Comparison of short-term DAPT and long-term DAPT on the prognosis of PCI patients: a meta-analysis of randomized controlled trials

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Article

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Abstract

Background

This article aimed to evaluate the safety and effectiveness of short-term (3–6 months) dual antiplatelet therapy (DAPT) compared to long-term (12 months) DAPT.

Methods

We searched PubMed, Embase, Cochrane Library, and Web of Science for all the randomized controlled trials which compared the different durations of DAPT after the percutaneous coronary intervention within ten years before January 2021. The safety endpoint included major bleeding and any bleeding. The efficacy endpoints included all causes of death, cardiac death, myocardial infarction, definite or probable stent thrombosis, target vessel revascularization, and stroke. The hazard ratio and 95% confidence interval were abstracted.

Result

11 trials and 24242 patients were finally included in this meta-analysis. Short-term DAPT was associated with a reduced risk of major bleeding [HR 0.65, 95%CI 0.48–0.89] and any bleeding [HR 0.64, 95%CI 0.53–0.79] compared with long-term DAPT. No significant differences in the risks of other endpoints were observed. In acute coronary syndrome, short-term DAPT was associated with a lower risk of major bleeding [HR 0.57, 95%CI 0.37–0.87].

Conclusion

Compared with long-term DAPT, short-term DAPT reduced bleeding after PCI with DES. Besides, short-term DAPT was also feasible and safely applicable if clinically required even in ACS patients.

1 Introduction

Dual antiplatelet therapy (DAPT), with aspirin and a P2Y12 receptor inhibitor, is the basic medication for patients after percutaneous coronary intervention (PCI) to reduce the risk of stent thrombosis and prevent coronary atherothrombotic events at sites outside the stented segment. International guidelines suggest that DAPT should be given for at least 12 months for patients with acute coronary syndromes (ACS) after drug-eluting stents (DES) implantation; and for patients with stable ischemic heart disease after DES, DAPT should be given for at least 6 months [1, 2]. Due to refinements in DES technology and the emergence of potent P2Y12 receptor inhibitors, the optimal duration of DAPT is still controversial.
The results of several randomized controlled trials (RCTs) had shown that three to six months of DAPT after PCI with DES had non-inferiority compared with long-term (≥ 12 months) DAPT [3–6]. The reason may be that shorter DAPT duration reduced all-cause mortality by reducing bleeding[7], whereas longer DAPT duration is associated with an increased risk of any bleeding[8]. However, the increased risk of myocardial infarction with 6-month DAPT prevented the researchers from concluding that short-term DAPT was safer in patients with ACS [9]. A meta-analysis also concluded that 3-month DAPT was associated with increased ischemic risk in patients with ACS, although most of the enrolled ACS patients were at relatively low-risk [10]. In addition, studies had shown that short-term DAPT followed by a P2Y12 receptor inhibitor monotherapy reduced the bleeding risk without increasing the risk of death, myocardial infarction, and stroke compared to long-term DAPT[11–14].

Considering the poor compliance of patients with long-term DAPT and the increasing risk of bleeding, shortening the duration of DAPT or followed by P2Y12 receptor inhibitor monotherapy may bring benefits from reducing bleeding risks and relieving the global health burden. Therefore, we included the most recent RCTs for the current meta-analysis to investigate the differences in bleeding and ischemic risks between short-term DAPT (3–6 months) and long-term DAPT (12 months). And subgroup analyses (such as patients with ACS and single antiplatelet therapy) were performed to provide a more comprehensive and accurate evaluation.

2 Methods

We registered our protocol with PROSPERO (CRD42021260473). The meta-analysis was prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidelines [15].

2.1 Search Strategy

To obtain qualified RCTs, we searched PubMed, Embase, Cochrane Library, and Web of Science for all trials within ten years before February 15, 2021, which investigated the impact of DAPT duration on the prognosis of PCI patients. The MeSH search terms included the following: Percutaneous Coronary Intervention, Drug-Eluting Stents, Dual Anti-Platelet Therapy, Aspirin, Clopidogrel, Prasugrel Hydrochloride, Ticagrelor, and Randomized Controlled Trials. Our search strategies were present in supplement detail 1.

2.2 Inclusion/Exclusion Criteria, Outcomes, and Quality Assessment

Trials that met the following criteria were included: original articles published in the English language; randomized controlled trials compared different durations of DAPT in patients undergoing PCI with DES; the durations of short-term DAPT were 3-6months and the durations of long-term DAPT were 12months; outcomes included main cardiovascular events and bleeding. We excluded non-RCTs, sub-studies of large studies, and those with missing data. After removal of duplicates, two investigators independently
screened the remaining articles at the titles and abstracts, then read the full texts in detail to identify included trials. Finally, cross-checked the data and negotiated to resolve differences.

The prespecified safety endpoints included major bleeding and any bleeding. The efficacy endpoints included all causes of death, cardiac death, myocardial infarction (MI), definite or probable stent thrombosis, target vessels revascularization (TVR), and stroke. Major bleeding and any bleeding are defined in Supplemental Table 1.1–1.2.

The two investigators reviewed the studies, extracted basic information and outcomes independently, and evaluated the included trials for selection bias, performance bias, detection bias, attrition bias, reporting bias, and other sources of biases according to the Cochrane Collaboration Assessment (16) for the risk of bias with Review Manager 5.4.

2.3 Statistical Analysis

The data was analyzed by Stata 14.2 software. The hazard ratio (HR) and 95% confidence interval were abstracted to quantify the effects of different durations. Use Cochrane’s Q and $I^2$ to assess the heterogeneity. The heterogeneity was regarded as low when $p > 0.10$ and $I^2 < 50\%$ and a fixed-effects model was used when heterogeneity was low. Egger test and funnel plot were used to complete the bias assessment. According to the short-term DAPT duration (S-DAPT), single antiplatelet therapy (SAPT), and patients who had ACS, subgroup analyses were performed. We also performed sensitivity analyses.

3 Result

3.1 Study characteristics and bias assessment

Of 2456 articles, 1646 were screened after removing duplications and 1608 articles were excluded at the title and abstract level. The full texts of 24 potentially eligible articles were scrutinized and 14 of them met the inclusion and exclusion criteria. Since 3 articles didn’t generate HR, a total of 11 trials encompassing 24278 patients were finally included in this meta-analysis. The specific process of selection was shown in Fig. 1.

For direct comparisons, 7 trials[4, 5, 9, 16–19] compared 6-month DAPT followed by aspirin monotherapy with 12-month DAPT. 2 trials[6, 20] compared 3-month DAPT followed by aspirin monotherapy and 2 trials[14, 21] compared 3-month DAPT followed by P2Y12 receptor inhibitor monotherapy with 12-month DAPT. Among these 11 trials, 5 trials[4, 9, 14, 18, 20] reported outcomes in patients with ACS. The median follow-up duration across all trials was 15 months. The baseline characteristics of the included trials and participants were shown in Table 1.

According to NOS, there were 8 trials[5, 9, 14, 16, 18–21] describing the methods of generating random sequences, such as computer-generated random sequences. 2 trials[17, 20] described sequence hid through central allocation. 1 trial[17] used double-blind methods, and all trials had blinded outcome
assessments. There were no incomplete outcome data and selective reporting. Biases from other sources were unknown. The results of the risk bias assessment of each RCT were summarized in Fig. 2.

3.2 Outcomes of Meta-Analysis

Due to p > 0.10 and I² < 50% which meant the low heterogeneity after testing of all endpoints, a fixed-effects model was used.

3.2.1 Bleeding endpoints

9 trials recorded major bleeding and 7 trials recorded any bleeding. Short-term DAPT was associated with a reduced risk of major bleeding (HR 0.65, 95%CI 0.48–0.89) and any bleeding (HR 0.64, 95%CI 0.53–0.79) compared with 12-month DAPT. The forest plots of major bleeding and any bleeding were shown in Fig. 3.

3.2.2 Mortality, Ischemia Endpoints, and Stroke

11 trials recorded all causes of death, and 9 trials recorded cardiac death. No differences were observed between short-term DAPT and long-term DAPT in the risks of all causes of death (HR 0.91, 95%CI 0.73–1.12) and cardiac death (HR 0.89, 95%CI 0.66–1.20).

10 trials recorded myocardial infarction, 9 trials recorded definite/probable thrombosis stent and 7 trials recorded target vessels revascularization. Compared with 12-month DAPT, short-term DAPT was not associated with higher risks of myocardial infarction (HR 1.15, 95%CI 0.91–1.46), definite/probable thrombosis stent (HR 1.41, 95%CI 0.96–2.07], and target vessels revascularization (HR 1.15, 95%CI 0.91–1.45).

9 trials recorded stroke. Short-term DAPT showed no significant differences compared with long-term DAPT (HR 1.05, 95%CI 0.72–1.55). And the forest plots of death, ischemia endpoints, and stroke were shown in Fig. 4.

3.3 Subgroup analysis

According to the short-term DAPT duration (S-DAPT), single antiplatelet therapy (SAPT), and patients who had ACS, subgroup analyses were performed (Supplement Table 1). Compared with 12-month DAPT, 3-month DAPT (HR 0.65, 95%CI 0.45–0.94), and short-term DAPT followed by P2Y12 receptor inhibitor monotherapy (HR 0.64, 95%CI 0.42–0.96) were associated with lower risks of major bleeding. In patients with ACS, it was given a reduced risk of major bleeding (HR 0.57, 95%CI 0.37–0.87) and non-significant risk of any bleeding (HR 0.73, 95%CI 0.53–1.01) compared with 12-month DAPT. There were no significant differences in mortality, ischemia endpoints, and stroke between the different DAPT strategies in these subgroups.

3.4 Sensitivity analysis and the meta-regression
We evaluated the stability of the outcomes by removing one trial and recombining the remaining trials, then performed a sensitivity analysis for each endpoint. As shown in Supplement Table 2, we obtained similar outcomes, which confirms the stability of our research.

By funnel plot and Egger test shown in Supplement Fig. 1 and Table 3, no publication bias was found.

4 Discussion

In this meta-analysis, we included 11 RCTs and 24278 patients to assess the effectiveness and safety of short-term (3–6 months) DAPT and long-term (12 months) DAPT among patients who underwent PCI with DES. Compared with 12-month DAPT, short-term DAPT was superior for major bleeding and any bleeding, and non-inferior for all causes of death, cardiac death, myocardial infarction, definite or probable stent thrombosis, target vessels revascularization, and stroke. Even in patients with ACS, short-term DAPT continued to be superior in reducing major bleeding. Besides, 3-month DAPT and short-term DAPT followed by P2Y12 receptor inhibitor monotherapy were associated with lower risks of major bleeding.

For balancing the risks of bleeding and ischemic, establishing the optimum duration of DAPT after DES implantation is crucial. The results of several RCTs concluded that short-term (3–6 months) DAPT was non-inferior to 12-month DAPT for the occurrence of death, ischemia, and bleeding among general and ACS patients[4, 6, 16, 20]. A previous network meta-analysis concluded that 12-month DAPT resulted in higher any bleeding than short-term DAPT[8]. Furthermore, subsequent bleeding complications after successful DES implantation were strongly associated with all causes of death, and the magnitude of the effect of bleeding on mortality exceeded that of MI[22]. Therefore, efforts to reduce the incidence of bleeding after PCI with DES may further improve the prognosis. With the rapid development of science and technology, DES is constantly being updated. Compared with bare-metal stents, the second-generation DES was associated with a reduction in the 1-year rate of definite stent thrombosis [23]; compared with the first-generation DES, they demonstrated larger stent coverage, less inflammation, fewer fibrin deposits, and less thrombosis[24]. On this basis, some researchers questioned whether the duration of DAPT should be shortened once again.

The results of our meta-analysis support the above conclusions. Short-term DAPT was associated with a reduced risk of major bleeding and any bleeding compared with 12-month DAPT. No differences were observed between short-term DAPT and 12-month DAPT in the risks of all causes of death, cardiac death, MI, definite or probable stent thrombosis, TVR, and stroke. Therefore, short-term DAPT was as effective as long-term DAPT with better safety. These important findings support the clinical necessity of defining a new DAPT regimen. Short-term DAPT has a more favorable balance between bleeding and ischemia, regardless of gender[25], age[26], and diabetes[27]. At the same time, clinicians should refer to the recommendations of the European Society of Cardiology guidelines[28] and the 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization[29] and pay attention to individualized risks (low bleeding risk vs high bleeding risk).
In patients with ACS, the 2021 ACC/AHA/SCAI Guideline for Coronary Artery Revascularization[29] recommended at least 12 months of DAPT, with consideration that the duration could be extended beyond 12 months in patients with no risk of bleeding, and 6 months of DAPT in patients with a higher risk of bleeding. Scientific societies have been in favor of DAPT after an ACS relied on CURE trial[30]. CURE demonstrated that 3 to 12 months (mean duration of treatment, 9 months) of DAPT reduced the risk of MI and recurrent ischemia and increased the risk of major bleeding in patients with ACS without ST-segment elevation[30]. However, it was conducted 2 decades ago comparing the differences between DAPT and aspirin alone, which supported DAPT per se rather than the duration of DAPT for 12 months or longer, whereas new generation DES technologies had been shown to minimize the risks of MI and stent thrombosis[31, 32]. Moreover, a landmark analysis from this trial demonstrated that nearly all the benefits of DAPT were achieved by the first 3 months after randomization[33]. In recent years, studies on the strategies of DAPT in ACS patients, including RCTs and meta-analyses, had shown that short-term DAPT was superior in reducing the occurrence of major bleeding, but no consistent results could be concluded in safety. The main problems were myocardial infarction and stents thrombus. In the multicenter SMART-DATE trial[9], a total of 2,712 ACS patients were randomly assigned to six-month (n = 1,357) and 12-month or longer DAPT (n = 1,355). Although 6-month DAPT was shown to be non-inferior to 12-month or longer DAPT for the primary endpoint of major adverse cardiac and cerebrovascular events, the rate of MI was significantly higher in the 6-month DAPT group. However, the rate of stent thrombosis did not differ significantly between the two groups. They analyzed that long-term DAPT might reduce the risk of MI by prevention of non-target vessel MI rather than by reduction of stent thrombosis. Similarly, a network meta-analysis [10] had found that three-month but not six-month DAPT was associated with higher rates of MI and definite or probable stent thrombosis, compared with 12-month DAPT. Since the included ACS patients in their study were 4758, this might affect the credibility of the conclusion. Conversely, no noticeable differences were observed with regard to MI and stent thrombosis between short-term and long-term DAPT in DAPT-STEMI[4], REDUCE[20] and TICO[14]. Our findings were in line with them. In our current meta-analysis, short-term DAPT resulted in an absolute reduction in the risk of major bleeding, whereas no difference in all causes of death, cardiac death, myocardial infarction, definite or probable stent thrombosis, target vessels revascularization, and stroke among the included 8890 ACS patients.

On the one hand, the low event rates might be attributed to the improved design of the second-generation DES. On the other hand, it might be related to the development of atherosclerosis. Compared with stable angina pectoris (SAP), multiple complex coronary plaques are more common and coronary plaques are more unstable in ACS[34], whether they are the target plaques or not. The remaining multiple complex lesions are generally treated during the primary PCI or subsequent elective PCI. Regarding the unstable plaques, 75% of them seem to stabilize or heal during the 12-month follow-up and 25% remain unchanged[35]. Thus, these plaques are much more likely to keep clinically silent or present stable rather than an ACS occurrence. DAPT as secondary prevention may reduce cardiovascular events, but these events are rare. Benefits from the reduction of ischemic events by long-term DAPT are not enough to compensate for the increase of bleeding events. In summary, short-term DAPT was also feasible and safely applicable if clinically required even in ACS patients, especially in those with high bleeding risk.
We also conducted subgroup analyses based on the different DAPT strategies. Compared with 12-month DAPT, 3-month DAPT and short-term DAPT followed by P2Y12 receptor inhibitor monotherapy were associated with lower risks of major bleeding and no significant differences were observed in mortality, ischemia endpoints, and stroke. It must be mentioned that three large RCTs[6, 14, 21] compared 3-month DAPT with 12-month DAPT and recorded major bleeding, two[14, 21] of them stopped aspirin and continued P2Y12 receptor inhibitor monotherapy for another 9 months after 3-month DAPT. In the TICO trial of patients with ACS, ticagrelor monotherapy resulted in a significant 2% absolute reduction in the composite outcome of major bleeding and major adverse cardiac and cerebrovascular events, with the significantly reduced risk of major bleeding[14]. In the SMART-CHOICE trial, clopidogrel monotherapy was non-inferior to 12-month DAPT for the major adverse cardiac and cerebrovascular events and was associated with a lower rate of bleeding (21). The activation of the P2Y12 receptor plays a critical role in the production of platelet thromboxane (TX) A2 in vitro and vivo[36]. A strong P2Y12 receptor inhibitor alone can block the platelet aggregation through the TXA2-dependent pathway, while aspirin has little enhancement effect on this[37]. In the presence of the P2Y12 receptor inhibitor, the additional inhibitory effect of aspirin on platelet aggregation may be minimal. A study had also shown that P2Y12 receptor inhibitor monotherapy and DAPT had the same extent to inhibit the activation of the hemostatic system[38]. Therefore, the P2Y12 receptor inhibitor monotherapy after short-term DAPT may be a suitable antiplatelet strategy to reduce the risk of bleeding in patients with SAP or ACS treated with DES while maintaining anti-ischemic benefits.

A published meta-analysis[39] had reached similar conclusions to ours and some differences in comparing the two articles are as follows. First, they compared 1–6 months DAPT with ≥ 12 months DAPT, which was different from that we compared 3-6 months DAPT with 12 months DAPT. Secondly, they extracted risk ratio (RR) and 95% confidence interval. We respected the original research results and directly extracted hazard ratio (HR) and 95% confidence interval, so our results were more accurate. Next, we included the most recent randomized controlled trial TICO[14] and ruled out the studies that accepted other anticoagulant drugs or lacked HR, which was more credible. Finally, we performed a subgroup analysis of ACS patients so that our conclusions could be applied to different populations.

Although this meta-analysis is the most comprehensive by far and its low heterogeneity after testing of all endpoints, it has the following limitations. At first, part of the implanted DES was the first-generation devices, and these devices were no longer used in clinical practice. The balance of risks and benefits may be more conducive to shortening the duration of DAPT by using second-generation DES because it is more secure than the first-generation DES [24]. Then, the effectiveness and safety of aspirin monotherapy after 3 months of DAPT need to be further studied. Finally, all trials included in the meta-analysis are open-label and may lead to bias. In addition, different experiments have slightly different definitions of certain clinical endpoints, which may introduce effect modification. The determination of bleeding and bleeding-related deaths can also be challenging, so these findings should be interpreted with caution.

5 Conclusion
Compared with long-term DAPT, short-term DAPT reduced bleeding after PCI with DES, indicating safer. Of course, the effectiveness of short-term DAPT was not inferior to long-term DAPT. Besides, short-term DAPT was also feasible and safely applicable if clinically required even in ACS patients. And P2Y12 receptor inhibitor monotherapy after short-term DAPT might be a good strategy.

**Declarations**

6. **Authors’ contributions**

Hailong Ge designed the study. Jiaxin Yang and Yaodong Ding performed the literature search, study selection, data extraction, quality assessment, and statistical analysis. Jiaxin Yang drafted the manuscript. Yaodong Ding, Rui Wang, Kexin Wang, and Hailong Ge revised the draft. Xiaoli Liu, Hua Shen, Yujie Zhou and Zhe Fang modified the English. All authors approved the final version of the manuscript.

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8. **Conflict of Interest**

The authors declare that the research was conducted in the absence of any commercial or financial relationships that could be construed as a potential conflict of interest.

9. **Availability of data and material**

The datasets used and analyzed during the current study will be available from the corresponding author on reasonable requests after study completion.

10. **Ethics approval**

The study was approved by the Beijing Anzhen Hospital Ethics Committee of Capital Medical University

11. **consent to participate**

Not applicable.

12. **Consent for publication**

Not applicable.
13. Acknowledgements

Not applicable.

14. Research involving Human Participants and/or Animals

Not applicable.

15. Informed consent

Not applicable.

References


31. Palmerini T, Benedetto U, Biondi-Zoccai G, Della Riva D, Bacchi-Reggiani L, Smits PC et al: Long-Term Safety of Drug-Eluting and Bare-Metal Stents: Evidence From a Comprehensive Network Meta-


**Table 1**

Table 1 is available in the Supplementary Files section.

**Figures**
Figure 1

The selection process included studies

Records identified through database searching (Pubmed=278, Embase=1193, Cochrane Library=466, Web of science=522) (n = 2459)

Records after duplicates removed (n = 1646)

Records screened based on titles and abstract (n = 1646)

Records excluded (n = 1622)

Excluded: 3 didn’t compare the outcomes of different DAPT duration; 2 didn’t record ischemia or bleeding outcomes; 5 didn’t match the durations of short- or long-term DAPT (n = 10)

Full-text articles assessed for eligibility (n = 24)

Didn’t generate hazard ratio (n=3)

Studies included in qualitative synthesis (n = 14)

Studies included in final quantitative synthesis (meta-analysis) (n = 11)
Figure 2

Quality assessment of included studies

![Quality Assessment Matrix](image)

Figure 3

The forest plots of major bleeding and any bleeding.
Figure 4

The forest plots of death, ischemia endpoints, and stroke.

Supplementary Files

This is a list of supplementary files associated with this preprint. Click to download.
• supplement.docx
• Table1.docx