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Dual Antiplatelet Therapy Duration in Patients on Oral Anticoagulant Therapy: a meta-analysis of randomized trials.

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Brief Title: DAPT duration after PCI with indication for OAC

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Abstract

Background: Optimal duration of dual antiplatelet therapy (DAPT) in patients with concomitant indication to oral anticoagulation (OAC) is still debated.
Methods. A systematic review was performed on electronic databases to search for randomized controlled trials comparing an abbreviated (<3 months) or prolonged (≥3 months) DAPT regimen in patients with OAC and they were analyzed in the framework of standard and network meta-analyses. Co-primary safety 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 efficacy endpoint.
Results. 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 to short (≤6 weeks) or longer (≥3 months) 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 ischemic events. Peri-procedural DAPT and $P2Y_{12}$ inhibitor monotherapy after DAPT withdrawal appear to be the best strategies to optimize the bleeding and ischemic risk tradeoff.

Keywords: Dual antiplatelet therapy, Oral anticoagulant therapy, Percutaneous Coronary Intervention, Atrial fibrillation, Aspirin, P2Y12 inhibitor, Monotherapy
Study registration: PROSPERO registration number 284001

Condensed Abstract

Five randomized controlled trials comparing abbreviated or prolonged (≥3 months) dual antiplatelet therapy (DAPT) regimens were included in this systematic review and meta-analysis. Both major and clinically relevant bleedings (MCRB) and major bleeding were lower with abbreviated DAPT while major adverse cardiovascular events and individual ischemic endpoints did not differ. In a network meta-analysis, peri-procedural DAPT had the highest probability to prevent MCRB and major bleeding when compared to short or longer regimens. In conclusion, patients with concomitant OAC indication treated with an abbreviated DAPT experienced reduced MCRB and major bleeding without increasing ischemic events.

Abbreviations

ACS, Acute Coronary Syndromes
CI, Confidence Interval
CrIn, Credible Intervals
CV, Cardiovascular
DAPT, Dual Antiplatelet Therapy
DOAC, Direct Oral Anticoagulant
MACE, Major Adverse Cardiovascular Events
MCRB, Major or Clinically Relevant Bleedings
OAC, Oral Anticoagulant
OR, Odds Ratio
PCI, Percutaneous Coronary Intervention
RR, Relative Risk
SUCRA, Surface Under Cumulative Ranking curve Analysis
VKA, Vitamin-K Antagonist

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 ischemic events including stent thrombosis.(1, 2) However, DAPT is inherently associated with increased risk of bleeding that strongly and consistently impacts patient's prognosis(3, 4). DAPT intensity and duration should therefore be finely tuned.(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 to the peri-procedural/in-hospital phase after PCI, to a longer DAPT duration. Reducing DAPT duration was associated to a reduction of bleeding, yet a signal for a small but significant excess of stent thrombosis and MI was observed in some meta-analyses.(8, 9) Importantly, owing to the design of some of these trials, that concealed DAPT strategy with a type of OAC (very short DAPT + DOAC vs. standard DAPT + VKA), it is difficult to disentangle the efficacy and safety of a shorter DAPT duration from that of DOAC therapy. Hence, to fully understand the 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 AUGUSTUS trial, thanks to its factorial 2 x 2 randomization design, was the first to clarify that the addition of aspirin to OAC (with apixaban or warfarin) and clopidogrel significantly increased bleedings

without an advantage on ischemic endpoints.(10) However, it only featured a relatively small number of coronary ischemic events, which were numerically, albeit not significantly, higher in the short DAPT group, paving the way for further investigation.(11)

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 (up to 6 weeks) 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 to longer treatments.

Methods

Literature Search and Study selection

Two authors (CM, FC) independently searched electronic databases for articles published between Jan 1, 2000, and Sep 1, 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 (CM, FC); duplicate extractions and conflicting cases were discussed and adjudicated by a senior author (MV). The present work was conducted in accordance with the PRISMA and MOOSE guidelines.(12, 13) The study protocol was submitted to PROSPERO (284001).(14)

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) influence the incidence of bleeding, studies that randomized patients to a 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.(15, 16) Two authors (CM, FC) 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.(17) 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.(18) All studies included had appropriate ethical oversight and approval.

Study outcomes

The two co-primary safety 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 efficacy

endpoint was the composite of major adverse cardiovascular events (MACE) at the longest follow-up available. These endpoints were analyzed as reported by each individual study. (**Supplementary Table 1**). As 3 studies reported MACE including all-cause deaths and 2 only cardiovascular (CV) deaths, an alternative MACE endpoint was calculated and analyzed by subtracting non-CV deaths from the study-reported MACE. Individual endpoints according to different definitions were also collected and analyzed. 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. longer (≥ 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 indication to DAPT, atrial fibrillation as 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.(19) 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 >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.(20) 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.(21) 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*).(22)

Results

Search results and study details

A total of 5 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.(10, 15, 23–25) 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,(10) in which the factorial 2x2 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 Table 2**.

The mean DAPT duration in the prolonged DAPT arm was 6 months, ranging from a minimum of 3 months to a maximum of 12 months in the WOEST trial. Abbreviated DAPT instead ranged from peri-procedural/in-hospital administration (defined as time from index event to randomization) 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.

The mean age was 72 years, atrial fibrillation was the main indication to OAC (92.2%) and 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.

A PRISMA flowchart is reported in **Supplementary Figure 1**; the risk of bias was overall low in all studies and direct comparisons (**Supplementary Tables 3-4**). No publication bias was detected by means of funnel plots and Egger's tests. (**Supplementary Figure 2**).

Co-primary safety endpoints

When compared with a prolonged DAPT course, the abbreviated regimen was associated with a significantly reduced risk of both co-primary safety endpoints of MCRB (10.2% vs. 16.3%; RR:

0.69 [0.52–0.91]; *p*=0.01; I^2 = 76%; **Figure 1A**) as well as of major bleedings (3.4% vs. 5.1%; RR: 0.70 [0.52-0.95]; *p*=0.01; I^2 = 33%; **Figure 1B**). 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 Figure 3A**). Bleeding events adjudicated according to different classifications are shown in **Supplementary Figure 4**.

Meta-regression analysis for MCRB and major bleedings confirmed that the RR reduction was consistent among the features explored 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 Figure 5-6**)

Efficacy Endpoints

No significant difference in the key efficacy 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 1C**). This result remained consistent at sensitivity analyses using a different definition of MACE that included only cardiovascular mortality for all studies (**Supplementary Figure 7**). 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 ischemic 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 Table 5**) No difference for all-cause or cardiovascular death was observed between the two treatment regimens. (**Figure 2**) Meta-regression analysis for MACE showed no effect heterogeneity by age, sex, or ACS

presentation or other characteristics explored (**Supplementary Figure 8**).

Network meta-analysis

Bleeding and ischemic endpoints were further explored across the three DAPT duration regimens: peri-procedural vs. short (4-6 weeks) or longer 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 3B-C** and **Table 2**). With respect to ischemic endpoints, probabilities for being the best treatment were more evenly distributed among treatment strategies for MACE (SUCRA: periprocedural 58.4%, short 18.4%, longer 23.2%)(**Figure 3D** and **Table 2**), for MI (SUCRA: periprocedural 50.3%, short 4.4%, longer 45.3%) and for ST (SUCRA: periprocedural 52.1%, short 12.5%, longer 35.4%; **Supplementary Figure 9** and **Supplementary Table 6**) 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 to longer DAPT duration and of 0.53 [0.22-1.02; moderate confidence] compared to 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 to longer 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 to a reduction of major bleedings and of major

or clinically relevant non-major bleeding compared to prolonged DAPT duration

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

This is the first meta-analysis exploring the impact of DAPT duration in patients treated with long-term OAC, irrespective of OAC type and indication. 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 a 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. The use of DOAC is associated itself with less bleeding risk compared with VKA in patients with AF.(31–34) Understanding the impact of DAPT duration irrespective of OAC type is 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 to a treatment with DOAC and anticoagulation with VKA might be the only viable option. Hence, obtaining precise estimates of the bleeding/ischemic trade-off with an abbreviated vs. prolonged DAPT irrespective of the type of OAC implemented is of upmost importance to inform optimal DAPT duration.(15) 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 bleedings compared to 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 ischemic 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 are more frequent and associated to 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 ischemic 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 ischemic events. It

has also been speculated that a more intense antithrombotic therapy could be associated to intravascular hemorrhagic events triggering myocardial ischemia.(36)

Notably, our data suggests that a larger reduction of bleedings is to be expected if a $P2Y_{12}$ inhibitor is preferred over aspirin after DAPT discontinuation. In our meta-analysis, most patients with $P2Y_{12}$ inhibitor 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 ischemic events with clopidogrel compared to 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 (≤ 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 ischemic endpoints was observed with a shorter DAPT course, including peri-procedural DAPT. 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 Table 6**) This might be explained by the relatively large impact of peri-procedural DAPT on our results, as clarified in our network meta-analysis. 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.(15) 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 MI and ST. Although our results with regards to the composite endpoint of MACE are reassuring, we cannot exclude an increase of individual ischemic 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 investigations. 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 ischemic 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.

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Perspectives

Competency in Patient Care and Procedural Skills: Abbreviated DAPT duration (≤ 6 weeks) after a PCI or ACS, and peri-procedural DAPT in particular, reduces the risk of major bleedings with no apparent excess of ischemic risk in patients with indication to long-term OAC.

Translational Outlook: Comparison between peri-procedural and short DAPT courses for bleeding and ischemic risk trade-off, and type of antiplatelet agent to prefer at the time of DAPT discontinuation require further investigation.

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Figure Legend

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.

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.

Figure 3. Network meta-analysis of peri-procedural vs. short vs. longer 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

Central Illustration. 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

Table 1. Studies Included

Author	Trial	Enrollment	Study population	Abbreviated DAPT	Prolonged DAPT	OAC	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 ≥12m (DES)	VKA	12	279/284
Fiedler at al. JACC 2015	ISAR-TRIPLE	2008-2013	PCI for stable coronary syndromes or ACS	6w DAPT (aspirin + clopidogrel) followed by aspirin	6m DAPT (aspirin + clopidogrel)	VKA	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]	6m DAPT (aspirin + P2Y12-i[a])	VKA or apixaban[c]	6	2307/2307
Hoshi et al. EuroIntervention 2020	SAFE-A	2015-2018	PCI for stable coronary syndromes or ACS	1m DAPT (aspirin + P2Y12-i[a]) followed by SAPT[a]	6m DAPT (aspirin + P2Y12-i[a])	Apixaban	12	102/106
Valgimigli et al. NEJM 2021	MASTER-DAPT	2016-2019	PCI for stable coronary syndromes or ACS	1m DAPT (aspirin + P2Y12-i[a]) followed by SAPT[a]	≥3m DAPT (aspirin + P2Y12-i[a]) followed by SAPT[a]	[VKA or DOAC][c]	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

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*	*Longer*	*Periprocedural*	*Short*	*Longer*	*Periprocedural*	*Short*	*Longer*
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.