Review Article

Short vs Standard Duration Dual Antiplatelet Therapy after Percutaneous Coronary Intervention with New-Generation Drug-Eluting Stents: A Meta-Analysis

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Abstract

Objective: In patients with coronary artery disease, dual antiplatelet therapy (DAPT) is recommended after percutaneous coronary intervention, but the duration is still debated. This meta-analysis compared short-duration (1 to 3 months) to standard-time (twelve months) double antiplatelet treatment in patients who received coronary intervention with new generation drug eluting Stent.

Methodology: To conduct this examination, we methodically looked at PubMed, Cochrane CENTRAL, Embase, and Web of Science databases for randomized controlled trials, evaluating varying durations of double antiplatelet treatment following new generation stents implantation from July to September 2023. Seven randomized controlled trials were included with a total of 22,945 patients. The primary efficacy endpoint was the incidence of Major adverse cardiovascular events, such as cardiac mortality, heart attack, stent coagulation, and target vessel revascularization; while the safety endpoint was the incidence major bleeding. Secondary endpoints were major adverse cardiovascular and cerebro-vascular complications, any bleeding, and net adverse cardiovascular incidence for a year after stent implantation.

Results: Short-time DAPT was linked to a significantly less incidence of major bleeding (0.8% vs 1.5%), any bleeding (2.5% vs 4.2%) and NACE (2.5% vs 4.2%) compared to standard duration of DAPT. No significant variation was noticed among the two groups regarding major adverse cardiovascular events (4.1% vs. 4.2%) and acute cardiovascular and cerebrovascular incidents (4.7% vs. 4.8%). Short-duration DAPT in patients with acute coronary syndrome was linked with decreased risk of bleeding and net adverse cardiovascular events.

Conclusion: Short-duration (1- or 3-month) DAPT significantly lowers bleeding risk and reduces net clinical adverse events without increasing ischemic risk, making it a reasonable choice for people with new-generation drug eluting stents, particularly those with high bleeding risk or recent surgery.

Keywords: Acute coronary syndrome, Coronary artery disease, New generation drug eluting stents, Dual antiplatelet therapy.

Introduction

To reduce the likelihood of stent clots and restenosis in patients with coronary artery disorders, double anti-platelet therapy (DAPT), which consists of aspirin and a P2Y12 channel antagonist, is a crucial intervention.[1,2] Based on evidence from studies using bare-metal and initial-generation pharmaceutical stents, the latest suggestions indicate a DAPT time of 12 months after percutaneous coronary intervention (PCI) for people with coronary artery disease.[3] Nowadays, many new-generations drug eluting stents (DES) contain a better biocompatible polymer or does not contain a polymer, which tends to cause a lower stent thrombosis rate and has a lower tendency to DAPT.[4,5] Therefore, the 12-month duration of DAPT may no longer be appropriate in the arrival of the latest generations DES.[6] Previous studies demonstrated that prolonged DAPT increased the likelihood of blood loss despite reducing ischemic events.[6,7] The appropriate length of DAPT following the placement of a new-generation DES stent is still unknown. To determine the proper period of DAPT, a careful balance of bleeding and ischemia risk should be measured.

Due to the 2017 policies of the European Society of Cardiology, after the placing of the latest version of pharmaceutical stents, persons with sTable coronary artery disorder should have a 6-month DAPT, and individual at elevated hazards of bleeding should have a 1- to 3-month DAPT.[8] It is unknown whether short-duration DAPT will decrease blood loss without raising the probability of major adverse cardiovascular conditions in contrast to standard-period DAPT in peoples with coronary arteries disorder and acute coronary syndrome. Several RCTs have examined the protection and effectiveness of short-term DAPT (e.g., 1-3 months) compared to the usual 12-month DAPT for patients with unique pharmaceutical stents.[9,10] This meta-analysis sought to assess the protection and effectiveness of short-time DAPT (one to three months) towards standard-period DAPT (12 months) in person undergoing coronary intervention with new generation drug eluting stents.

Methodology

This meta-analysis followed the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines.[11]

Database Search

To conduct this research, we extensively searched the PubMed, Cochrane CENTRAL, Embase, and Web of Science databases for RCTs evaluating various periods of DAPT following new-generation drug-eluting stent placement from July to September 2023. Trials relevant to this topic were also searched at https://clinicaltrials.gov/. Language restrictions were not imposed on the search. The search was limited to RCTs that compared short-duration DAPT (one to three months) and long duration DAPT (12 months) following drug-eluting stent implantation. Search terms included: "percutaneous coronary therapy" OR "coronary stent installation" OR "drug-eluting stent" AND "time of DAPT" OR "period of double anti-platelet treatment". An overview of the choice of eligible studies screened by titles, abstracts, and a full-text review for final determination is illustrated in Figure 1a.

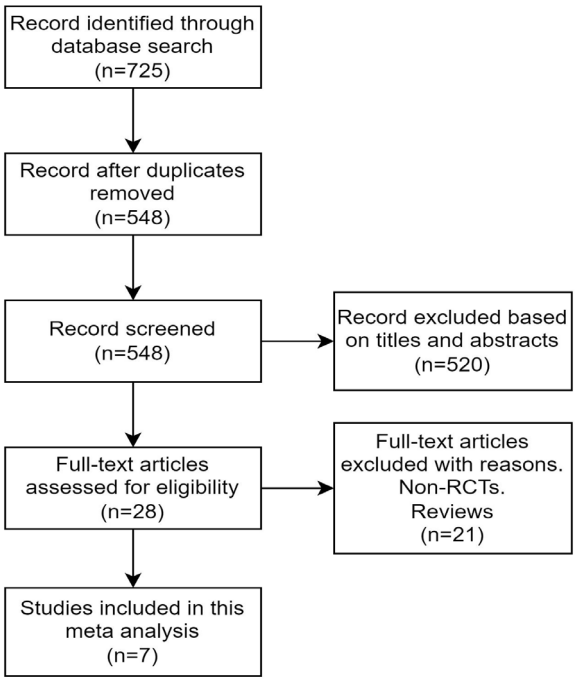


Figure 1a. Prisma flow chart for the articles selection process

Inclusion and exclusion criteria

All randomized controlled trials for comparison of three-month DAPT to twelve-month DAPT after the installment of new-generation drug-eluting stents were systematically reviewed. All potentially relevant randomized trials were independently reviewed by two investigators (I.U, M.A) to identify studies that met the following criteria: enrolled coronary artery disease patients were ≥18 years and underwent novel drug-eluting stents implantation; participants were allocated at random to get a DAPT of aspirin coupled with a P2Y12 channel blocker (clopidogrel, prasugrel or ticagrelor) for short duration (3 months) or a standard duration (twelve months) following coronary implantation by percutaneous; at least 12-month monitoring; outcomes, including cardio-cerebro-vascular events and bleeding events. The exclusion criteria were non-randomized controlled designs, editorial comments, reviews, conference abstracts, reports on the same population or duplicated data.

Outcomes measured

The main safety outcome was significant adverse cardiovascular events, which included mortality, heart attack, stent thrombosis, and target vessel regeneration after 12 months of treatment. The key protection result was substantial blood loss at 12 months, as defined by BARC or TIMI criteria.[12] The 2nd outcome was significant harmful cardiovascular and cerebro-vascular conditions, any bleeding, and gross unfavorable cardiovascular problems at twelve months.

Data collection

The data was gathered, and the manuscripts of the listed publications were examined irrespectively by two investigators (IU and MA). The principal effectiveness outcome, key safety measurement, and secondary outcomes were examined above.

Bias assessment

Cochrane Collaboration's tool was used by two investigators (IU, MA) to independently assess bias risk for the following items: sequencing, concealing allocations (selection bias), blinded people and respondents (performance bias), hiding result evaluation (detection bias), ensuring that result data are full (attrition bias), and selectively disclosing outcomes (reporting bias) (Figure 1b).

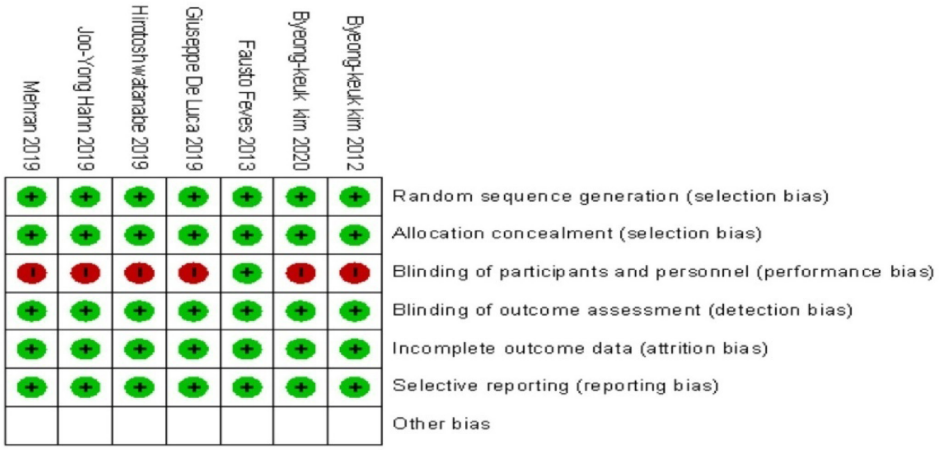


Figure 1b. Bias assessment using the risk of bias assessment tool (RoB) developed by the Cochran Collaboration, evaluate bias risk.

Statistical Analysis

Using Review Manager Version 5.4.1, the statistical analysis was conducted following the Cochrane Collaboration recommendations. The Mantel-Haenszel Fixed Effects method was used to calculate odds ratios and confidence intervals at 95% to quantify the effects of different DAPT durations. The research variation was determined using Cochrane's Q test and the I2 statistic, which calculates the percentage of the overall variance among trials caused by variation rather than chance. Additionally, I2 statistics with values of <50% and ≥50% indicated low and high variability, correspondingly. A sensitivity analysis was conducted in cases of high heterogeneity to identify any study that might be considered outliers. If no data for a specific outcome was available, the trial was excluded from the pooled analysis corresponding to that endpoint. Forest plots were utilized to assess the entire effectiveness of the investigations. All tests were two-tailed, with a p-value of < 0.05 indicating significance. A prespecified analysis of people with acute coronary disorder was also conducted to assess the relative benefits and risks of short-duration DAPT. Publication bias was visually evaluated based on the asymmetry of the funnel plot.

Results

A total of 7 RCTs, which enrolled 22,945 patients, were included in our meta-analysis [9,10,13-17] to compare short-duration (1- to 3-month) with standard-duration (12-month) DAPT. Among them, 11,473 (50.00%) were randomized to short-term DAPT, and 11,472 (50.00%) were randomized to standard-duration DAPT. According to the study plan, the period of DAPT in the experimental arm was 1 month in STOPDAPT-2[15] and 3 months in the remaining 6 trials.[9,10,13,14,16,17] The main characteristics of the listed trials are presented in Table 1.

REDUCE [13] and TICO [17] trials recruited people with acute coronary disorder (n = 4,552), while the other five trials, [9,10,14-16] recruited patients with sTable coronary artery disease (n = 11,409) and ACS (n = 6,984). The following latest version stents that encapsulate drugs were utilized: everolimus-eluting stents, zotarolimus-eluting stents, sirolimus-eluting stents, and COMBO bioabsorbable polymer stents in these seven trials. The DAPT of aspirin with a $P2Y_{12}$ inhibitor was used as follows: clopidogrel was used in RESET[9] and OPTIMIZE[10] trials, while ticagrelor was administered in TWILIGHT[16] and TICO[17] trials, respectively. The $P2Y_{12}$ inhibitor was not confined to clopidogrel, prasugrel or ticagrelor in REDUCE[13] and SMART-CHOICE[14] trials. Clopidogrel or prasugrel was given on the physician's prescription in STOP DAPT-2 trial.[15] Figure 1b displays the potential evaluation of bias for every randomized controlled trial that was a part of the investigation. Other biases were low in all trials except that blinding was only performed in the OPTIMIZE trial[10]. The publication bias was accepTable in all enrolled trials shown in the funnel plot. Heterogeneity among the trials was low in all endpoints among the 7 trials (Figure 2).

Primary efficacy composite endpoint: MACE

All 7 trials, including 22,873 participants, reported the end point of MACE. There were 475 events among 11, 432 patients in the short-duration DAPT group versus 472 events among 11,441 patients receiving the standard-duration DAPT. The pooled analysis revealed no statistically significant variations among the two classes (4.2% *vs.* 4.1%, OR 1.01, 95% CI 0.88-1.15, p=0.93, Figure 2a).

Primary safety endpoint: Major bleeding

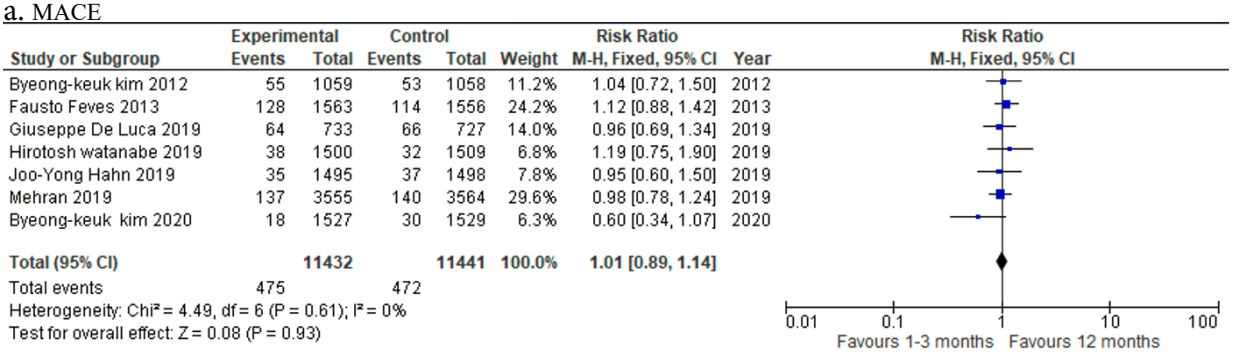
The principal safety endpoint of significant blood loss was reported by all the trials (21,413 participants) except the RECUCE trial.[13] Major bleeding in patients receiving DAPT for a short duration occurred in 86 out of 10,699 patients, and in patients receiving DAPT for a standard duration occurred in 164 out of 10,714 patients. A statistically significant reduction of 48.1% in major bleeding risk was observed for the short DAPT group, as shown in Figure 2b (0.8% vs. 1.5%, OR 0.52, 95% CI 0.40-0.68, p=0.00001).

Table 1. Characteristics of the Included Trials

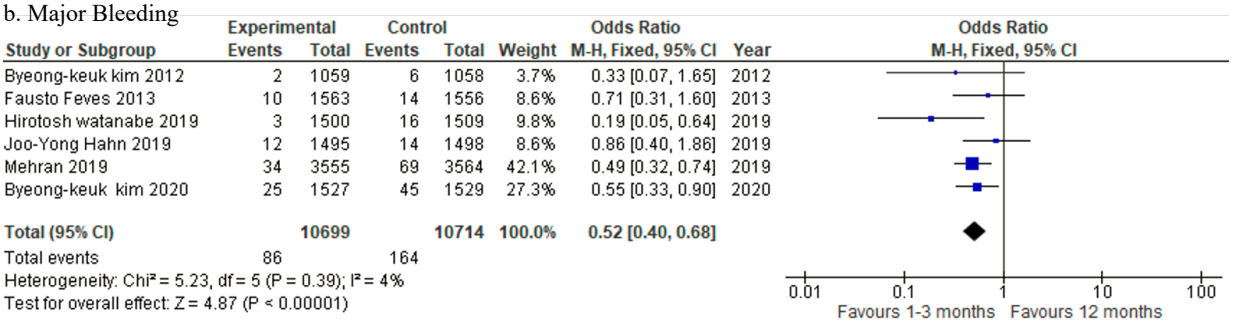
No	Trial (year)	Country	Journal	Sample size	DAPT Duration	Stents	CAD diagnosis	Follow-up
1	RESET 2012	Korea	JACC	2117	Three-month *vs.* twelve-month	ZES/EES/SES	ACS, sTable CAD	12-months
2	OPTIMIZE 2013	Brazil	JAMA	3119	Three-month *vs.* twelve-month	ZES	ACS, sTable CAD	12-months
3	REDUCE 2019	Italy	Euro Intervention	1496	Three-month *vs.* twelve-month	COMBO	ACS	12-months
4	SMART CHOICE 2019	Korea	JAMA	2993	Three-month *vs.* twelve-month	EES/ZES/BES	ACS, sTable CAD	12-months
5	STOP DAPT-2 2019	Japan	JAMA	3045	Three-month *vs.* twelve-month	EES	ACS, sTable CAD	12-months
6	TWILIGHT 2019	US	NEJM	7119	Three-month *vs.* twelve-month	ZES/EES/SES	ACS, sTable CAD	12-months
7	TICO 2020	Korea	JAMA	3056	Three-month *vs.* twelve-month	SES/AG	ACS	12-months

ZES: zotarolimus-eluting stent; EES: everolimus-eluting stent; SES: sirolimus-eluting stent; COMBO: SES; bioabsorbable polymer (Orbus Neich, Hong Kong, China), BES: biolimus-eluting stents; ACS: Acute coronary syndrome, CAD: coronary artery disease, DAPT: dual antiplatelet therapy.

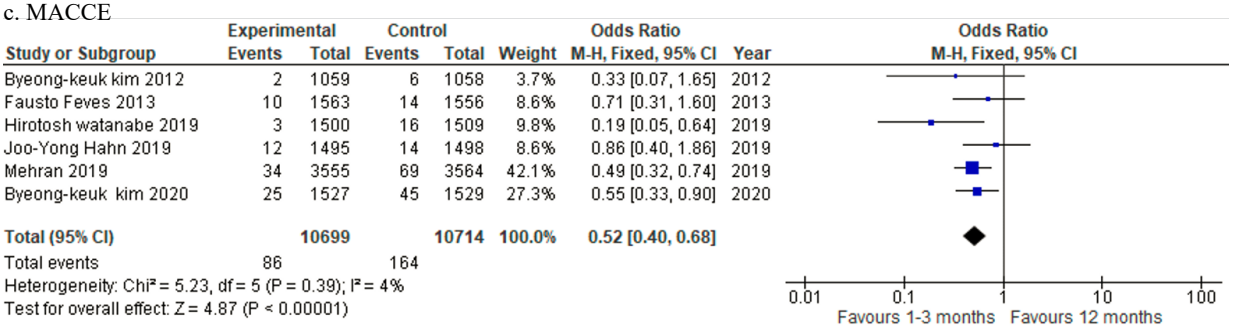
a. MACE



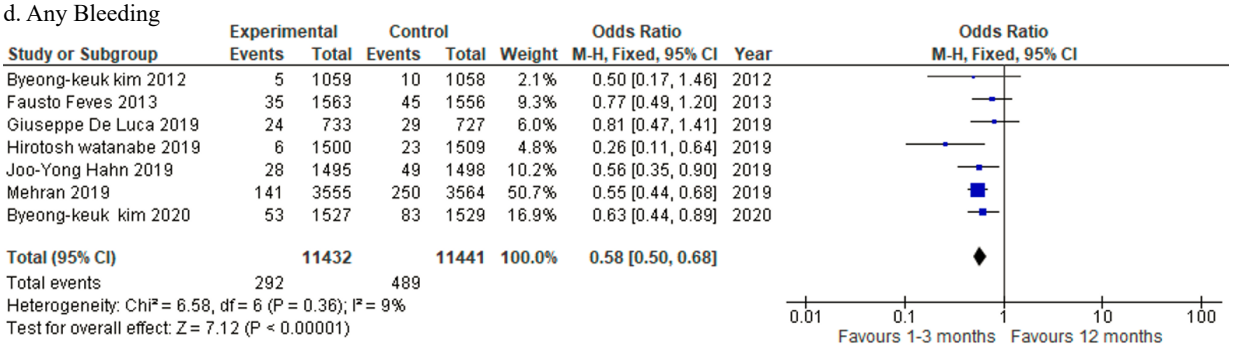
b. Major Bleeding



c. MACCE



d. Any Bleeding



e. NACE

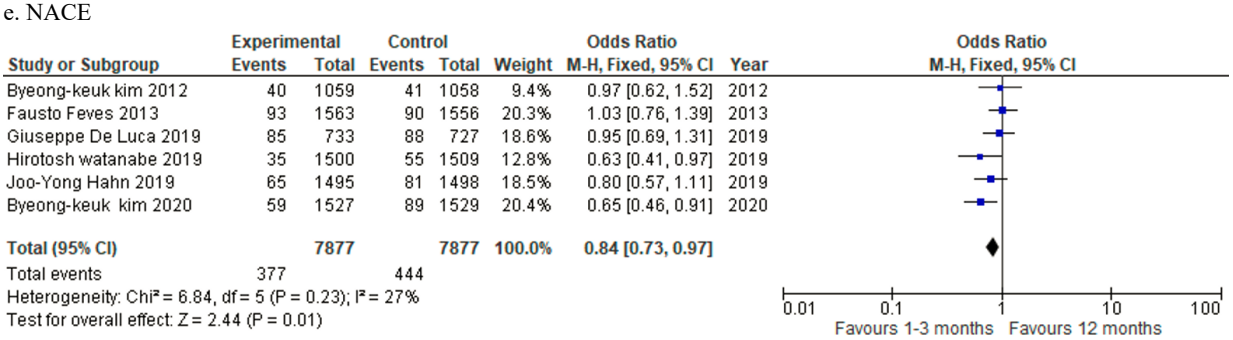


Figure 2. Forest plot for efficacy and safety endpoints.

Comparison of efficacy and safety outcomes among short-duration and standard-duration DAPT classes (a) MACE: major adverse cardio-vascular events, (b) Major blood loss, (c) any bleeding, (d) MACCE: major adverse cardio-cerebrovascular events, (d) NACE: net adverse cardiovascular events.

Supplementary Figure 2. Forest plots for ACS patients analysis (click here)

Secondary endpoint: MACCE

The endpoint of MACCE was presented in 6 trials. MACCE events were recorded in 370 out of 7,877 patients medicated with one to three months of DAPT and 378 out of 7,877 patients receiving twelve-month DAPT. Moreover, the pooled analysis revealed no statistically significant variation among the two classes (4.7% *vs.* 4.8%, OR 0.98, 95% CI 0.84-1.13, *p*=0.74, Figure 2c).

Secondary endpoint: any bleeding

The endpoint of any bleeding was reported by all the 7 trials (22,873 patients). The incidence of bleeding was found in 292 patients among 11,432 patients treated with short-duration DAPT. In contrast, 489 out of 11,441 patients in the standard-duration DAPT presented with any bleeding. In comparison to the standard DAPT, there was a statistically significant 42% decrease in the likelihood of blood loss among the individuals undergoing the short DAPT (25.0% vs 4.5%, OR 0.58, 95% CI 0.50-0.86, p=0.00001, Figure 2d).

Secondary endpoint: NACE

NACE was demonstrated in 6 trials. NACE was observed in 377 and 444 patients in the little-duration and standard-time DAPT groups, respectively. NACE chances were reduced by 16% in the short DAPT class (2.5% vs 4.2%, OR 0.84, 95% CI 0.73-0.97, p=0.01, Figure 2e). The ischemic risk in acute coronary syndrome patients would be higher than in sTable CAD patients under short-term DAPT, so the benefits and risks were

analyzed for acute coronary syndrome patients under different durations of DAPT.

The findings showed no statistically significant difference in the frequency of MACE (3.6% *vs.* 3.8%, OR 0.94, 95% CI 0.70-1.26, *p*=0.68, Supplementary Figure 2a) and MACCE (4.0% vs. 4.7%, OR 0.84, 95% CI 0.66-1.07, p=0.16, Supplementary Figure 2b) among short-time and standard-time DAPT in individuals with acute coronary disorder. However, the risk of any bleeding (2.7% vs. 4.0%, OR 0.66, 95% CI 0.51-0.86, p=0.002, Supplementary Figure 2c) and NACE (5.52% vs. 6.51%, OR 0.83, 95% CI 0.70-0.99, p=0.04, Supplementary Figure 2d) was significantly reduced by 34% and 17%, respectively, in the short duration DAPT group.

Discussion

This meta-analysis included seven RCTs that evaluated short-time (one to three months) and standard-time (twelve months) DAPT in individuals who had coronary intervention through percutaneous with the latest generation DES and received standard medical treatment.[9,10,13-17] Our study found that short-duration DAPT reduced the risk of principal blood loss, any kind of bleeds, and NACE (Figure 2b, d, e). Short-duration DAPT significantly reduced major bleeding risk by 48.1% as compared to standard-duration DAPT (0.8% vs 1.5%, OR 0.52, 95% CI 0.40-0.68, p=0.00001) without raising the chance of MACE (4.1% vs. 4.2%) and MACCE (4.7% vs. 4.8%) when compared with standard-duration DAPT (Figure 2).

Regarding the efficacy endpoints, we did not find that a 12-month DAPT could decrease the risk of MACE or MACCE (Figure 2a, c) compared to a 3- or 1-month DAPT, consistent with the findings of the published meta-analysis.[18] Regarding safety endpoints, our results demonstrate that short-duration (1-3 months) DAPT significantly reduced major bleeding risks by 48.1% and any bleeding risks by 42% compared with standard-duration DAPT (Figure 2b, d).

The latest RCT, such as the TICO trial, has been included, and the heterogeneity in our meta-analysis is low for all endpoints. The incidence of the secondary endpoint of NACE was significantly reduced by 16% for short-duration (1-3 months) DAPTs relative to standard-duration DAPTs (2.5% vs 4.2%, OR 0.84, 95% CI 0.73-0.97, p=0.001). A meta-analysis by *Khan et al.* reported similar findings.[19] Our results added a new advantage of a remarkable decrease in net unfavourable medical conditions for short-duration DAPT.

Besides, major and total bleeding risks are significantly reduced with comparable risks of MACE and MACCE in short-duration DAPT, which concur with the present evidence.[18] DAPT is a combination of aspirin and P2Y12 receptor inhibitors (clopidogrel, ticagrelor, and prasugrel), mainly employed to decrease the chance of ischemia in persons receiving transdermal coronary implantation.

According to the European Society of Cardiology's 2017 and the Canadian Cardiovascular Association's 2018 recommendations, individuals with acute coronary disease getting coronary implantation through percutaneous method ought to be on the DAPT for twelve months, while people with sTable coronary artery disorder through PCI must remain on the DAPT for six months.[8,20] However, our meta-analysis revealed that one to three months of DAPT was better than the twelve-month DAPT at safety endpoints, and NACE differs from the current guidelines, which recommend a 6- or 12-month DAPT duration.

It's vital to remember that the recommendation for DAPT is based mainly on evidence from first-generation DES. In contrast, RCTs using new-generation DES only were enrolled in this meta-analysis. Improving the stent's texture and using potent P2Y12 inhibitors makes it feasible to minimize the time of DAPT. DES has reduced the incidence of restenosis by creating metal frames, polymer coverings, and antiproliferative chemicals.[21] In the LEADERS FREE trial,[22] Polymer-free umirolimus-coated stents were linked with a substantially decreased incidence of cardiac mortality, heart attack, and coagulation of the stent than stents with bare metal in individuals under one month of DAPT following coronary intervention through percutaneous.

The latest P2Y12 enemy, ticagrelor and prasugrel, have a stronger inhibitory impact on the accumulation of platelets than clopidogrel and are more useful in individuals who do not respond well to the medication.[23,24] The DAPT time may theoretically be reduced due to using powerful antiplatelet medications and new-generation stents in clinical settings. However, there is no generally accepted optimal period of

DAPT after new-generation DES installation; short DAPT must be further explored for its efficacy and safety.

Clinical implication

According to our meta-analysis, the short-duration (1 or 3 months) DAPT following an innovative pharmacutical stent placement greatly decreased the probability of blood loss and improved net medicinal value without raising the chance of likelihood cardiovascular and cerebrovascular events compared with 12-month DAPT.

Notably, the results imply that a short duration of DAPT is suiTable for individuals with high blood loss chance or those who need non-cardiac surgery or invasive procedures within 3 months. Besides, the short-duration DAPT alleviates the medical burden. Our results align with the 2019 and 2020 ESC guidelines that suggest that DAPT duration be shortened in particular clinical scenarios.[25]

Limitations

Several limitations exist in this study. Firstly, the baseline characteristics, drug-eluting stents and P2Y12 inhibitors, and randomization method were not the same among the 7 RCTs in this meta-analysis. However, the heterogeneity across the trials was low in all endpoints. Secondly, the ischemic and bleeding risks may differ individually, confounding the results. Thus, the acute coronary disorder persons were analyzed, and the endpoint results were consistent with the study. Anyhow, the conclusions need to be interpreted cautiously, and the duration of DAPT is suggested based on specific clinical conditions.

Conclusion

Compared to standard-duration (≥12-month) DAPT, short-duration (1- or 3-month) DAPT substantially decrease the bleeding likelihood (main blood loss and any blood loss) by more than 40% without increasing the ischemic risk for patients after new-generation DES implantation. Besides, a significant reduction of up to 16% in net clinical adverse events was found in the short-duration DAPT arm, including the acute coronary syndrome subgroup. It is reasonable to reduce DAPT time to 1- or 3 months in individuals implanted with new-generation drug-eluting stents, especially those with high bleeding risk or scheduled to receive surgery recently.

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Conflict of interest: The authors declare that they have no competing interests.

Authors' contributions: IU and MA did the original draft preparation, study design, validation and analysis; MU and HZ did the writing—review and editing; IU, MA did data extraction and quality assessment; HZ did supervision. All authors listed have made a substantial, direct and intellectual contribution to the manuscript, All authors have read and agreed to the published version of the manuscript.

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