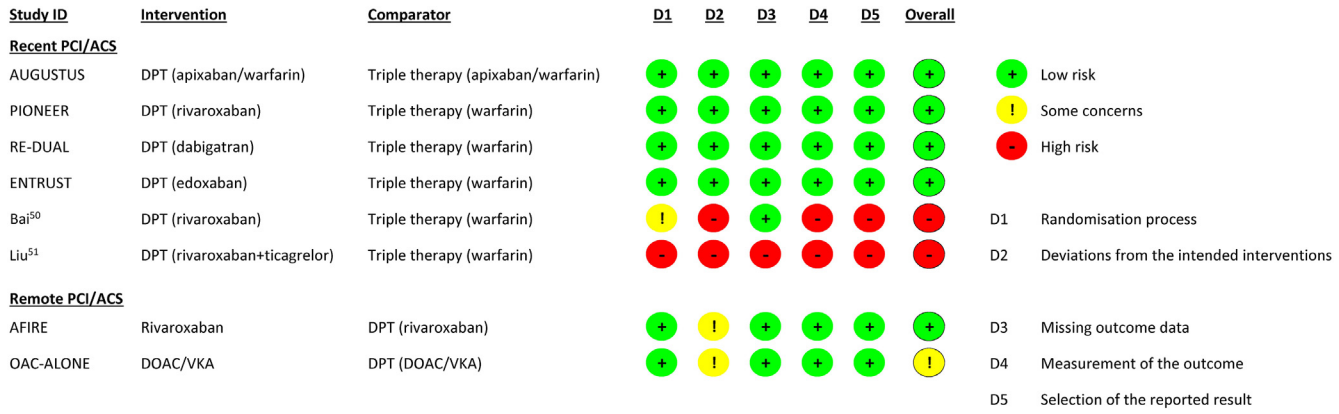

Figure 2. Cochrane Risk of Bias 2 tool summary for considered trials. ACS, acute coronary syndrome; AFIRE, **A**trial **F**ibrillation and **I**schemic Events with **R**ivaroxaban in Patients with Stable Coronary Artery Disease; AUGUSTUS, Apixaban Versus Warfarin in Patients with AF and ACS or PCI; DOAC, direct oral anticoagulant; DPT, dual-platelet therapy; ENTRUST, **E**doxaban **Tr**eatment Vers**us** Vitamin K Antagonist in Pa**t**ients With **A**trial **F**ibrillation Undergoing **P**ercutaneous **C**oronary **I**ntervention (ENTRUST-AF-PCI); ID, identification; OAC-ALONE, **O**ptimizing **A**ntithrombotic **C**are in Patients With **A**trial Fibri**ll**ation and Cor**on**ary St**e**nt; PCI, percutaneous coronary intervention; PIONEER, Exp**l**orat**i**on of Tw**o** Treatmen**t** Strat**e**g**i**es of **R**ivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects With **A**trial **F**ibrillation Who Undergo a **P**ercutaneous **C**oronary **I**ntervention (PIONEER-AF PCI); RE-DUAL, **R**andomized **E**valuation of **Dual** Therapy With Dabigatran vs Triple Therapy With Warfarin in Patients With AF That Undergo a **PCI** With Stenting (RE-DUAL PCI); VKA, vitamin-K antagonist.

occurred in major bleeding < 30 days and > 30 days after randomization with dabigatran-based DPT, compared with warfarin-based triple-antithrombotic therapy, with no statistically significant difference in thrombotic events at either timepoint. Landmark analysis of ENTRUST-AF-PCI[11] at 14 days demonstrated heterogeneity of treatment effect, suggesting an increased risk of major or clinically-relevant major bleeding with edoxaban-based DPT vs warfarin up to day 14, followed by a reduction in bleeding events after 14 days. Notably, this analysis could not disentangle the effect of different OACs (with warfarin taking time to achieve therapeutic range, and spending a low amount of time in the therapeutic range in this early phase) and cessation of ASA.

OAC monotherapy vs combination therapy (OAC plus ASA) in AF patients with remote ACS or PCI

Characteristics of included studies. We selected one of the highest-quality systematic reviews for this question, and updated their search to extend it to October 2022.[23] From 68 records screened, we identified no additional trials for inclusion. Because this previous systematic review pooled RCTs with observational studies, without analyses limited to randomized data, we replicated the meta-analyses including only RCTs. Both RCTs (n = 2932) were conducted exclusively in Japan; the mean age was 74.6 years; and 19.5% of participants were women (Table 3). The **O**ptimizing **A**ntithrombotic **C**are in Patient With **A**trial Fibri**ll**ation and Cor**on**ary St**e**nt (OAC-ALONE) trial[54] compared OAC monotherapy to OAC plus an antiplatelet agent in patients with AF and CAD beyond 1 year after stenting. The AFIRE study[55] compared rivaroxaban monotherapy to rivaroxaban plus a single antiplatelet. The choice of the antiplatelet agent, which was left to the discretion of the physician, was consistent between the trials, with the majority using ASA (85.9% in the OAC-ALONE trial, and 70.2% in the AFIRE study). In the OAC-ALONE trial, all patients had received coronary stents > 1 year prior. whereas in the AFIRE study, 781 patients (70.6%) had a history of PCI (723 of them with stent implantation), and 125 patients (11.3%) had a history of coronary artery bypass grafting.

RoB and certainty of evidence. We rated the AFIRE study as having a low RoB. We rated the OAC-ALONE trial as having some concerns for bias arising from deviations from intended interventions (12% of the patients in the intervention group added an antiplatelet agent due to a coronary procedure, and 9% of the patients in the comparator group stopped their antiplatelet therapy due to a bleeding event).

We rated the certainty of evidence as very low for MACE and death, due to serious inconsistency and very serious imprecision. Inconsistency (explored by contrasting both studies' characteristics) between the AFIRE and OAC-ALONE studies for these 2 outcomes could not be readily explained; however, the AFIRE study had a lower RoB and demonstrated a statistically significant reduction in both outcomes. We rated the certainty of evidence for stent thrombosis as low, due to very serious imprecision, and rated major bleeding as having high certainty of evidence.

Outcomes. Both trials reported on all outcomes of interest. The differences in MACE (RR 0.91, 95% CI 0.58-1.41, I^2 = 75%; Fig. 4A), death (RR 0.85, 0.37-1.92, I^2 = 87%; Fig. 4B), and stent thrombosis (RR 5.03, 95% CI 0.24-104.37; Fig. 4C) between OAC monotherapy and the combination therapy were not statistically significant. OAC monotherapy reduced the risk of major bleeding, compared with the combination therapy (RR 0.66, 95% CI 0.49-0.91, I^2 = 0%; Fig. 4D), translating to a 2.2% absolute risk reduction.

Discussion

The main findings of this systematic review with meta-analysis are as follows: (i) in patients with AF and CAD

Table 3. Patient characteristics across all included studies for atrial fibrillation plus remote (> 1 year) ACS and/or PCI

	AFIRE (n = 2236)		OAC-ALONE (n = 696)
Country	Japan		Japan
Age, mean, y	74.4		75.1
Female sex, %	21.0		14.8
$CHADS_2$, mean	2		2.5
CHA_2DS_2-VASc, mean	4		4.6
HAS-BLED, mean	2		2
ACS, %	35.1		38.6
PCI, %	70.7		100
DES, %	67.7		70.4
Time from index event, y	> 1		> 1 (median 4.5)
Baseline antiplatelet, %			
ASA	56.7		85.9
Clopidogrel	23.3		14.5
Other	7.8		-
Baseline anticoagulant, %			
Apixaban	10.6		10
Dabigatran	5.7		5.9
Edoxaban	2.8		2.9
Rivaroxaban	60.9		5.9
Warfarin	13		75.2
Study OAC in both groups	Rivaroxaban 15 mg		Warfarin or DOAC
Antiplatelet in comparator group	ASA or P2Y12 inhibitor		ASA or clopidogrel
Post-randomization antiplatelet			
	OAC monotherapy	**Dual-pathway therapy**	
ASA	0.7	70.2	—
Clopidogrel	0.1	25.4	—
Prasugrel	0.1	1.5	—
MACE definition	Death, MI, stroke, systemic embolism, unstable angina requiring revascularization		Death, MI, stroke, systemic embolism
Major bleeding definition	ISTH		ISTH
Non-major clinically-relevant bleeding definition	ISTH		TIMI
Follow-up duration, mo	24.1		30

ACS, acute coronary syndrome; AFIRE, **A**trial **F**ibrillation and **I**schemic Events With **R**ivaroxaban in Patients With Stabl**e** Coronary Artery Disease; ASA, acetylsalicylic acid; $CHADS_2$, **C**ongestive Heart Failure, **H**ypertension, **A**ge ≥ 75, **D**iabetes, and Prior **S**troke/Transient Ischemic Attack (doubled); CHA_2DS_2-VASc, **C**ongestive Heart Failure, **H**ypertension, **A**ge [≥ 75 years] [doubled], **D**iabetes Mellitus, **S**troke/Transient Ischemic Attack [doubled], **V**ascular Disease, **A**ge [65-74] Years, **S**ex **C**ategory [female]); DES, drug-eluting stent; HAS-BLED, **H**ypertension, **A**bnormal Renal/Liver Function, **S**troke, **B**leeding History or Predisposition, **L**abile INR, **E**lderly (> 65 Years), **D**rugs/Alcohol Concomitantly; ISTH, International Society on Thrombosis and Haemostasis; MACE, major adverse cardiovascular events; MI, myocardial infarction; OAC, oral anticoagulant; OAC-ALONE, **O**ptimizing **A**ntithrombotic **C**are in Patients With **A**trial Fibri**l**lation and Cor**on**ary St**e**nt; PCI, percutaneous coronary intervention; TIMI; thrombolysis in myocardial infarction.

and/or ACS medically treated or with PCI (< 1 year), DOAC-based DPT regimens reduced rates of bleeding and increased in-stent thrombosis, compared to triple-antithrombotic therapy, with no significant differences in MACE or death; (ii) in patients with AF and remote PCI and/or ACS (> 1 year), OAC monotherapy reduced major bleeding, compared to OAC plus a single antiplatelet agent.

Finding the balance between thrombosis and bleeding risks in this high-risk population remains a clinical challenge. The **W**hat Is the **O**ptimal Antiplat**e**let and Anticoagulation

Table 2. Summary-of-findings table

Outcome	Certainty of evidence	Effect estimate	
		RR (95% CI)	Absolute difference, per 1000
DOAC-based dual-pathway therapy vs triple-antithrombotic therapy in AF after PCI or medically-managed ACS			
MACE	Moderate*	1.12 (0.97−1.28)	8 more (from 2 fewer to 19 more)
Death	Moderate*	1.07 (0.88−1.30)	—
Stent thrombosis	Moderate*	1.55 (1.02−2.36)	4 more (from 0 to 9 more)
Major bleed	High	0.62 (0.52−0.73)	23 fewer (from 16 to 29 fewer)
OAC monotherapy vs OAC plus single antiplatelet in AF plus remote (> 1 y) ACS/PCI			
MACE	Very low†,‡	0.91 (0.58−1.41)	—
Death	Very low†,‡	0.85 (0.37−1.92)	—
Stent thrombosis	Low‡	5.03 (0.24−104.37)	—
Major bleed	High	0.66 (0.49−0.91)	22 fewer (from 6 to 33 fewer)

ACS, acute coronary syndrome; AF, atrial fibrillation; CI, confidence interval; DOAC, direct OAC; MACE, major adverse cardiovascular events; OAC, oral anticoagulation; PCI, percutaneous coronary intervention; RR, risk ratio.

*Rated down 1 category for serious imprecision.

†Rated down 1 category for serious inconsistency.

‡Rated down 2 categories for very serious imprecision.

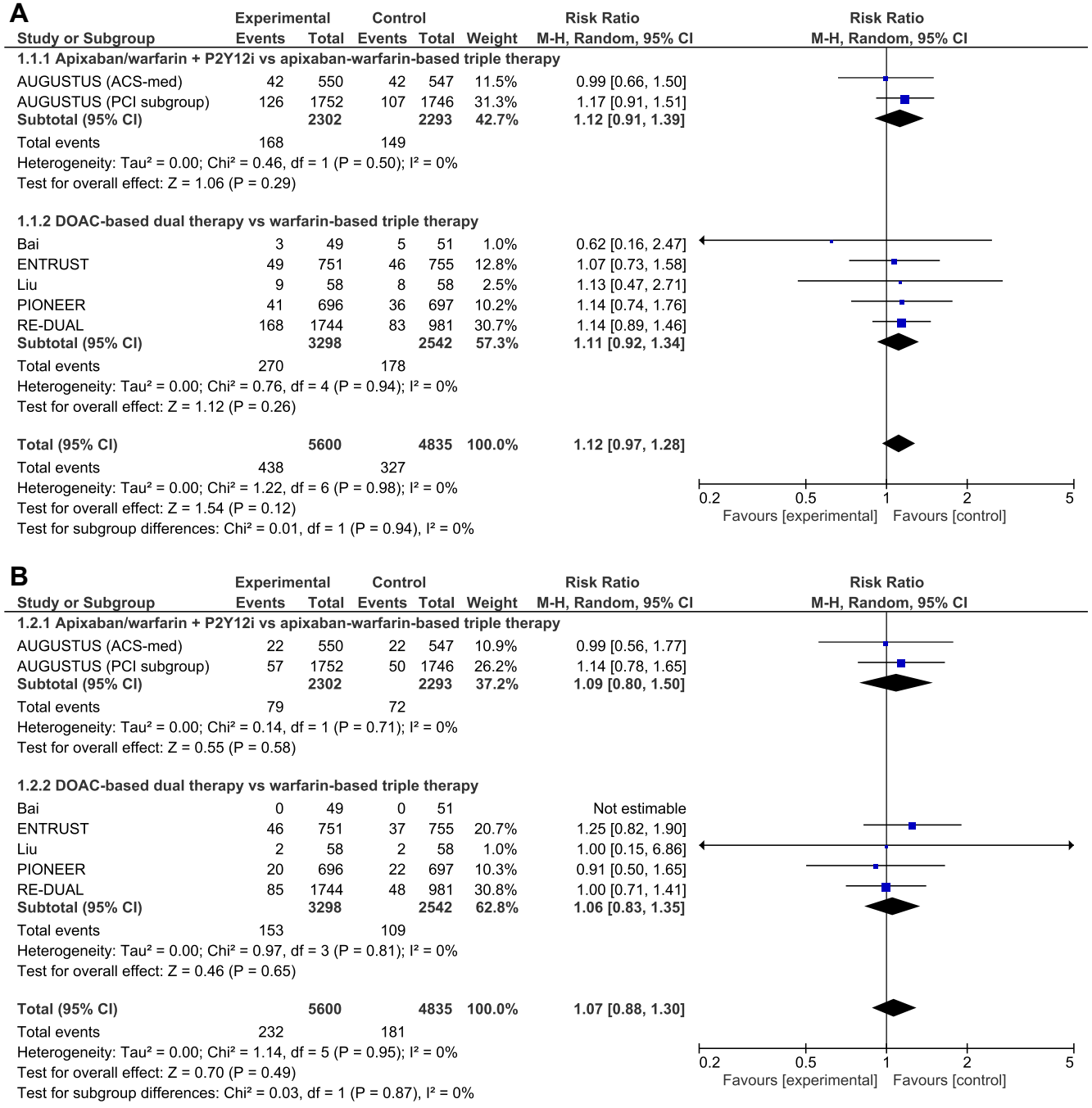

Figure 3. Forest plot for (**A**) major adverse cardiovascular events, (**B**) death, (**C**) stent thrombosis, and (**D**) bleeding. ACS, acute coronary syndrome; AUGUSTUS, Apixaban Versus Warfarin in Patients with AF and ACS or PCI; CI, confidence interval; DOAC, direct oral anticoagulant; ENTRUST, **E**doxaba**n** **Tr**eatment Vers**us** Vitamin K Antagonist in Pa**t**ients With **A**trial **F**ibrillation Undergoing **P**ercutaneous **C**oronary **I**ntervention (ENTRUST-AF-PCI); M-H, Mantel-Haenszel; PCI, percutaneous coronary intervention; PIONEER, Exp**l**orat**i**on of Tw**o** Treatme**n**t Strat**e**g**i**e**s** of **R**ivaroxaban and a Dose-Adjusted Oral Vitamin K Antagonist Treatment Strategy in Subjects With **A**trial **F**ibrillation Who Undergo a **P**ercutaneous **C**oronary **I**ntervention (PIONEER-AF PCI); P2Y12i, P2Y12 inhibitor; RE-DUAL, **R**andomized **E**valuation of **Dual** Therapy With Dabigatran vs Triple Therapy With Warfarin in Patients With AF That Undergo a **PCI** With Stenting (RE-DUAL PCI).

Therapy in Patients With Oral Anticoagulation and Coronary **S**ten**t**ing (WOEST) trial[56] was the first randomized trial to explore a "less-is-more" approach to antithrombotic therapy in patients with AF and CAD, by comparing DPT (warfarin plus clopidogrel) vs triple-antithrombotic therapy, and demonstrating lower rates of bleeding and death with DPT. The **I**ntracoronary **S**tenting and **A**ntithrombotic **R**egimen: **Triple** Therapy in Patients on Oral Anticoagulation After Drug Eluting Stent Implantation (ISAR-TRIPLE) trial[57] further suggested that 6 weeks, compared with 6 months, of

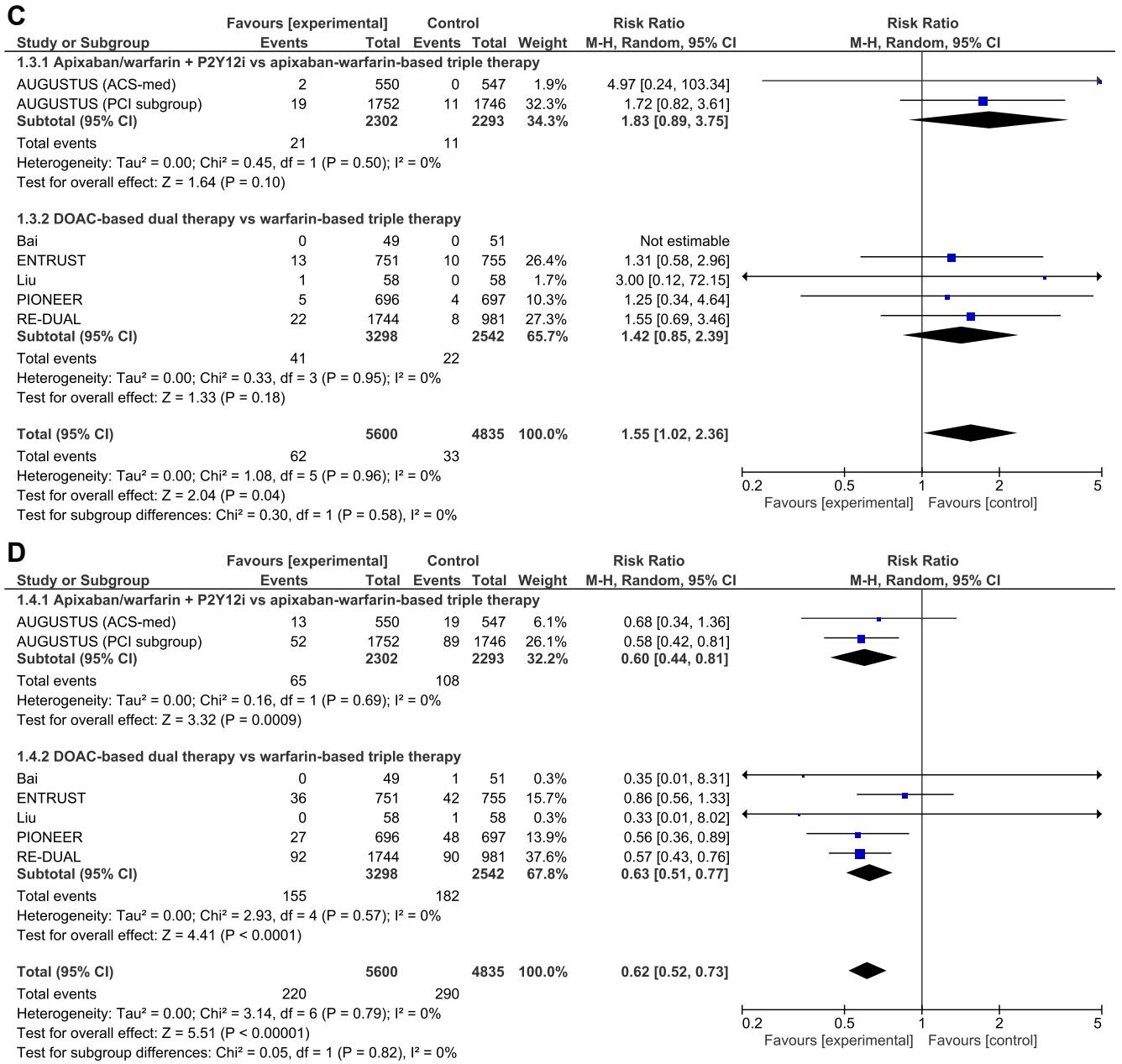

Figure 3. (*continued*).

VKA-based triple-antithrombotic therapy had similar efficacy and safety. In light of DOACs having replaced VKA as the first-line OAC choice for nonvalvular AF, trials evaluating DOAC-based regimens are more applicable to contemporary practice than the VKA-based trials.

Regarding the first study question regarding antithrombotic regimens early after PCI or ACS, meta-analyses demonstrated that 23 fewer patients had major bleeds, at the expense of 4 more stent thromboses, for every 1000 patients treated with DPT instead of triple therapy (ie, 6 major bleeds avoided for each stent thrombosis caused by a more conservative approach). In other words, in the study by Marquis-Gravel et al.,[58] a major bleeding event experienced after ACS was associated with an increase in death at 1 year, similar to the incidence of death following recurrent MI. From a patient-oriented perspective, the goal is to reduce mortality and maintain quality of life, and given the similar impact of the 2 outcomes, avoiding bleeding after PCI should be considered as critical as reducing ischemic events. That said, the patient's perspective is important to consider in the risk-benefit balance, as they may value these outcomes differently than do clinicians, and their buy-in is important to ensure patient-centred care and treatment adherence.

Additional analyses from the included trials provide insights into the optimal timing of ASA discontinuation. The *post hoc* analysis of AUGUSTUS[59] showed a narrow tradeoff of an

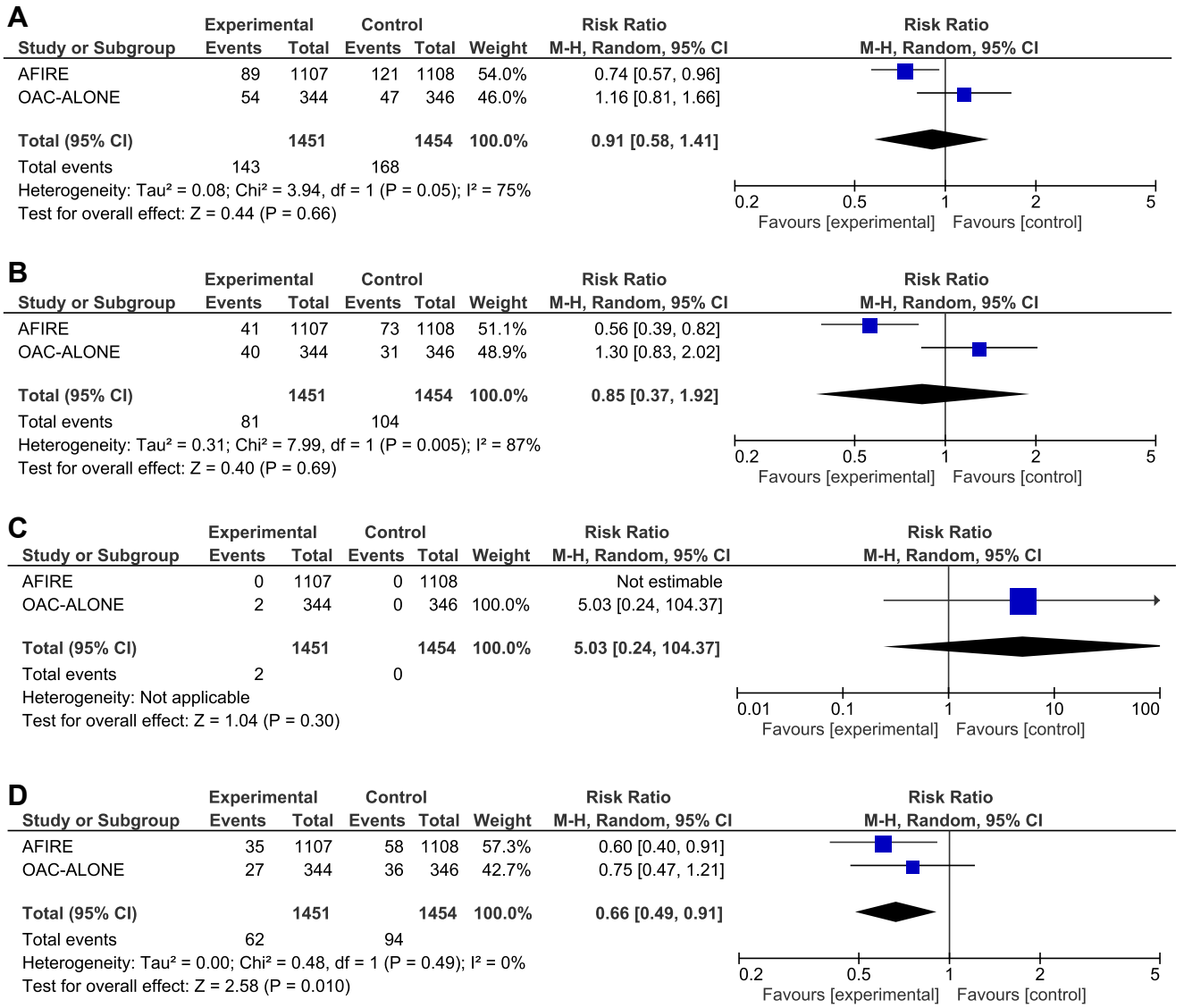

Figure 4. Forest plot for (**A**) major adverse cardiovascular events; (**B**) death, (**C**) stent thrombosis, and (**D**) bleeding 1 year after percutaneous coronary intervention. AFIRE, **A**trial **F**ibrillation and **I**schemic Events With **R**ivaroxaban in Patients With Stable Coronary Artery Disease; CI, confidence interval; df, degrees of freedom; M-H, Mantel-Haenszel; OAC-ALONE, **O**ptimizing **A**ntithrombotic **C**are in Patients With **A**trial Fibrillation and Coronary Stent.

~0.9% absolute reduction in thrombotic events and an ~0.9% increase in major bleeding events with ASA continuation up to 1 month among trial all-comers, followed by net harm after 30 days. Routine ASA discontinuation before 1 month should be the default approach, with the potential to continue ASA for 1 month or longer among patients at higher risk of stent thrombosis with low bleeding risk who may yet derive net benefit. Specifically, patients with a history of stent thrombosis, who were systematically excluded from all identified trials, or multiple thrombotic high-risk clinical or angiographic features, such as those outlined in the Canadian Cardiovascular Society antiplatelet guidelines, may benefit.[60-62] This approach is also in line with the latest European recommendations for patients with high-risk ischemic features.[60]

In terms of $P2Y_{12}$ inhibitor selection, clopidogrel was the predominant $P2Y_{12}$ inhibitor used in the included RCTs, and no trial randomized patients to different $P2Y_{12}$ inhibitors. One prior meta-analysis included observational comparisons of potent $P2Y_{12}$ inhibitors (prasugrel and ticagrelor) to clopidogrel and found an associated increased risk of major bleeding without reducing MACE.[33] In the absence of evidence for their superiority in this population, use of potent $P2Y_{12}$ inhibitors should be restricted to those patients with clopidogrel intolerance or allergy, documented clopidogrel resistance identified by platelet-function or pharmacogenomic testing, recurrent MACE on clopidogrel, or who are part of a research protocol.

Our results are in accordance with previous meta-analyses on this topic. Overall, the most recent[12,13,24,46] showed similar results, with a significant and conclusive reduction of bleeding with DPT, compared to triple therapy. We found a small but significant increase in stent thrombosis among those randomized to DPT, with a similar signal identified in prior

meta-analyses.[43,46] The study by Potpara et al.[12] showed a decrease in bleeding and an increase in MACE with the use of DPT, and Khan et al.[24] also found a decrease in bleeding, but results regarding ischemic events were less convincing. Capodanno et al.[1] encouraged the use of an initial course of triple-antithrombotic therapy in selected patients, whereas Lopes et al.[46] emphasized the importance of avoiding such an association. However, some methodological differences should be highlighted when comparing the present study to the most recent meta-analysis including the 4 major RCTs. First, RoB assessments in the present study were conducted by independent reviewers rather than a trial author. Second, the present study employed the GRADE rating of certainty of evidence, which was not done in prior reviews. Third, we added a summary-of-findings table, putting the results in context in absolute terms, to properly weigh tradeoffs. Fourth, the current analysis brings additional information regarding medically treated patients with no PCI.

As for our second question, few trials have assessed antithrombotic strategies in patients with chronic CAD and remote ACS or revascularization. For a long time, debate remained as to whether antiplatelet therapy should be continued chronically after the index event, or whether OAC monotherapy would suffice. Only the OAC-ALONE[54] and AFIRE[55] studies have addressed this question directly, with conflicting results. The main differences between the 2 trials are the premature termination of the OAC-ALONE trial, and the use of OAC in only one-quarter of the patients, in contrast to the exclusive use of rivaroxaban in the AFIRE study. Both trials were conducted in Japan, where OAC dosing differs from that in non-Asian countries, particularly for rivaroxaban, due to population-level pharmacokinetic and pharmacodynamic differences. [63] Overall, the AFIRE study had a lower RoB and provided high-certainty evidence for the superiority of OAC monotherapy, compared with DPT, with respect to bleeding. This finding is further supported by indirect evidence from the pre-stent era demonstrating similar thrombotic outcomes and fewer bleeds with VKA monotherapy, compared with ASA plus VKA post-MI.[64] Overall, 1 year after the index procedure, OAC monotherapy with the omission of an antiplatelet agent seems to decrease the risk of bleeding. However, only low-certainty evidence remains for death and MACE.

Limitations

Our study results should be contextualized based on several limitations. First, we only had access to published trial-level data, and therefore certain subgroup analyses, such as analyses based on thrombotic risk or PCI complexity, were not possible. Second, only one included trial (AUGUSTUS) directly compared DOAC to VKA therapy, and DPT to triple-antithrombotic therapy, whereas all others compared DOAC-based DPT to VKA-based triple antithrombotic therapy. Despite this issue, results were consistent between trials. Finally, only 2 conflicting trials (with data limited to Japanese populations) were available for the comparison of patients with AF and remote ACS and/or PCI, and further trials may meaningfully change the pooled estimates for MACE. Future trials are required to address the following knowledge gaps: timing of aspirin discontinuation after PCI, as part of the DPT strategy; safety of potent P2Y12 inhibitors in combination with chronic OAC; safety and efficacy of DPT in patients undergoing complex PCI (who were underrepresented in trials); and development of tools to tailor antithrombotic strategies based on individual ischemic and bleeding risk in this population.

Conclusion

In patients with AF and recent PCI or ACS, DPT reduces major bleeding, but it increases stent thrombosis without increasing MACE or all-cause death. A tailored approach should be considered, as special attention should be given to patients with high ischemic risk in whom triple-antithrombotic therapy could be a reliable initial option. In patients with AF and remote PCI or ACS, OAC monotherapy reduces major bleeding and seems not to increase thrombotic events. After 1 year, an OAC may be continued as a monotherapy.

Ethics Statement

The research being reported has adhered to the relevant ethical guidelines. This study did not require approval by an ethics review board as no individual patient data was used.

Patient Consent

The authors confirm that patient consent is not applicable to this article. This meta-analysis used publicly-available aggregate data; therefore, patient consent was not required.

Funding Sources

The present work was funded by the Canadian Cardiovascular Society (CCS) to support the development of the 2023 Canadian Cardiovascular Society Antiplatelet Guidelines Update.

Disclosures

The authors have no conflicts of interest to disclose.

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Supplementary Material

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