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ORIGINAL ARTICLE
Thrombosis and antithrombotic therapy

Dual antiplatelet therapy duration after percutaneous coronary intervention in patients with indication to oral anticoagulant therapy. A systematic review and meta-analysis of randomized controlled trials

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Aims Optimal duration of dual antiplatelet therapy (DAPT) in patients with concomitant indication to oral anticoagulation (OAC) is still debated.

Methods and results A systematic review was performed on electronic databases to search for randomized controlled trials comparing an abbreviated or prolonged (≥3 months) DAPT regimen in patients with OAC and they were analysed in the framework of standard and network meta-analyses. Co-primary endpoints were major or clinically relevant non-major bleedings (MCRB) and major bleeding, while the composite of major adverse cardiovascular events (MACE) was the key safety endpoint. Five studies and 7 665 patients (abbreviated DAPT $n = 3\,843$; prolonged DAPT $n = 3\,822$) were included. Both MCRB and major bleeding were lower with abbreviated DAPT [risk ratio (RR) 0.69 (0.52–0.91); $P = 0.01$ and 0.70 (0.52–0.95); $P = 0.01$, respectively] while MACE [RR: 0.96 (0.70–1.33); $P = 0.6$], all-cause death, cardiovascular death, stent thrombosis, or myocardial infarction did not differ. Network meta-analysis showed that peri-procedural DAPT had the highest probability to prevent MCRB and major bleeding (97.1 and 92.0% respectively) when compared with both short (4–6 weeks) and longer (≥3 months) DAPT regimens. Sensitivity analyses and meta-regressions showed consistency in different clinical scenarios and suggested a larger bleeding reduction with $P2Y_{12}$ inhibitors vs. aspirin after DAPT discontinuation.

Conclusion In patients undergoing PCI with concomitant OAC indication, an abbreviated DAPT regimen reduced MCRB and major bleeding without increasing MACE or other ischaemic events. Peri-procedural DAPT and $P2Y_{12}$ inhibitor monotherapy after DAPT withdrawal appear to be the best strategies to optimize the bleeding and ischaemic risk tradeoff.

Trial registration. PROSPERO CRD284001

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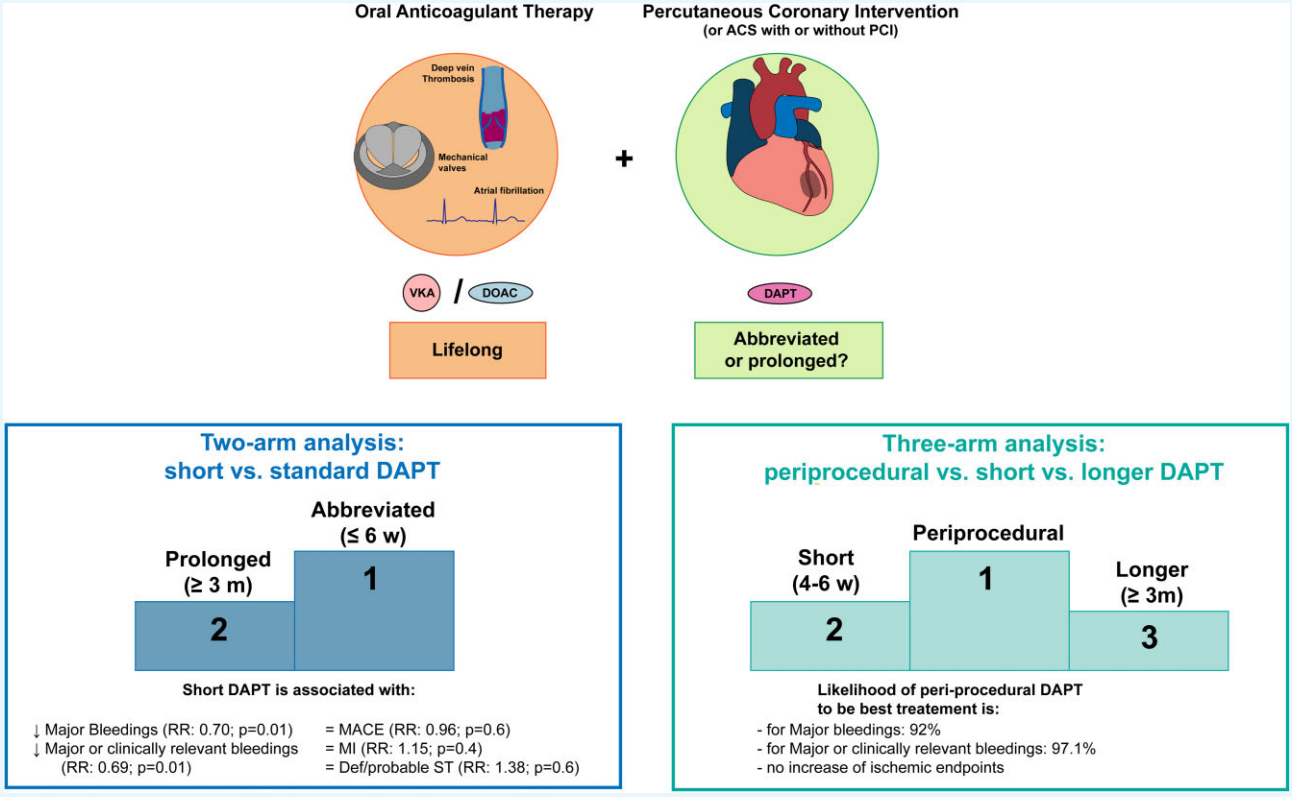
Graphical Abstract



Abbreviated vs. prolonged Dual Antiplatelet Therapy after Percutaneous Coronary Intervention or Acute Coronary Syndromes in patients with indication to long-term Oral Anticoagulation. This Figure shows the PICO summary for the analysis (Population of interest, Intervention, Comparison, and Outcomes). *DAPT*, Dual Antiplatelet Therapy; *MACE*, Major Adverse Cardiovascular Events; *MI*, Myocardial Infacrtion; *RR*, Relative Risk; *SUCRA*, Surface Under Cumulative Ranking curve Analysis

Keywords Dual antiplatelet therapy • Oral anticoagulant therapy • Percutaneous Coronary Intervention • Atrial fibrillation • Aspirin • P2Y12 inhibitor • Monotherapy

Introduction

Acute coronary syndrome (ACS) and percutaneous coronary intervention (PCI) mandate the use of dual antiplatelet therapy (DAPT) with aspirin and a $P2Y_{12}$ inhibitor to prevent recurrent coronary ischaemic events including stent thrombosis.[1,2] However, DAPT is inherently associated with an increased risk of bleeding that strongly and consistently impacts the patient's prognosis.[3,4] DAPT intensity and duration should therefore be finetuned.[5] Long-term oral anticoagulation (OAC), due to atrial fibrillation, deep vein thrombosis, or mechanical heart valves, is required in association with antiplatelet agents in up to 15% of patients undergoing PCI, which further increases the risk of bleeding events.[6] Several trials demonstrated the superiority of direct oral anticoagulants (DOAC) as compared with Vitamin-K antagonist (VKA) in patients undergoing PCI or with ACS who also receive concomitant DAPT.[7] However, the optimal duration of DAPT in this setting is still uncertain. Clinical trials and meta-analysis compared a short course of DAPT or DAPT limited with the peri-procedural/in-hospital phase after the index event to a longer DAPT duration. Reducing DAPT duration was associated with a reduction of bleeding, yet a signal for a small but significant excess of stent thrombosis and myocardial infarction was observed in some meta-analyses.[8,9] Importantly, owing to the design of some of these trials, that entangled DAPT strategy with a type of OAC (very short DAPT + DOAC vs. standard DAPT + VKA), it is not possible to disentangle the efficacy and safety of a shorter DAPT duration from that of the effect of DOAC therapy as compared with VKA. Hence, to fully understand the sole impact of DAPT duration after PCI in OAC-treated patients, only studies that randomized to different DAPT duration, irrespectively of concomitant OAC therapy, could help informing this treatment decision.

The aim of the present meta-analysis was to evaluate the impact of DAPT duration after PCI irrespective of OAC type in patients with indication for such treatment. We evaluated current evidence from clinical trials that randomly assigned patients to an abbreviated or prolonged (≥3 months) DAPT on top of OAC therapy. Moreover, in the setting of a network meta-analysis, we explored the additional impact of peri-procedural DAPT compared with longer treatments.

Methods

Literature search and study selection

Two authors (C.M., F.C.) independently searched electronic databases for articles published between 1 January 2000, and 1 September 2021; the full search strategy is in Supplementary Methods 1. Articles were initially screened by title and abstract content. In addition, the reference lists from all eligible studies were screened to identify any additional citations. Articles that reported clinical outcomes at follow-up of adult patients with concomitant indication to OAC and DAPT, and randomized to different DAPT duration, were included. Relevant study data were extracted by the first two Authors (C.M., F.C.); duplicate extractions and conflicting cases were discussed and adjudicated by a senior author (M.V.). The present work was conducted in accordance with the PRISMA and MOOSE guidelines.[10,11] The study protocol was submitted to PROSPERO (284 001).[12]

Eligibility criteria

Studies were considered eligible if they fulfilled all the following criteria:

i. Randomized controlled trials
ii. Included patients with concomitant indication to OAC and DAPT
iii. Compared a strategy of abbreviated (<3 months) vs. prolonged (≥ 3 months) DAPT duration

Since the type of OAC (i.e. DOAC or VKA) influences the incidence of bleeding, studies that randomized patients to concomitant treatment with short DAPT and DOAC vs. longer DAPT and VKA were excluded, as by design it was not possible to disentangle the impact of DAPT duration from the contribution of OAC type. The MASTER-DAPT study included both OAC and non-OAC patients and randomization was stratified according to this characteristic; in this case, only the former group was included.[13,14] Two authors (C.M., F.C.) independently assessed the quality of studies and risk of bias according to the Cochrane Collaboration Risk of Bias tool (RoB-2) across five domains: randomization process, deviations from intended intervention, missing outcome data, measurement of the outcome and selection of the reported results.[15] We used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) approach to assess confidence in estimates of effect (quality of evidence) associated with specific comparisons.[16] All studies included had appropriate ethical oversight and approval.

Study outcomes

The two co-primary endpoints of this analysis were (i) the occurrence of major bleedings and (ii) the composite of major or clinically relevant non-major bleedings (MCRB). Key safety endpoint was the composite of major adverse cardiovascular events (MACE) at the longest follow-up available. These endpoints were analysed as reported by each individual study. (Supplementary Table 1). As 3 studies reported MACE including all-cause deaths and 2 only cardiovascular deaths, an alternative MACE endpoint including only cardiovascular mortality was calculated by subtracting non-cardiovascular deaths from the study-reported MACE. Individual endpoints according to different definitions were also collected and analysed. Additional analyses were also planned and performed. First, we performed a sensitivity analysis including only subjects that underwent PCI; for the only study that included a minority of patients managed conservatively, data on the PCI cohort were available only for MCRB and for MACE. Second, we performed a Bayesian network meta-analysis to directly compare a peri-procedural (from index event to randomization) vs. short (4–6 weeks) vs. prolonged (≥ 3 months) DAPT duration regimen. Finally, a meta-regression was used to test the effect of baseline characteristics of interest on the endpoints of interest, including age, sex, ACS as an indication to DAPT, atrial fibrillation as an indication to OAC, DOAC prescription (vs. VKA), use of $P2Y_{12}$ inhibitor after DAPT discontinuation (vs. aspirin) and complexity of index PCI (measured as proportion of treated left-main stem and mean total stent length).

Statistical analysis

Risk ratios (RR) and 95% Confidence intervals (CI) were used as summary statistics for outcomes of interest and were calculated using both a fixed- and a random-effect model according to DerSimonian and Laird.[17] Statistical heterogeneity of exposure was assessed by calculating the I^2 index which summarizes the amount of variance among studies beyond chance. Heterogeneity was considered low if $I^2 < 25\%$, moderate if $I^2 < 75\%$ and high if $I^2 \geq 75\%$. A weighted meta-regression with a random-effect model was used. Furthermore, a Bayesian hierarchical network meta-analysis for our endpoints of interest was performed using a random effect model with the Markov-chain Monte Carlo methods based on 100 000 iterations with a burn-in of 10 000. Convergence was assessed with the Gelman-Rubin convergence diagnostic test.[18] We used a random seed and vague priors. Transitivity (similarity between sets of trials with respect to important effect modifiers) was assessed by constructing summary to qualitatively assess baseline clinical similarities of trial populations. (Supplementary Table 2) The probability that each treatment class ranked in each position (from best to worst) was estimated and presented in Surface Under Cumulative Ranking curve analysis (SUCRA) plots. Summary of effect is presented as Odds Ratio (OR) and 95% Credible Intervals [CrIn]. Publication bias was assessed for primary endpoints by visual inspection of funnel plots and by Egger's and Begg's test.[19] Finally, a trial sequential analysis[20] was performed to assess the statistical power needed to detect a significant difference in MACE with a RR increase of 30%, and an alfa of 1%, given the observed rates in our analysis. Statistical significance was set at p-value < 0.05 (two-sided). Data analysis was performed in the R environment (R Foundation for Statistical Computing, Vienna, Austria; packages *meta*, *metafor*, *BUGSnet*).[21]

Results

Search results and study details

A total of five randomized controlled trials (RCTs) and 7 665 patients (3 843 in the abbreviated DAPT group and 3 822 in the prolonged DAPT group) undergoing PCI or suffering ACS, with concomitant indication to long-term OAC, and randomly allocated to an abbreviated or prolonged DAPT course were included.[13,22–25] Trials comparing a strategy of dual antithrombotic therapy with DOAC vs. triple antithrombotic therapy with VKA were excluded with the exception of the AUGUSTUS trial,[24] in which the factorial 2 × 2 design allowed to separately account for the effect of DAPT duration and of DOAC/VKA. The characteristics of the included trials are reported in *Table 1*, whilst patient characteristics by treatment arm are reported in supplementary material online, *Table S2*.

The mean DAPT duration in the prolonged DAPT arm was 6 months, ranging from a minimum of 3 months in the MASTER-DAPT trial to a maximum of 12 months in the WOEST trial, while the other trials included DAPT for 6 months. Abbreviated DAPT regimen instead ranged from peri-procedural/in-hospital administration (defined as time from index event to randomization) in the WOEST and AUGUSTUS trials to 4 weeks in the MASTER-DAPT and SAFE-A trials and up to 6 weeks in the ISAR-TRIPLE trial. All the studies randomized patients within the index hospitalization, except for the MASTER-DAPT trial, which randomized uneventful subjects 1-month after PCI. After DAPT discontinuation, all patients were maintained on single antiplatelet therapy as described in *Table 1*.

The mean age was 72 years, atrial fibrillation was the main indication to OAC (7 066; 92.2%) while deep vein thromboembolism (200; 2.6%), a prosthetic mechanical heart valve (174; 2.3%) and other conditions were globally less prevalent. DOACs were used in 46.7% of the cases, with apixaban representing 81.5% of DOAC use. Approximately half of the patients (51.1%) presented with ACS. In the abbreviated DAPT arm, clopidogrel (79.2%) was the most common single antiplatelet agent used after DAPT discontinuation.

Table 1 Studies Included

Author	Trial	Enrollment	Study population	Abbreviated DAPT	Prolonged DAPT	OAC [indication]	FU (m)	Sample size (abbreviated/ prolonged DAPT)
Dewilde et al. Lancet 2013	WOEST	2008–2012	PCI for stable coronary syndromes or ACS	Periprocedural DAPT followed by clopidogrel	≥1 m (BMS) or ≥ 12 m (DES)	VKA [any long-term indication]	12	279/284
Fiedler at al. JACC 2015	ISAR-TRIPLE	2008–2013	PCI for stable coronary syndromes or ACS	6 w DAPT (aspirin + clopidogrel) followed by aspirin	6 m DAPT (aspirin + clopidogrel)	VKA [any long-term indication]	9	307/307
Lopes et al. NEJM 2019	AUGUSTUS	2015–2018	PCI for stable coronary syndromes; ACS with or without indication to PCI	Periprocedural DAPT followed by P2Y12-i[a]	6 m DAPT (aspirin + P2Y12-i[a])	VKA or apixaban[b] [atrial fibrillation]	6	2307/2307
Hoshi et al. EuroIntervention 2020	SAFE-A	2015–2018	PCI for stable coronary syndromes or ACS	1 m DAPT (aspirin + P2Y12-i[a]) followed by SAPT[a]	6 m DAPT (aspirin + P2Y12-i[a])	Apixaban [atrial fibrillation]	12	102/106
Valgimigli et al. NEJM 2021	MASTER-DAPT	2016–2019	PCI for stable coronary syndromes or ACS	1 m DAPT (aspirin + P2Y12-i[a]) followed by SAPT[a]	≥3 m DAPT (aspirin + P2Y12-i[a]) followed by SAPT[a]	VKA or DOAC[c] [any long-term indication]	12	2295/2284

[a] choice at the physician's discretion.
[b] as per randomization arm.
[c] no significant difference of VKA/DOAC distribution were observed between randomization arms.
ACS, Acute Coronary Syndromes; BMS, Bare Metal Stents; DAPT, Dual Antiplatelet Therapy; DES, Drug Eluting Stent; DOAC, Direct Oral Anticoagulant; FU, Follow-up; m, months; OAC, Oral Anticoagulation; PCI, Percutaneous Coronary Intervention; SAPT, Single Antiplatelet Therapy; VKA, Vitamin-K Antagonist; w, weeks.

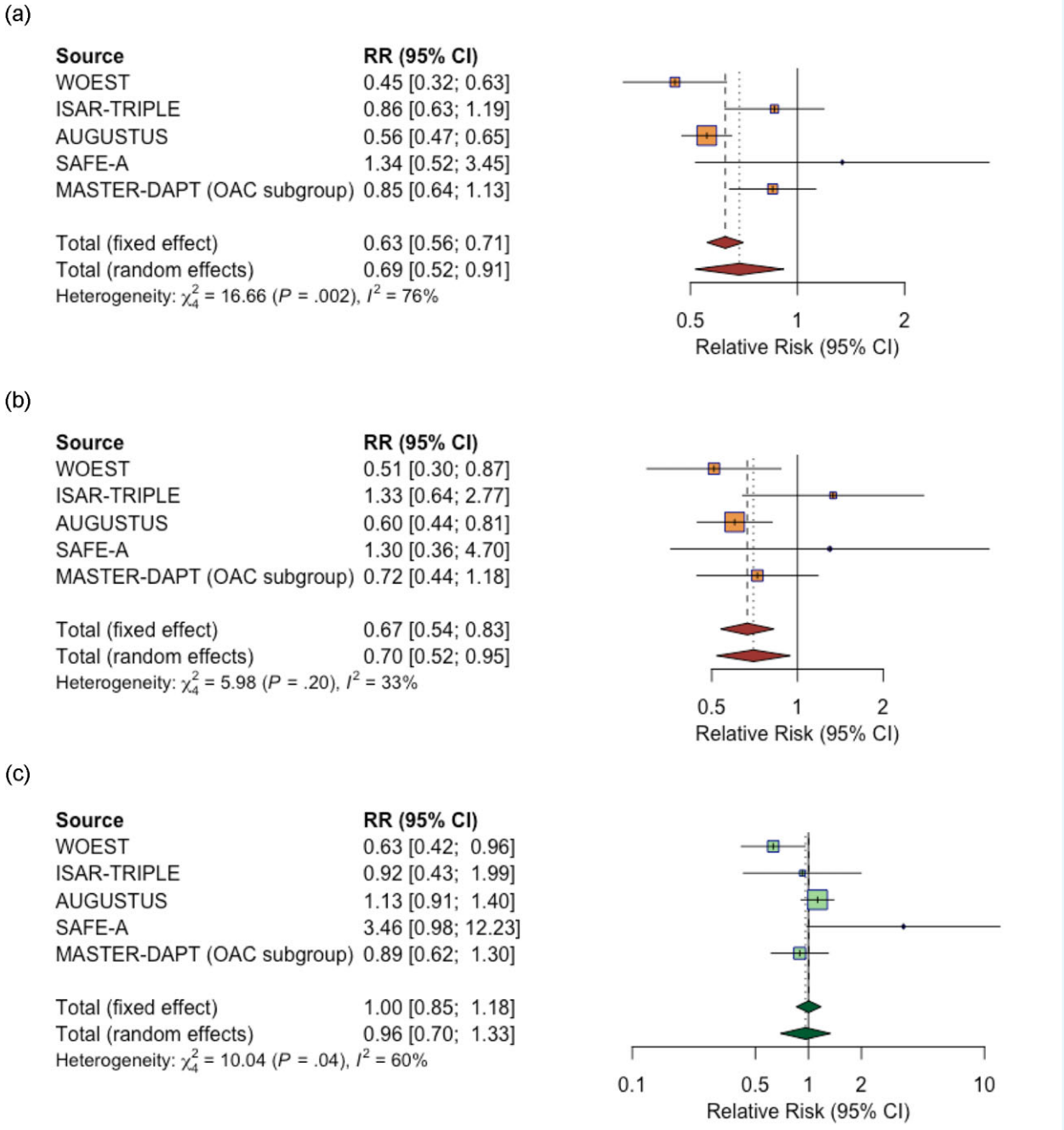


Figure 1 Forest plot for major or clinically relevant bleedings (a), major bleedings (b) and major cardiovascular events (c). RR < 1 favors abbreviated DAPT, RR > 1 favors prolonged DAPT. MACE, Major Adverse Cardiovascular Events; CI, Confidence Interval; RR, Relative Risk.

A PRISMA flowchart is reported in supplementary material online, *Figure S1*; the risk of bias was overall low in all studies and direct comparisons (Supplementary materials online, *Tables S3–4*). No publication bias was detected by means of funnel plots and Egger's tests. (Supplementary material online, *Figure S2*).

Co-primary endpoints

When compared with a prolonged DAPT course, the abbreviated regimen was associated with a significantly reduced risk of both co-primary endpoints of MCRB [10.2% vs. 16.3%; RR: 0.69 (0.52–0.91); $P = 0.01$; $I^2 = 76\%$; Number Needed to Treat (NNT) 16.4; *Figure 1*a] as well as of major bleedings [3.4% vs. 5.1%; RR: 0.70 (0.52–0.95); $P = 0.01$; $I^2 = 33\%$; NNT 58.8; *Figure 1*b]. These results were consistent in the sensitivity analysis including only patients treated with PCI [RR for MCRB: 0.67 (0.46–0.96); $P = 0.03$; Supplementary material online, *Figure S3A*]. Bleeding events adjudicated according to different classifications are shown in supplementary material online, *Figure S4*.

Meta-regression analysis for MCRB and major bleedings confirmed that the RR reduction was consistent among the features explored

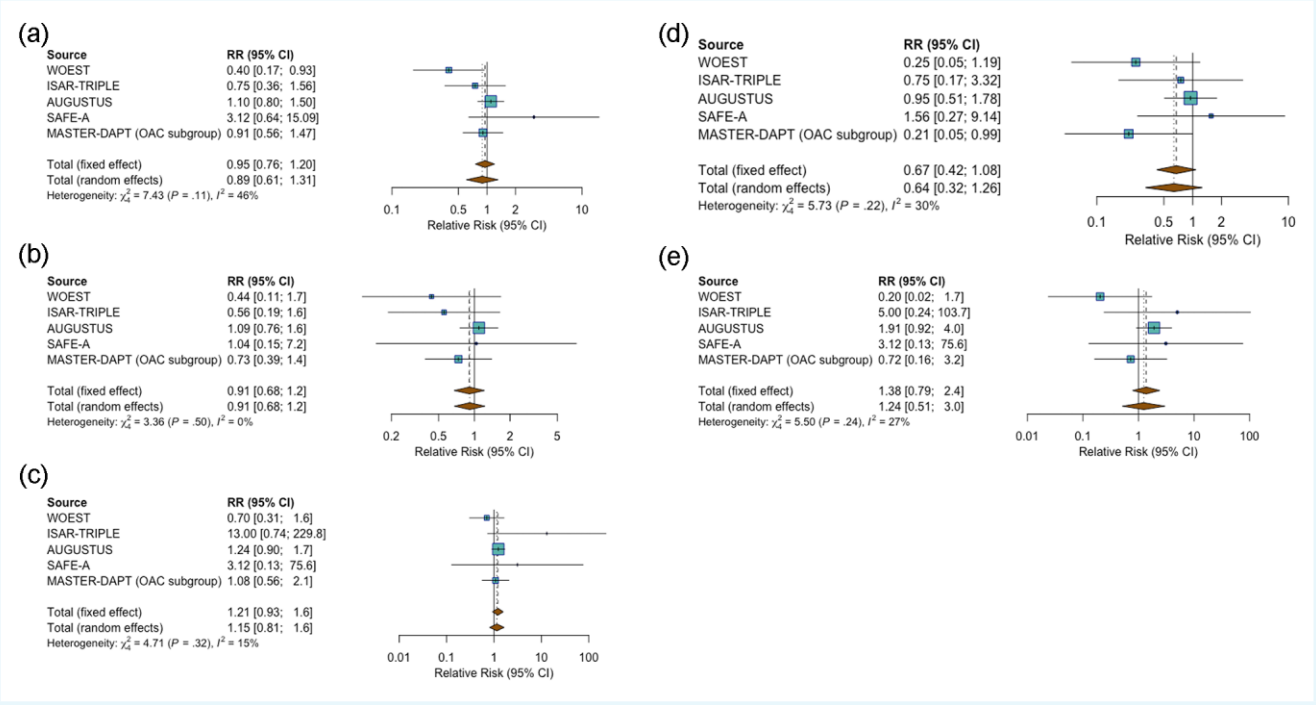


Figure 2 Forest plot for individual endpoints. (a) All-cause death; (b) cardiovascular death; (c) myocardial infarction; (d) stroke; (e) definite or probable stent thrombosis. RR < 1 favors abbreviated DAPT, RR > 1 favors prolonged DAPT. CI, Confidence Interval; RR, Relative Risk.

and revealed a significantly larger protective effect with $P2Y_{12}$ inhibitor as the drug to continue after DAPT discontinuation in the abbreviated DAPT arm (RR 0.59 [0.34–0.98]; $P = 0.05$ for MCRB and RR 0.44 [0.22–0.87]; $P = 0.01$ for major bleedings). (Supplementary materials online, *Figure S5–6*)

Safety endpoints

No significant difference in the key safety endpoint of MACE was observed between abbreviated and prolonged DAPT regimen [7.1 vs. 7.0%; RR 0.96 (0.70–1.33); $P = 0.6$; $I^2 = 60\%$; *Figure 1*c]. This result remained consistent when using an alternative MACE endpoint that included only cardiovascular mortality (instead of all-cause death) for all studies [RR 0.95 (0.75–1.2); $P = 0.7$; $I^2 = 60\%$; Supplementary material online, *Figure S7*) and in several meta-regression analysis by age, sex, ACS presentation, or other characteristics explored, (Supplementary material online, *Figure S8*) with the exception of atrial fibrillation ($P = 0.01$), although this result might be impacted by heterogeneity of the WOEST trial which holds a relatively low number of MACE events in the short DAPT arm. Finally, a trial sequential analysis revealed that, with currently available data, a RR increase of 30% or more could be excluded with abbreviated compared with prolonged DAPT. (Supplementary material online, *Figure S9*). No excess of definite or probable stent thrombosis [0.7 vs. 0.5%; RR: 1.24 (0.5–3.0); $P = 0.6$] nor of myocardial infarction [MI; 3.1 vs. 2.5%; RR: 1.15 (0.81–1.60); $P = 0.4$] was observed in the abbreviated DAPT arm; rates of ischaemic stroke were similar in the two arms [0.7 vs. 1.2%; RR: 0.64 (0.32–1.26); $P = 0.1$]. These results remained consistent in a sensitivity analysis that excluded individual studies one-by-one. (Supplementary material online, *Table S5*) No difference for all-cause or cardiovascular death was observed between the two treatment regimens. (Figure 2)

Network meta-analysis

Bleeding and ischaemic endpoints were further explored across the three DAPT duration regimens: peri-procedural vs. short (4–6 weeks) or prolonged DAPT (≥ 3 months). Peri-procedural DAPT was consistently shown to be the most likely best treatment for reduction of bleeding events (SUCRA for MCRB and major bleedings: 97.1 and 92.0%, respectively; *Figure 3*b-c and Table 2). With respect to ischaemic endpoints, probabilities for being the best treatment were more evenly distributed among treatment strategies for MACE (SUCRA: periprocedural 58.4%, short 18.4%, prolonged 23.2%) (*Figure 3*d and *Table 2*), for myocardial infarction (SUCRA: periprocedural 50.3%, short 4.4%, prolonged 45.3%) and for stent thrombosis (SUCRA: periprocedural 52.1%, short 12.5%, prolonged 35.4%; Supplementary materials online, *Figure S10 and Table S6*) which did not imply a clear superiority of any strategy with regards to these endpoints.

With regards to MCRB, periprocedural DAPT showed an OR of 0.46 [0.25–0.77; high confidence] compared with prolonged DAPT duration and of 0.53 [0.22–1.02; moderate confidence] compared with short DAPT. Similarly, with regards to major bleedings, RRs were 0.55 [0.29–0.97; high confidence] and 0.58 [0.23–1.26; moderate confidence] when compared with prolonged and short DAPT, respectively.

Discussion

The main findings of our study are as follows: (Central Illustration)

- Abbreviated DAPT duration (up to 6 weeks) in patients undergoing PCI or with ACS and concomitant OAC indication is associated with a reduction of major bleedings and of major or clinically relevant non-major bleeding compared with prolonged DAPT duration

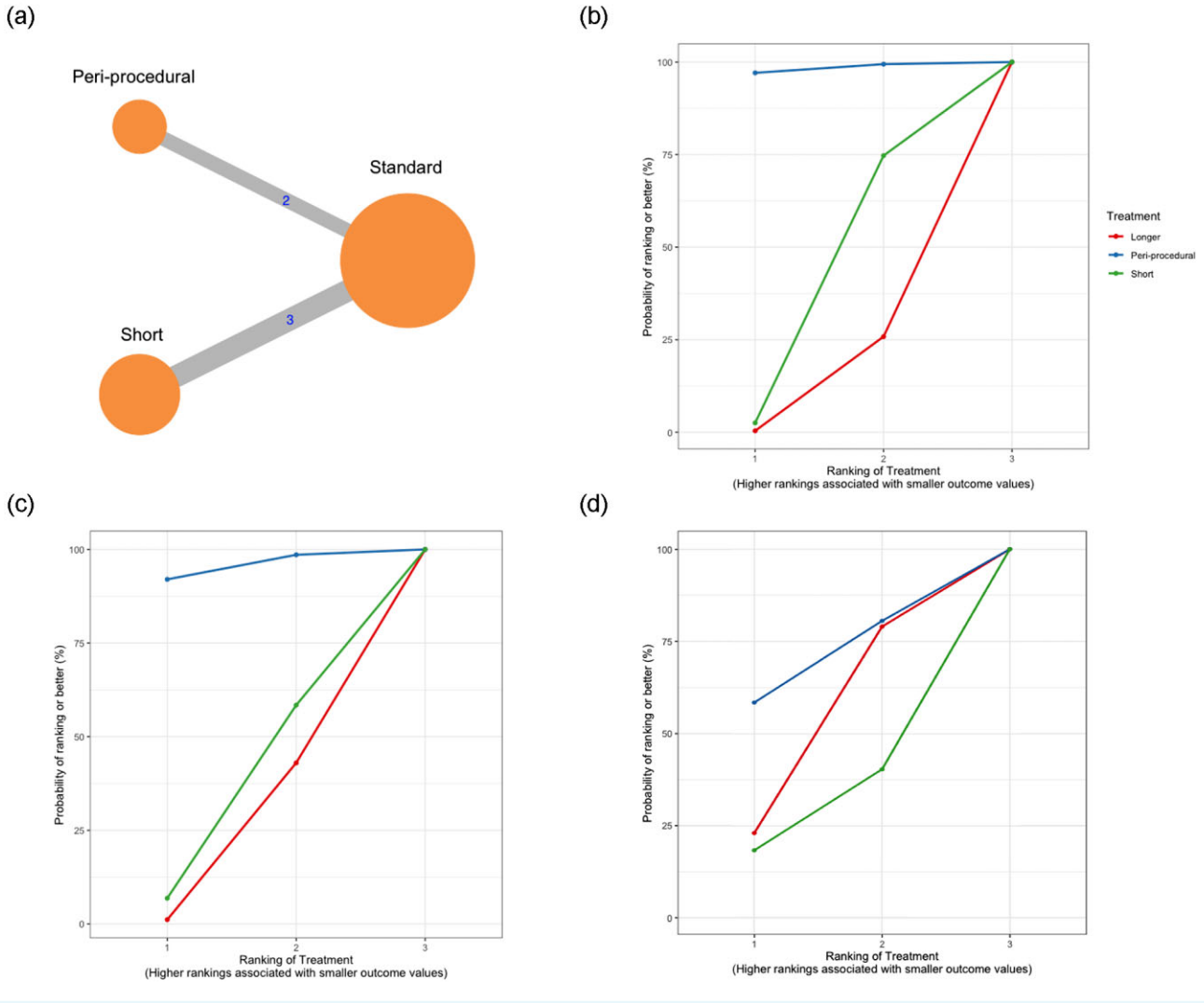


Figure 3 Network meta-analysis of peri-procedural vs. short vs. prolonged DAPT. The network of the analysis (a) and SUCRA plots for major and clinically relevant bleedings (b), major bleedings (c) and major cardiovascular events (d) are shown. DAPT, Dual Antiplatelet Therapy; SUCRA, Surface Under Cumulative Ranking curve Analysis

- Abbreviated DAPT was not associated with an excess of cardiac ischaemic events
- DAPT limited to the peri-procedural/in-hospital period ranked highest to be the best treatment strategy to reduce bleeding events when compared with a short (4–6 weeks) and prolonged (≥3 months) DAPT duration while ischaemic endpoints did not differ.

Optimal duration of DAPT in patients treated with OAC is of upmost importance since OAC is mostly maintained long-term or lifelong whereas DAPT duration is a key modifiable factor to balance ischemia and bleeding risks. The most recent European Society of Cardiology guidelines recommend the use of an OAC and a peri-procedural DAPT up to 1 week (class IA) in patients undergoing PCI for any reason.[26,27] These guidelines incorporated the evidence from 4 large RCTs that compared a strategy of dual antithrombotic therapy with DOAC and peri-procedural DAPT with a strategy of triple antithrombotic therapy with VKA on top of a short or standard course of DAPT in patients with AF undergoing PCI.[7,28–30] Even though these trials showed a convincing reduction of bleeding events with the former strategy, the use of DOAC was firmly bound to a shorter course of DAPT (with the notable exception of the AUGUSTUS trial) confounding the effect size attributable to the use of DOAC (vs. VKA) or of an abbreviated DAPT course. In fact, the use of DOAC is associated itself with less bleeding risk compared with VKA in patients with AF.[31–34] With this regard, this analysis is the first to explore the impact of DAPT duration in patients treated with long-term OAC, irrespective of OAC type and indication. While other meta-analysis already explored the role of abbreviated DAPT in this context, due to the design of included studies, the role of shorter DAPT (vs. prolonged DAPT) was entangled with that of the use of DOAC (vs. VKA). As a matter of fact, the PIONEER AF-PCI, RE-DUAL PCI, and ENTRUST-AF PCI studies[28–30] all randomized patients to peri-procedural DAPT and DOAC (rivaroxaban, dabigatran, and edoxaban, respectively) vs. longer DAPT and VKA and demonstrated the superiority of the former strategy. (Supplementary

Table 2 Surface Under Cumulative curve Ranking Analysis for primary and secondary endpoints

	SUCRA table: probability of ranking *n* as best treatment									
	Major or clinically relevant bleeding			Major bleeding			MACE			
n	Periprocedural	Short	Prolonged	Periprocedural	Short	Prolonged	Periprocedural	Short	Prolonged
1	97.1	2.54	0.39	92.0	6.87	1.12	58.4	18.4	23.2
2	2.33	71.9	25.8	6.55	51.5	42.0	22.3	21.9	55.8
3	0.59	25.6	73.8	1.44	41.6	56.9	19.4	59.7	21.0

The probability of ranking *n* is shown; the highest probability of ranking best is highlighted in orange.
MACE, Major Adverse Cardiovascular Events; SUCRA, Surface Under Cumulative curve Ranking Analysis.

material online, *Table S7*) However, one should consider that both peri-procedural DAPT and DOAC individually have biological plausibility to reduce bleeding events and improve outcomes, and therefore their particular role into determining better outcomes is not clarified either by these studies or by any meta-analysis that includes them. In particular, one could argue that it is DOAC treatment (vs. VKA) to be responsible for improved outcomes instead of abbreviated DAPT.

Understanding the impact of DAPT duration irrespective of OAC type is of clinical important for several reasons. First, DOACs are recommended in most patients with AF or deep vein thrombosis, therefore a comparison of DOAC with abbreviated DAPT vs. VKA with prolonged DAPT is no longer informative for practice. Second, in some instances, such as in presence of a mechanical heart valve or advanced chronic kidney disease, patients undergoing PCI or with an ACS might not be eligible for treatment with DOAC and anticoagulation with VKA might be the only viable option. Hence, obtaining precise estimates of the bleeding/ischaemic trade-off with an abbreviated vs. prolonged DAPT irrespective of the type of OAC implemented is of utmost importance to inform optimal DAPT duration.[13] Of note, our analysis included both patients treated with DOAC or a VKA, and both patients anticoagulated for atrial fibrillation and for other indications.

In our analysis, the use of an abbreviated DAPT duration, irrespective of concomitant OAC type, showed a 30% reduction of both MCRB and major bleeding compared with a prolonged DAPT course of three months or more. An abbreviated DAPT was associated with a low NNT (16.4) to reduce MCRB and was not associated with an increase of ischaemic endpoints, including stent thrombosis.

Bleeding prevention is key in the optimal management of patients.[5] Major bleeding has been associated with prognostic impairment,[3] while minor bleeding is more frequent and associated with worsened quality of life, higher healthcare costs, and less drug adherence. This latter is of great clinical relevance: in fact, patients on OAC therapy and suffering even minor bleeding events are more likely to interrupt or disrupt their antithrombotic regimen with a potential to precipitate cerebral ischaemic events, further bleedings or other cardiovascular events.[35] In our study we observed a trend towards a higher risk of stroke among patients assigned to a prolonged DAPT duration. While we recognize that the following is speculative and require conformation in dedicated studies, we hypothesize that, for the aforementioned reasons, a longer course of DAPT may trigger major, minor or nuisance bleeding, and impair adherence to the overall antithrombotic regimen with a paradoxical surge of ischaemic events. It has also been speculated that a more intense antithrombotic therapy could be associated to intravascular haemorrhagic events triggering myocardial ischaemia.[36]

Notably, our data suggest that a larger reduction of bleeding is to be expected if a $P2Y_{12}$ inhibitor is preferred over aspirin after DAPT discontinuation. In our meta-analysis, most patients with $P2Y_{12}$ inhibitors were treated with clopidogrel. In this setting, clopidogrel is considered the $P2Y_{12}$ inhibitor of choice[27] as an exaggerated risk of bleeding was observed with concomitant use of OAC with ticagrelor or prasugrel[37,38] and they are generally avoided in this setting. These results are in line with those of the recent HOST-EXAM trial,[39] which assigned clopidogrel vs. aspirin as secondary prevention for patients with chronic coronary disease showing a reduction of both bleeding and ischaemic events with clopidogrel compared with aspirin. This finding arises from an exploratory meta-regression analysis and as such requires further investigation. Moreover, it has been recently demonstrated that gastric or small intestinal injury is common with both aspirin and clopidogrel in selected low-bleeding risk patients,[40] but the gastro-intestinal effect of aspirin might be less well tolerated among high-bleeding risk patients.[41]

Our meta-analysis includes studies with different DAPT durations, even within the pre-specified cut-off of abbreviated (4–6 weeks)

and prolonged (≥3 months) DAPT regimen. However, a network meta-analysis was developed to further investigate DAPT duration regimens, including patients treated with DAPT only before randomization in the WOEST and AUGUSTUS trial. Peri-procedural DAPT emerged as the most likely best treatment to prevent MCRB and major bleeding, while a short DAPT regimen was the second-best treatment. No apparent excess of the explored ischaemic endpoints was observed with a shorter DAPT course, including peri-procedural DAPT. It should be highlighted that none of the included trials was powered to detect a difference in ischaemic events. For this reason, our trial sequential analysis is of particular interest. In fact, given the observed event rates, we demonstrated that currently available data are sufficient to exclude an excess of MACE of 30% or more with abbreviated compared to a more prolonged treatment course. (Supplementary Figure 9)

Importantly, all 3 arms of the network comprised anticoagulation with either VKA and DOAC and therefore are interpretable independently of the OAC strategy. Such a drastic reduction of DAPT duration was made possible by technological improvements in stent design, procedural optimization including radial access[42] and wider use of stent optimization techniques,[43] therefore our results should be interpreted in the context of a modern PCI setting. The comparison between peri-procedural and short DAPT duration should be interpreted with caution as it derives entirely from indirect evidence (Figure 3a). Future studies directly comparing peri-procedural and short-term (4–6 weeks) DAPT duration remain desirable to more definitively inform practice.

Limitations

Several limitations should be acknowledged, First, this is an aggregate-data meta-analysis, which holds the limitations of the included trials, whereas a patient-level analysis would allow more detailed analysis for subgroups of interest. For instance, the type of coronary stent implanted might also be relevant after an abbreviated or prolonged course of DAPT, and the lack of patient-level data limits our ability to give insights on this matter. Second, despite persisting at fixed-effect analysis, formal statistical significance was not maintained in the random-effects sensitivity analysis excluding the WOEST trial or the AUGUSTUS trial. (Supplementary material online, *Table S6*) This might be explained by the relatively large impact of peri-procedural DAPT on our results, as clarified in our network meta-analysis. It should also be emphasized that the evidence in favor of peri-procedural DAPT are limited, as they are derived from only the two aforementioned trials. Third, the MASTER-DAPT trial randomized patients 1-month after the index procedure and bleeding events in the first month was a possible inclusion criterion although they were not counted as study events.[13] Fourth, there is heterogeneity in clinical endpoint definitions between studies included. Albeit in our main analysis we accepted the definition reported by each study, we also performed subgroup analysis of studies that reported these outcomes homogeneously, which confirmed the results of the main analysis. In addition, despite our analysis includes the largest available population of patients with OAC indication after PCI, it still suffers from relatively limited statistical power when relatively rare events are considered, such as myocardial infarction and stent thrombosis. Although our results with regards to the composite endpoint of MACE are reassuring, we cannot exclude an increase of individual ischaemic endpoints; hence, future studies in the OAC population remain important to increase the precision of current estimates. Fifth, the comparison between periprocedural versus short DAPT duration remains derivative and requires further investigation. Finally, mild heterogeneity in the follow-up durations across trials should be acknowledged.

Conclusions

In patients treated with OAC undergoing PCI or with ACS, abbreviated DAPT is associated with a significant reduction of bleeding without an increase of ischaemic events in patients either receiving VKA or DOAC. Peri-procedural DAPT and continuation with a $P2Y_{12}$ inhibitor rather than aspirin after DAPT discontinuation appear to augment the benefit of an abbreviated DAPT course but this is based on limited evidence at present.

Supplementary material

Supplementary material is available at *European Heart Journal—Cardiovascular Pharmacotherapy* online.

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Data availability

The data underlying this article are publicly available in electronic databases (see *Supplementary Methods 1*)

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