Cardiovascular Revascularization Medicine 36 (2022) 99–106

Contents lists available at ScienceDirect

Cardiovascular Revascularization Medicine

Antithrombotic Therapy With or Without Aspirin After Percutaneous Coronary Intervention or Acute Coronary Syndrome in Patients Taking Oral Anticoagulation: A Meta-Analysis and Network Analysis of Randomized Controlled Trials

Róisín Colleran [a], Robert A. Byrne [b,c,*], Gjin Ndrepepa [a], Hector A. Alvarez-Covarrubias [a,d], Katharina Mayer [a], Constantin Kuna [a], Himanshu Rai [a], Adnan Kastrati [a,e], Salvatore Cassese [a]

[a] Deutsches Herzzentrum München, Technische Universität München, Munich, Germany
[b] Dublin Cardiovascular Research Institute, Mater Private Hospital, Dublin, Ireland
[c] School of Pharmacy and Biomolecular Science, Royal College of Surgeons in Ireland, Dublin, Ireland
[d] Hospital de Cardiología, Centro Médico Nacional Siglo XXI, IMSS, Mexico City, Cd. de México, Mexico
[e] German Center for Cardiovascular Research (DZHK), Partner Site Munich Heart Alliance, Munich, Germany

ARTICLE INFO

Article history:
Received 26 January 2021
Received in revised form 14 May 2021
Accepted 14 May 2021

Keywords:
Acute coronary syndrome
Anticoagulation
Antithrombotic therapy
Aspirin
Percutaneous coronary intervention

ABSTRACT

Introduction: Trials investigating aspirin omission in patients taking oral anticoagulation (OAC) after percutaneous coronary intervention (PCI) or acute coronary syndrome (ACS) were not powered to assess rates of major bleeding or ischemic events.
Methods: We performed an updated meta-analysis and network analysis of randomized trials comparing treatment with or without aspirin in patients taking OAC and a P2Y12-inhibitor after PCI or ACS. The primary outcome was TIMI major bleeding.
Results: Five trials enrolling 11,542 patients allocated to antithrombotic regimens omitting (n = 5795) or including aspirin (n = 5747) were included. Aspirin omission was associated with a lower risk of TIMI major bleeding (RR = 0.56, 95% CI [0.44–0.71]; P < 0.001) but a trend towards a higher risk of MI (RR = 1.21, 95% CI [0.99–1.47]; P = 0.06), which was significantly higher when only non-vitamin K antagonist OAC (NOAC)-based trials were considered ($P_{interaction}$ = 0.02). The risk of stent thrombosis was comparable with both strategies (RR = 1.29, 95% CI [0.87–1.90]; P = 0.20), with a trend towards a higher risk of ST with aspirin omission when only NOAC-based trials were considered ($P_{interaction}$ = 0.06). Risks of stroke and death were similar with both strategies. Network meta-analysis ranked dabigatran (low dose) without aspirin as the best strategy for bleeding reduction (P-score = 0.86) and apixaban with aspirin as the best strategy for MI reduction (P-score = 0.66).
Conclusions: In patients taking OAC after PCI or ACS, aspirin omission is associated with a lower risk of TIMI major bleeding, with a numerically increased risk of MI, which is statistically significant when only NOAC-based trials are considered. This supports individualization of the treatment regimen based on patient risk.

1. Introduction

Patients with an indication for oral anticoagulation (OAC) who undergo percutaneous coronary intervention (PCI) or have an acute coronary syndrome (ACS) continue to pose a therapeutic dilemma with respect to antithrombotic therapy. The most common indication for OAC in such patients is atrial fibrillation (AF), which affects up to 15% of patients undergoing PCI [1]. Such patients are often treated with a period of triple antithrombotic therapy, consisting of OAC plus dual antiplatelet therapy (DAPT) to reduce the risks of thromboembolism with AF and stent thrombosis (ST) or myocardial infarction (MI) after PCI, respectively. However, such a strategy is associated with an increased risk of bleeding. Whether a period of triple therapy is necessary in such patients has not been fully elucidated.

Randomized trials have compared antithrombotic regimens based on dual (without aspirin) versus triple (with aspirin) therapy after PCI/ACS in patients taking OAC [2–6]. All trials were powered to show either superiority or non-inferiority of dual- versus triple-therapy with respect to bleeding. However, only two of these trials showed a

* Corresponding author at: Cardiovascular Research Institute Dublin, Mater Private Hospital, Eccles St., Dublin 7, Ireland.
E-mail address: robert.byrne@materprivate.ie (R.A. Byrne).

https://doi.org/10.1016/j.carrev.2021.05.013

reduction in major bleeding with aspirin omission [3,5]. Moreover, the increased risk of ischemic events was not comprehensively evaluated: although no statistically significant increase in thrombotic events was observed in the groups without versus with aspirin, no trial was powered to rule out such a difference.

Against this background, we performed an updated meta-analysis of randomized trials comparing antithrombotic regimens without or with aspirin in PCI/ACS patients taking OAC to investigate the risk of major bleeding and thrombotic outcomes.

2. Methods

2.1. Data sources and searches

We updated the literature search from a previous systematic review [7]. We searched Medline, EMBASE, the Cochrane Central Register of Controlled Trials (CENTRAL), scientific session abstracts and relevant websites without restricting language or publication status. The references listed in all eligible studies were checked to identify further citations. The search strategy is shown in the Supplementary appendix. Inclusion criteria were: (1) randomized clinical trial, (2) allocation to an antithrombotic regimen including OAC and a P2Y12-inhibitor with versus without aspirin after PCI with stent implantation or ACS, and (3) follow-up duration ≥6 months. The last search was performed on 26th January 2021.

2.2. Study selection and quality assessment

Publications were independently assessed for eligibility by two investigators (RC and SC) at title and/or abstract level. Divergences were resolved by a third investigator (AK). Studies that met eligibility criteria were selected for further analysis. Freedom from bias was independently evaluated for each study by the same investigators in accordance with The Cochrane Collaboration method [8]. Composite quality scores were not assigned [9].

2.3. Data extraction and outcome variables

Data was extracted from studies by two investigators (RC and SC) and divergences were resolved by a third investigator (AK). The primary outcome was Thrombolysis in Myocardial Infarction (TIMI) major bleeding [10,11]. The main secondary outcome was MI. Other outcomes included ST, all-cause death, and stroke. Aggregated outcomes data from selected studies were analyzed according to the intention-to-treat or the "modified" intention-to-treat population (the latter was based on data for all participants who underwent randomization and received at least one dose of a trial drug during the treatment period) as per the protocol of each included trial. All outcomes were extracted at maximum follow-up and in accordance with the definitions provided in the individual trial protocols.

2.4. Data synthesis and analysis

The means of continuous variables and the frequencies or percentages of categorical variables were extracted for exploratory purposes from baseline characteristics of participants enrolled in each study. Risk ratios (RRs) with 95% confidence intervals [95% CI] and P-values were used to compare outcomes of interest between the group assigned to antithrombotic regimens without (dual therapy, experimental) or with aspirin (triple therapy, control). RRs were pooled using the Mantel-Haenszel random-effect model (package *meta*). P-values <0.05 were considered statistically significant. The weighted median follow-up duration was calculated based on the sample size of each study. Heterogeneity between trials was quantified using the I^2 statistic accompanied by a chi^2 test: I^2 values of approximately 25%, 50% and 75% were considered to indicate low, moderate or high heterogeneity, respectively [8]. We also estimated the between-study variance with the Paule-Mandel estimator for τ^2 and displayed the 95% prediction interval of each pooled estimate [12]. Treatment effect was not assessed in trials in which no events were reported within groups. The possibility of small study effects resulting from publication bias or other biases was examined for the main outcomes by means of visual inspection of funnel plots of the RRs of individual trials against their standard errors. We also performed a test of asymmetry for the main outcomes. We performed several sensitivity analyses: 1) using a chi^2 test for treatment-by-subgroup interaction, we tested whether the administration of a vitamin K antagonist (VKA) in the investigational arm (as in the WOEST trial) [2] was associated with significant changes in the estimated RRs for major bleeding, MI and ST. 2) An influence analysis, in which meta-analysis estimates are computed omitting one study at a time, was performed for the main outcomes and we tested a possible statistical difference between the estimated overall RRs for main outcomes and RRs generated after omitting each trial. 3) To further account for the different treatment regimens investigated in this study, we performed a frequentist network meta-analysis (package *netmeta*) for the main outcomes, providing a treatment ranking based on the P-scores according to Rucker et al. [13], which measure the mean extent of certainty that a treatment is better than the competing treatments. 4) Finally, a random effects meta-regression analysis assessed the modification of treatment effect for main outcomes according to age, proportion of females, diabetics, ACS at admission, drug-eluting stents (DES) implanted, CHA_2DS_2-VASc score, and duration of aspirin treatment in the dual-therapy arm, as reported in each study. This study was performed in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) statement (Supplementary Table 1) [14]. All analyses were completed in R (version 3.3.2; R Foundation for Statistical Computing, Vienna, Austria) or in Stata 13.1 (STATA Corp, College Station, Texas, USA).

3. Results

3.1. Eligible studies

The flow diagram for the trial selection process is shown in Supplementary Fig. 1. Five randomized trials met eligibility criteria, including 11,542 randomized patients, of whom data was available for 11,532: 5790 allocated to regimens without aspirin and 5742 allocated to regimens with aspirin. All were published as full-length manuscripts. The indication for OAC was AF in all but the WOEST trial [2], which included patients with any indication for OAC. Main trial-level characteristics are shown in Supplementary Table 2.

AUGUSTUS had a 2 × 2 factorial design, with four treatment groups, whereby patients were allocated to treatment with either apixaban (5 mg twice daily [or 2.5 mg twice daily in the presence of dose-reduction criteria]) or a VKA plus a P2Y12-inhibitor plus either placebo or aspirin [5]. AUGUSTUS was the only trial in which a control (triple therapy with aspirin) group was treated with a NOAC. In ENTRUST-AF PCI, patients were allocated to treatment with edoxaban (60 mg daily) plus a P2Y12-inhibitor or a VKA plus DAPT [6]. In PIONEER AF-PCI, one group was allocated to treatment without aspirin, consisting of low-dose rivaroxaban (15 mg once daily) plus a P2Y12-inhibitor and two groups were allocated to treatment without aspirin, one with very low-dose rivaroxaban (2.5 mg twice daily) plus DAPT and the other with a VKA plus DAPT [4]. The latter two groups were combined in the control group in the current analysis. In the RE-DUAL PCI trial, two groups were allocated to therapy without aspirin, consisting of either low-dose dabigatran (110 mg twice daily) or high-dose dabigatran

(150 mg twice daily) plus a P2Y12-inhibitor and one group was allocated to a VKA plus DAPT [3]. In this trial, patients in Japan could be assigned only to the 110-mg dual-therapy group in accordance with restrictions with respect to dabigatran labelling in that country. For the purpose of this meta-analysis, risk estimates associated with either a regimen of low-dose or high-dose dabigatran plus a P2Y12-inhibitor versus triple-therapy were derived from this study separately and then pooled in the summary estimates for each outcome of interest, as previously described [15]. WOEST was the only trial in which the OAC was a VKA in both the experimental and control groups [2].

The choice of P2Y12-inhibitor was at the discretion of the operator in all but two trials, in which it was restricted to clopidogrel [2] and clopidogrel or ticagrelor [3], respectively. All but two trials reported the incidence of permanent discontinuation of trial drugs: in the aspirin omission group, it ranged between 8.8% and 20.5%, while in the group with aspirin, it ranged between 13.4% and 25.0%. The study-defined outcomes are displayed in Supplementary Table 3. The risk of bias with each study is reported in Supplementary Table 4.

Baseline characteristics are shown in Table 1. The majority of patients were male, median age was 70.2 years [interquartile range, 68.6; 70.4], and median CHA_2DS_2-VASc score was 3.8 [interquartile range, 3.3; 4.0]. Half of participants presented with ACS at the time of inclusion. Clopidogrel was the predominant P2Y12-inhibitor, prescribed in >90% of patients. Two thirds of participants who underwent PCI were treated with DES. In the aspirin omission group, aspirin was withdrawn, per protocol, after a median time of 5 days [interquartile range, 3; 5]. The weighted median follow-up available for the assessment of outcomes of interest was 9 months.

3.2. Clinical outcomes

3.2.1. Primary outcome

The risk of TIMI major bleeding was lower in patients allocated to an antithrombotic regimen without versus with aspirin (1.7% versus 3.0%, respectively; RR = 0.56, 95% CI [0.44–0.71]; P < 0.001, Fig. 1A). The number needed to treat to avoid one case of TIMI major bleeding with dual therapy was 76 patients [60–115]. The 95% prediction interval for this outcome was 0.49–0.71, without evidence of heterogeneity. The magnitude of the treatment effect for TIMI major bleeding did not change after the exclusion of the WOEST trial [2], in which patients received a VKA in both the investigational and control arms (RR = 0.56, 95% CI [0.43–0.72]; P for interaction [P_{int}] = 0.95, Supplementary Fig. 2A; Graphical Abstract).

3.2.2. Main secondary outcome

There was a trend towards a higher risk of MI in patients assigned to an antithrombotic regimen without versus with aspirin (3.6% versus 2.9%, respectively; RR = 1.21, 95% CI [0.99–1.47]; P = 0.057, Fig. 1B). The 95% prediction interval for this outcome was 0.92–1.59. The risk of MI was higher with dual therapy when the WOEST trial was excluded from the pooled estimate (RR = 1.25, 95% CI [1.02–1.52]; P_{int} = 0.019, Supplementary Fig. 2B; Graphical Abstract) [2]. In the latter case, the number needed to harm to cause one case of MI with dual therapy was 119 patients [66–724].

3.2.3. Other secondary outcomes

The risk of ST was comparable in patients assigned to an antithrombotic regimen without versus with aspirin (1.1% versus 0.8%, respectively; RR = 1.29, 95% CI [0.87–1.90]; P = 0.20, Fig. 2A). The 95% prediction interval for this outcome was 0.66–2.51, without significant heterogeneity. There was a trend towards a higher risk of ST with dual therapy when the WOEST trial was excluded from the pooled estimate (RR = 1.47, 95% CI [1.00–2.17]; P_{int} = 0.06, Graphical Abstract) [2]. The risk of definite ST occurred was also comparable in both groups (1.0% versus 0.8%, respectively; RR = 1.24, 95% CI [0.77–2.02]; P = 0.38, data available for 7654 patients).

The risk of all-cause death was comparable between patients assigned to an antithrombotic regimen without versus with aspirin (4.0% versus 3.7%, respectively; RR = 1.01, 95% CI [0.79–1.30]; P = 0.91, Fig. 2B), with a similar risk of cardiac death in both groups (2.6% versus 2.3%, respectively; RR = 1.10, 95% CI [0.86–1.40]; P = 0.44, data available for 10,738 patients).

Finally, the risk of stroke was comparable between patients assigned to an antithrombotic regimen without versus with aspirin (1.1% versus 1.2%, respectively; RR = 0.96, 95% CI [0.69–1.34]; P = 0.44, Fig. 2C), with a similar risk of hemorrhagic stroke in both groups (0.4% versus 0.6%, respectively; RR = 0.59, 95% CI [0.30–1.15]; P = 0.12).

3.3. Assessment of risk of bias and sensitivity analyses

The risk of bias due to small study effect was judged to be low by visual inspection of contour-enhanced funnel plots of main

Table 1
Main baseline characteristics of patients enrolled in included trials.

Trial	Patients, n	Age, years	Females, %	Diabetes, %	CHA_2DS_2-$VASc_2$ score	Presentation with ACS, %	Treatment with DES versus BMS only	Treatment with clopidogrel, %	Treatment with ticagrelor or prasugrel, %
AUGUSTUS	4614	70.7	1337 (29.0)	1678 (36.4)	3.9	2811/4595 (61.2)	NR	4165/4496 (92.6)	331/4496 (7.4)
ENTRUST AF-PCI	1506	69.5	386 (25.6)	517 (34.3)	4.0	777 (51.6)	NR	1391 (92.4)	114 (7.6)
PIONEER AF-PCI	2124	70.1	543 (25.6)	624 (29.4)	4.0	951/2095 (45.4)	1403 (66.2) vs. 675 (31.9)	1974 (92.9)	120 (5.6)
RE-DUAL PCI	2725	70.9	655 (24.0)	993 (36.4)	3.7	1375 (50.5)	2251/2717 (82.8) vs. 404/2717 (14.9)	2397 (88.0)	293 (10.8)
WOEST	573	69.9	115/563 (20.4)	140/563 (24.9)	2.9[a]	155/563 (27.5)	364 (64.5) vs. 175 (31.0)	557/557 (100)	0/557 (0)

Data are reported as counts (proportions) or mean. ACS: acute coronary syndrome.
Official titles and acronyms: AUGUSTUS: A Study of Apixaban in Patients With Atrial Fibrillation, Not Caused by a Heart Valve Problem, Who Are at Risk for Thrombosis (Blood Clots) Due to Having Had a Recent Coronary Event, Such as a Heart Attack or a Procedure to Open the Vessels of the Heart; ENTRUST AF-PCI: EdoxabaN TReatment versUS VKA in paTients with AF undergoing PCI; PIONEER AF-PCI: A Study Exploring Two Strategies of Rivaroxaban and One of Oral Vitamin K Antagonist in Patients With Atrial Fibrillation Who Undergo Percutaneous Coronary Intervention; RE-DUAL PCI: Randomized Evaluation of Dual Antithrombotic Therapy with Dabigatran versus Triple Therapy with Warfarin in Patients with Nonvalvular Atrial Fibrillation Undergoing Percutaneous Coronary Intervention; WOEST: What is the Optimal antiplatElet and anticoagulant therapy in patients with oral anticoagulation and coronary StenTing.
[a] $CHADS_2$ score.

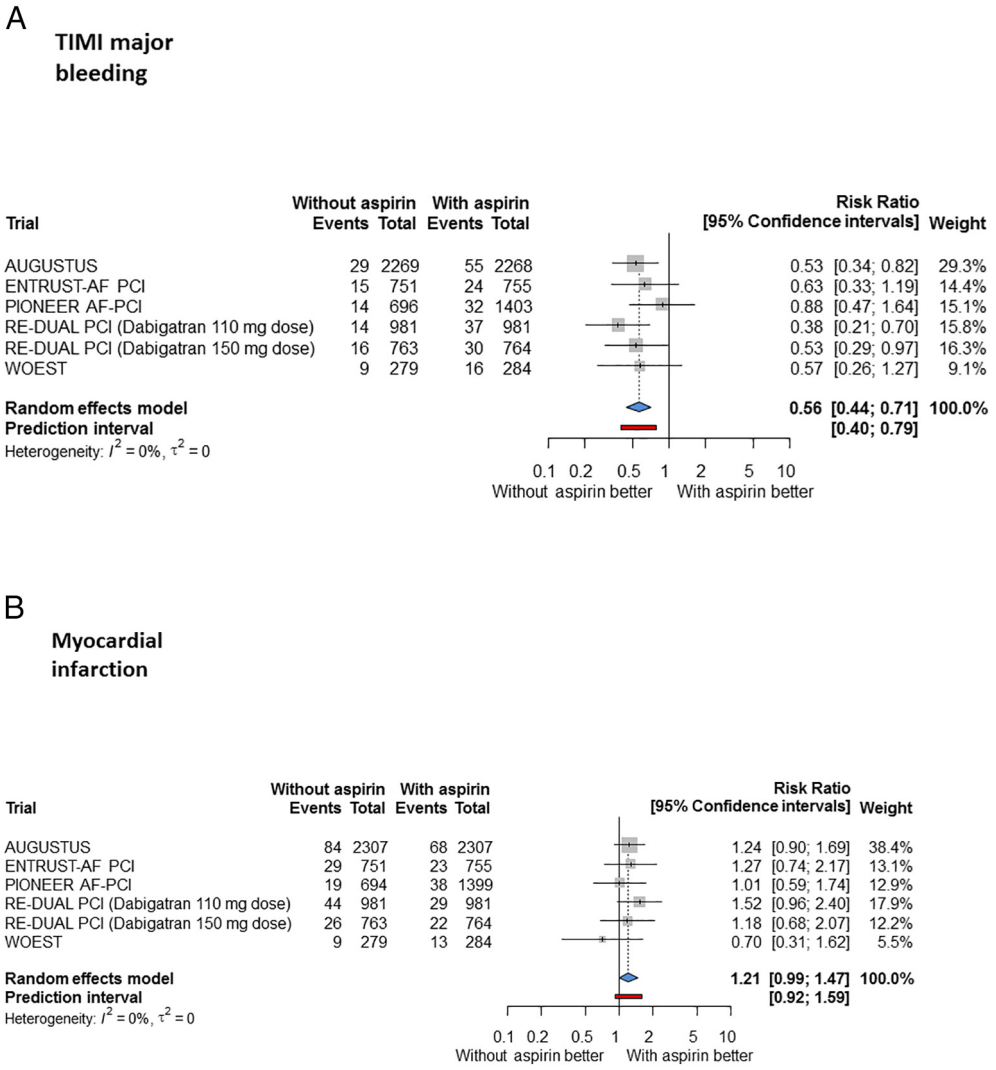


Fig. 1. Forest plots for the primary and main secondary outcome Risk ratio for TIMI major bleeding (Panel A) and myocardial infarction (Panel B) in patients allocated to an antithrombotic regimen without or with aspirin.

outcomes (Supplementary Fig. 3, Panels A–B). The results were confirmed by a linear regression test of funnel plot asymmetry based on sample size, although the proficiency of this test for these outcomes is reduced due to the relatively small number of studies available for this analysis.

In the influence analysis for TIMI major bleeding, no single study significantly altered the direction of the summary RR for this outcome. In contrast, in the influence analysis for MI, the sequential omission of the PIONEER AF-PCI and WOEST trials from summary estimates resulted in a higher risk of this outcome among patients allocated to antithrombotic regimens without aspirin as compared with the control therapy [2,4]. However, there was no evidence of a statistical difference between the estimated overall RRs for these outcomes and RRs generated after omitting each trial (Supplementary Fig. 2, Panels A–B).

The networks of treatment strategies for TIMI major bleeding and MI associated with an antithrombotic regimen without or with aspirin are shown in Supplementary Fig. 4A and B, respectively. The network meta-analysis for TIMI major bleeding ranked the antithrombotic regimen consisting of dabigatran 110 mg twice daily plus a P2Y12-inhibitor for 12 months as the best treatment option (P-score = 0.86) and the regimen consisting of a VKA plus DAPT (for 1–12 months after BMS-implantation and 12 months after DES-implantation or ACS) as the worst (P-score = 0.07). The network meta-analysis for MI ranked the antithrombotic regimen consisting of apixaban 5 mg (or 2.5 mg in the presence of dose-reduction criteria) twice daily plus DAPT for 6 months as the best treatment option (P-score = 0.66) and the regimen consisting of dabigatran 110 mg twice daily plus a P2Y12-inhibitor for 12 months as the worst (P-score = 0.30). The complete list of risk estimates for the outcomes tested with the network meta-analysis are provided in Supplementary Tables 5 and 6.

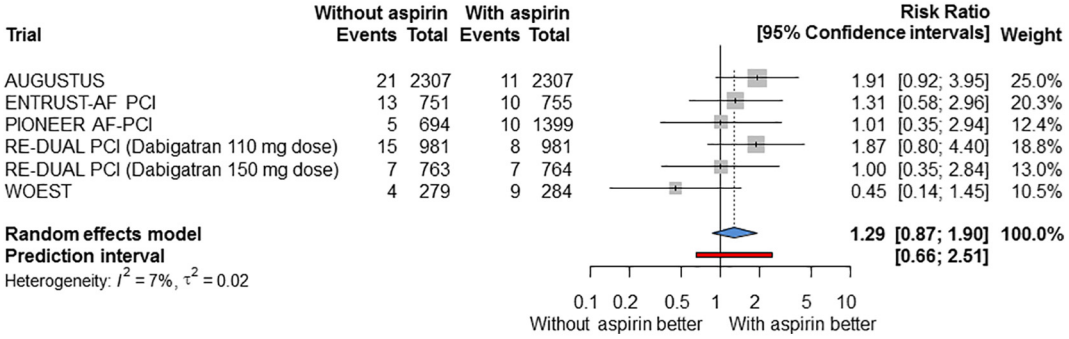
The treatment effect for TIMI major bleeding and MI was independent of age (P_{int} = 0.58 and 0.57), proportion of females (P_{int} = 0.98 and 0.19), diabetics (P_{int} = 0.29 and 0.48), ACS on admission (P_{int} = 0.64 and 0.13), or DES implanted (P_{int} = 0.60 and 0.14), as well as CHA_2DS_2-VASc score (P_{int} = 0.50 and 0.29) and duration of aspirin treatment in the dual-therapy arm (P_{int} = 0.59 and 0.62).

4. Discussion

The main findings of this meta-analysis can be summarized as follows: in patients taking OAC after PCI/ACS,

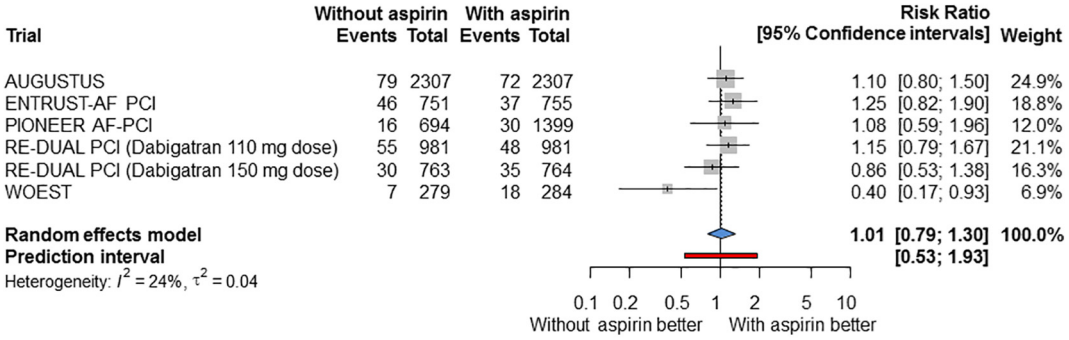
A

Stent thrombosis



B

All-cause death



C

Stroke

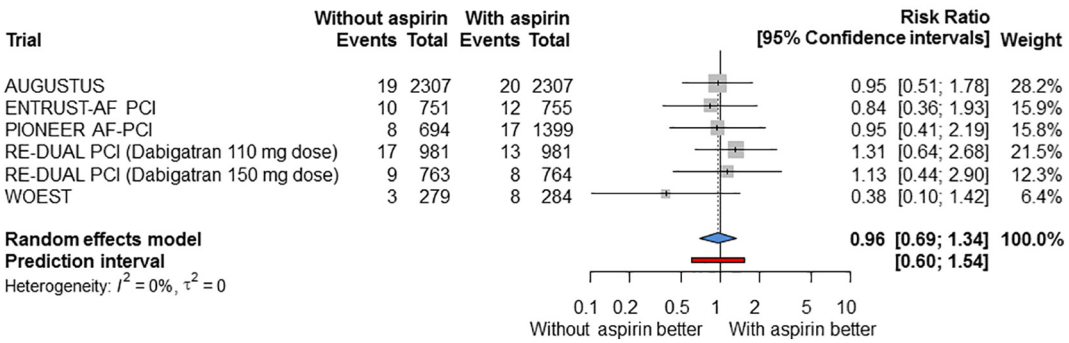


Fig. 2. Forest plots for other secondary outcomes Risk ratio for stent thrombosis (Panel A), all-cause death (Panel B) and stroke (Panel C) in patients allocated to an antithrombotic regimen without or with aspirin.

1) Aspirin omission is associated with a 44% relative reduction in the risk of TIMI major bleeding compared with aspirin-inclusion, an effect that does not change when including only NOAC-based trials;
2) The bleeding reduction associated with aspirin omission is offset by a signal towards a higher risk of thrombotic events. Specifically, a trend towards a higher risk of MI was observed in patients treated with aspirin omission versus aspirin-inclusion, an effect that was statistically significant when including only NOAC-based trials. There was also a trend towards a higher risk of ST when including only NOAC-based trials.
3) Network meta-analysis of all treatment combinations investigated ranked dabigatran (low dose) without aspirin (dual therapy) as the best treatment option for bleeding reduction and apixaban (standard dose) with aspirin (triple therapy) as the best treatment option for MI reduction (P-score = 0.66).

The reduction in the risk of major bleeding defined according to TIMI classification observed in this meta-analysis is important. All included trials used liberal bleeding definitions for their bleeding primary endpoint (shown in Supplementary Table 3) in order to power for bleeding. In WOEST, the primary endpoint was any bleeding and although the rate was lower with aspirin omission, rates of major bleeding did not significantly differ between treatment groups [2]. In PIONEER AF-PCI, the primary endpoint was the composite of TIMI major or minor bleeding or bleeding requiring medical attention. While the rate of this endpoint was significantly lower in the group without aspirin, the difference was driven by bleeding requiring medical attention, with no differences in TIMI major or even TIMI minor bleeding between treatment groups [4]. In RE-DUAL PCI, AUGUSTUS, and ENTRUST-AF PCI, the primary endpoint was the composite of International Society on Thrombosis and Haemostasias (ISTH) major bleeding and clinically relevant non-major bleeding [3,5,6]. Indeed, RE-DUAL PCI and AUGUSTUS were the only trials to show significantly lower rates of TIMI major bleeding in patients treated with antithrombotic therapy with aspirin versus without aspirin.

Arguably, the finding that reducing the number of antithrombotic agents reduces bleeding events comes as no surprise. However, whether this benefit is offset by an increased risk of thrombotic events remains poorly investigated. No trial considered efficacy in preventing thrombotic events in its primary hypothesis testing, thus, no trial was powered to reliably detect or outrule such differences. In RE-DUAL PCI, a signal for increased risk of thrombotic events was observed in the aspirin omission group: non-inferiority criteria with respect to the composite of death or thromboembolic events (defined as MI, stroke, or systemic embolism) in the combined groups without aspirin (110-mg and 150-mg dabigatran groups) versus combined groups with aspirin were not met, driven by higher event rates in the 110-mg dose group, with a trend towards statistical significance [3]. There was also a trend towards higher rates of MI in this group. Consistent with this, our meta-analysis found that a strategy of low-dose dabigatran (110 mg twice daily) plus a P2Y12-inhibitor for 12 months was the antithrombotic regimen associated with the lowest risk of major bleeding but the highest risk of MI. Another recent meta-analysis that investigated dual versus triple antithrombotic therapy in NOAC-treated patients with atrial fibrillation undergoing PCI showed consistent findings: low dose dabigatran plus a P2Y12-inhibitor was associated with the highest risk of MACE of all treatment combinations investigated [16].

In contrast, the antithrombotic strategy associated with the highest risk of TIMI major bleeding was a VKA plus DAPT (recommended for 1–12 months after BMS-implantation and 12 months after DES-implantation or ACS) and the regimen associated with the lowest risk of MI was apixaban (standard dose) plus DAPT (for 6 months). It is notable that the latter was one of only two strategies with aspirin investigated that included a NOAC rather than a VKA and the only one to include a NOAC at an approved dose for prevention of stroke and systemic embolism. In combination, these findings support the recommendation that a NOAC at the full recommended dose for stroke prevention should be used in preference to a VKA in eligible patients on concomitant antiplatelet therapy in European guidelines for clinical practice (class I recommendation, level of evidence A), with consideration of reduced dose rivaroxaban (15 mg daily) or dabigatran (110 mg twice daily) for the duration of antiplatelet therapy only in patients in whom concerns regarding bleeding risk outweigh those regarding the risks of ST or ischemic stroke (class IIa recommendation, level of evidence B) [17,18]. Recent North American expert consensus recommendations are consistent with European guidelines in this respect [19].

Aspirin use in patients undergoing PCI has been the standard of care since the first coronary angioplasty performed by Andreas Grüntzig in 1977. In the era of coronary stenting, DAPT consisting of aspirin and a P2Y12-inhibitor was shown to reduce ST and MI compared with aspirin-monotherapy or aspirin and VKA [20,21]. While considerable progress with respect to improved stent technologies and more potent P2Y12-inhibitors and has been made in recent years, complete omission of aspirin in patients undergoing PCI has not been investigated in a large-scale randomized trial. It is important to note that in the trials included in the current meta-analysis, all patients were taking aspirin at the time of PCI, with discontinuation at various intervals post-procedure, ranging from 0 to 14 days per individual trial protocols (median interval of 5 days [interquartile range, 3; 5]). Although we found no statistical interaction between aspirin duration in patients in the aspirin omission group and treatment effects, the actual duration of therapy could not be reliably investigated as it was not reported in every trial.

All of the data synthesized appeared to show a trade-off between bleeding reduction and increased thrombotic risk, making adjudication of overall patient benefit challenging. In this respect, all-cause death might be a robust indicator of net clinical benefit. In our analysis, we observed a neutral treatment effect with an antithrombotic regimen without or with aspirin. Ultimately, this suggests that either approach may be justified depending on the clinical context, and that a one-size-fits-all approach cannot be systematically recommended. This is in keeping with recommendations of current clinical practice guidelines in Europe and expert consensus in North America: aspirin therapy is recommended in the peri-procedural period (up to 1 week) in all patients who undergo stenting, with consideration of early discontinuation in patients in whom bleeding risk predominates and consideration of longer therapy as an alternative in patients in whom thrombotic risk predominates [18,19,22].

Our meta-analysis is limited to the investigation of bleeding reduction strategies evaluated in the included trials. Three trials compared a strategy of NOAC plus a P2Y12-inhibitor in the aspirin omission group with a strategy of a VKA plus DAPT in the group with aspirin. Bearing in mind that bleeding was reduced with NOAC compared with VKA in randomized trials in patients not taking antiplatelet therapy [23], it is difficult to tease out whether the bleeding reduction is attributable to aspirin omission or the use of NOAC rather than VKA.

Furthermore, alternative bleeding reduction strategies in patients treated with aspirin have not been investigated. One such strategy would be to shorten the duration of triple therapy. There is wide variation with respect to the duration of aspirin used in the triple therapy groups among the included trials (1–3 months in RE-DUAL PCI; 6 months in AUGUSTUS; 1–12 months in WOEST, PIONEER AF-PCI, and ENTRUST-AF PCI). Given that there tend to be temporal differences in the occurrence of thrombotic events (which tend to be at highest risk of occurrence early after PCI before re-endothelialization is complete) and hemorrhagic events

(which may occur at a more stable rate over time), randomized trials are needed to investigate the optimal timing of cessation of triple therapy with respect to the bleeding-thrombosis trade-off. Another potential bleeding reduction strategy is the use of reduced-dose NOAC in patients treated with triple therapy. Although one included trial investigated such a strategy, a very low dose of NOAC (rivaroxaban 2.5 mg twice daily) not approved for prevention of stroke or systemic embolism was used in the triple therapy group, thus limiting its applicability to current practice [4].

Finally, this meta-analysis relies on aggregate study-level data. A meta-analysis based on individual patient data would be preferable in order to investigate the impact of different antithrombotic regimens on several features at patient (gender, comorbidities, clinical presentation, indication for OAC), procedural (anatomical or interventional complexity, stent type) and pharmacological (safety and efficacy profiles of different NOACs and P2Y12-inhibitors, genetic response to antithrombotic drugs) level. In addition, the P2Y12-inhibitor used in the majority of trials was clopidogrel and as such, results are not generalizable to patients treated with more potent P2Y12-inhibitors.

5. Conclusion

In patients taking OAC and a P2Y12-inhibitor after PCI or ACS, the risk of TIMI major bleeding is lower without than with aspirin. However, this is at the expense of a numerically increased risk of MI with aspirin omission, which is statistically significant when only NOAC-based trials are considered. There was no evidence of a treatment effect on mortality. Dabigatran (low dose) without aspirin was associated with the lowest risk of bleeding, whereas apixaban (standard dose) with aspirin was associated with the lowest risk of MI.

Funding

No external funding was provided for this study.

CRediT authorship contribution statement

Róisín Colleran: Conceptualization, Investigation, Writing – original draft. **Robert A. Byrne:** Writing – review & editing. **Gjin Ndrepepa:** Writing – review & editing. **Hector A. Alvarez-Covarrubias:** Writing – review & editing. **Katharina Mayer:** Writing – review & editing. **Constantin Kuna:** Writing – review & editing. **Himanshu Rai:** Writing – review & editing. **Adnan Kastrati:** Conceptualization, Writing – review & editing. **Salvatore Cassese:** Conceptualization, Investigation, Supervision, Writing – review & editing.

Declaration of competing interest

RAB reports lecture fees/honoraria from B. Braun Melsungen AG and Biotronik and grants to the institution of prior employment from Celonova Biosciences, not related to the current work. All other authors declared no conflict of interest.

Acknowledgements

None.

Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.carrev.2021.05.013.

References

[1] Shanmugasundaram M, Dhakal BP, Murugapandian S, Hashemzadeh M, Paul T, Movahed MR. Outcomes of patients with atrial fibrillation undergoing percutaneous coronary intervention analysis of national inpatient sample. Cardiovasc Revasc Med. 2019;21:14–9.
[2] Dewilde WJ, Oirbans T, Verheugt FW, Kelder JC, De Smet BJ, Herrman JP, et al. Use of clopidogrel with or without aspirin in patients taking oral anticoagulant therapy and undergoing percutaneous coronary intervention: an open-label, randomised, controlled trial. Lancet. 2013;381(9872):1107–15.
[3] Cannon CP, Bhatt DL, Oldgren J, Lip GYH, Ellis SG, Kimura T, et al. Dual antithrombotic therapy with dabigatran after PCI in atrial fibrillation. N Engl J Med. 2017;377(16):1513–24.
[4] Gibson CM, Mehran R, Bode C, Halperin J, Verheugt FW, Wildgoose P, et al. Prevention of bleeding in patients with atrial fibrillation undergoing PCI. N Engl J Med. 2016;375(25):2423–34.
[5] Lopes RD, Heizer G, Aronson R, Vora AN, Massaro T, Mehran R, et al. Antithrombotic therapy after acute coronary syndrome or PCI in atrial fibrillation. N Engl J Med. 2019;380(16):1509–24.
[6] Vranckx P, Valgimigli M, Eckardt L, Tijssen J, Lewalter T, Gargiulo G, et al. Edoxaban-based versus vitamin K antagonist-based antithrombotic regimen after successful coronary stenting in patients with atrial fibrillation (ENTRUST-AF PCI): a randomised, open-label, phase 3b trial. Lancet. 2019;394:1335–43.
[7] Lopes RD, Hong H, Harskamp RE, Bhatt DL, Mehran R, Cannon CP, Granger CB, Verheugt FWA, Li J, Ten Berg JM, Sarafoff N, Gibson CM, Alexander JH. Safety and efficacy of antithrombotic strategies in patients with atrial fibrillation undergoing percutaneous coronary intervention: a network meta-analysis of randomized controlled trials. JAMA Cardiol 2019.
[8] Higgins JP, Altman DG, Gotzsche PC, Juni P, Moher D, Oxman AD, et al. The Cochrane Collaboration's tool for assessing risk of bias in randomised trials. BMJ. 2011;343:d5928.
[9] Juni P, Witschi A, Bloch R, Egger M. The hazards of scoring the quality of clinical trials for meta-analysis. JAMA. 1999;282(11):1054–60.
[10] Mega JL, Braunwald E, Mohanavelu S, Burton P, Poulter R, Misselwitz F, et al. Rivaroxaban versus placebo in patients with acute coronary syndromes (ATLAS ACS-TIMI 46): a randomised, double-blind, phase II trial. Lancet. 2009;374(9683):29–38.
[11] Sabatine MS, Antman EM, Widimsky P, Ebrahim IO, Kiss RG, Saaiman A, et al. Otamixaban for the treatment of patients with non-ST-elevation acute coronary syndromes (SEPIA-ACS1 TIMI 42): a randomised, double-blind, active-controlled, phase 2 trial. Lancet. 2009;374(9692):787–95.
[12] IntHout J, Ioannidis JP, Rovers MM, Goeman JJ. Plea for routinely presenting prediction intervals in meta-analysis. BMJ Open. 2016;6(7):e010247.
[13] Rucker G, Schwarzer G. Ranking treatments in frequentist network meta-analysis works without resampling methods. BMC Med Res Methodol. 2015;15:58.
[14] Moher D, Liberati A, Tetzlaff J, Altman DG, Group P. Preferred reporting items for systematic reviews and meta-analyses: the PRISMA statement. Ann Intern Med 2009;151(4):264–9, W64.
[15] Rucker G, Cates CJ, Schwarzer G. Methods for including information from multi-arm trials in pairwise meta-analysis. Res Synth Methods. 2017;8(4):392–403.
[16] Capodanno D, Di Maio M, Greco A, Bhatt DL, Gibson CM, Goette A, et al. Safety and efficacy of double antithrombotic therapy with non-vitamin K antagonist oral anticoagulants in patients with atrial fibrillation undergoing percutaneous coronary intervention: a systematic review and meta-analysis. J Am Heart Assoc. 2020;9(16):e017212.
[17] Knuuti J, Wijns W, Saraste A, Capodanno D, Barbato E, Funck-Brentano C, Prescott E, Storey RF, Deaton C, Cuisset T, Agewall S, Dickstein K, Edvardsen T, Escaned J, Gersh BJ, Svitil P, Gilard M, Hasdai D, Hatala R, Mahfoud F, Masip J, Muneretto C, Valgimigli M, Achenbach S, Bax JJ, Group ESCSD. 2019 ESC Guidelines for the diagnosis and management of chronic coronary syndromes. Eur Heart J 2019.
[18] Collet JP, Thiele H, Barbato E, Barthelemy O, Bauersachs J, Bhatt DL, Dendale P, Dorobantu M, Edvardsen T, Folliguet T, Gale CP, Gilard M, Jobs A, Juni P, Lambrinou E, Lewis BS, Mehilli J, Meliga E, Merkely B, Mueller C, Roffi M, Rutten FH, Sibbing D, Siontis GCM, Group ESCSD. 2020 ESC Guidelines for the management of acute coronary syndromes in patients presenting without persistent ST-segment elevation. Eur Heart J 2020.
[19] Angiolillo DJ, Bhatt DL, Cannon CP, Eikelboom JW, Gibson CM, Goodman SG, et al. Antithrombotic therapy in patients with atrial fibrillation treated with oral anticoagulation undergoing percutaneous coronary intervention: a North American perspective: 2021 update. Circulation. 2021;143(6):583–96.
[20] Schomig A, Neumann FJ, Kastrati A, Schuhlen H, Blasini R, Hadamitzky M, et al. A randomized comparison of antiplatelet and anticoagulant therapy after the placement of coronary-artery stents. N Engl J Med. 1996;334(17):1084–9.

[21] Leon MB, Baim DS, Popma JJ, Gordon PC, Cutlip DE, Ho KK, et al. A clinical trial comparing three antithrombotic-drug regimens after coronary-artery stenting. Stent Anticoagulation Restenosis Study Investigators. N Engl J Med. 1998;339(23):1665–71.

[22] Neumann FJ, Sousa-Uva M, Ahlsson A, Alfonso F, Banning AP, Benedetto U, et al. 2018 ESC/EACTS Guidelines on myocardial revascularization. Eur Heart J. 2019;40:87–165.

[23] Ruff CT, Giugliano RP, Braunwald E, Hoffman EB, Deenadayalu N, Ezekowitz MD, et al. Comparison of the efficacy and safety of new oral anticoagulants with warfarin in patients with atrial fibrillation: a meta-analysis of randomised trials. Lancet. 2014;383(9921):955–62.