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Efficacy of Short-term Dual Antiplatelet Therapy after Implantation of Second-generation Drug-eluting Stents: A Meta-analysis and Systematic Review

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Key words: meta-analysis; drug-eluting stents; dual antiplatelet therapy; percutaneous coronary intervention; efficacy

Objective The benefit of short-term dual antiplatelet therapy (DAPT) following second-generation drug-eluting stents implantation has not been systematically evaluated. To bridge the knowledge gap, we did a meta-analysis to assess the efficacy of ≤6 months *versus* ≥12 months DAPT among patients with second-generation drug-eluting stents.

Methods We searched online databases and identified randomized controlled trials that assess the clinical impact of short-term DAPT (≤6 months) published before March 3, 2016. The efficacy endpoints included the incidence of all-cause death, myocardial infarction, cerebrovascular accidents, and definite or probable stent thrombosis. Safety endpoint defined as major bleeding was also evaluated and discussed.

Results We included 5 trials that randomized 9473 participants (49.8%, short-term DAPT duration *vs.* 50.2%, standard duration). A total of 9445 (99.7%) patients reported the efficacy endpoints, and the safety endpoint was available from 4 studies (n=8457). There was no significant difference in efficacy endpoints between short-term and standard DAPT duration (≥12 months) [risk ratio (*RR*) 0.96; 95% confidence intervals (*CI*), 0.80-1.15]. Short-term DAPT duration did not significantly increase the individual risk of all-cause death, myocardial infarction, cerebrovascular accidents, or definite or probable stent thrombosis. Although short-term DAPT obviously reduced risk of major bleeding compared with standard DAPT (*RR* 0.53; 95% *CI*, 0.29-0.96), significant publication bias was found when accessing the safety endpoint of the 4 studies (Egger's test, P=0.009).

Conclusions The efficacy of short-term DAPT was comparable with that of standard duration DAPT.

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DAPT less than 6 months may be appropriate for patients receiving second-generation drug-eluting stents implantation.

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DUAL antiplatelet therapy (DAPT) has been the cornerstone in secondary prevention after percutaneous coronary intervention (PCI) procedures. At first, extended DAPT was considered to be associated with a significant reduction in late and very late stent thrombosis in patients undergoing PCI with the first-generation drug-eluting stent (DES) implantation. However, prolonged DAPT could lead to a significant increase in bleeding events, which may offset the potential benefit.[1] In the second-generation DESs' era, with superior safety due to improved vascular healing and stent strut intimal coverage properties,[2-4] the new DESs raise the possibility to shorten DAPT duration while maintaining the efficacy.[5] Current European Society of Cardiology (ESC) and American Heart Association/American College of Cardiology (AHA/ACC) guidelines recommend a minimum duration of DAPT of 6 to 12 months and 12 months respectively,[6-7] for such circumstance. While neither of them provided specific recommendation of the DAPT for the second-generation DESs, despite they account for the vast majority of stents used nowadays.

In recent years, several randomized trials evaluated the outcome of short-term DAPT in patients undergoing PCI with the second-generation DESs, including zotarolimus-eluting stent (ZES) and everolimus-eluting stent (EES). Due to the rarity of ischemic and bleeding events, each trial had limited statistical power to conclude the noninferiority on shorter duration of DAPT. One newly published meta-analysis concluded it was safe with DAPT no more than 6 months in patients receiving second-generation DESs.[8] While it actually did not exclude randomized controlled trials enrolling patients undergoing bare metal stents (BMS) and the first-generation DESs. So far, barely systematic evidences particularly based on the second-generation DESs are available in the current cardiology practice.

Therefore, we sought to assess the efficacy of short-term DAPT (≤6 months) compared with that of standard DAPT (≥12 months) by doing a comprehensive meta-analysis of randomized controlled trials among patients undergoing the second-generation DESs implantation.

MATERIALS AND METHODS

Database search

The literature searches were performed in Medline (with the Ovid interface), EMBASE, Cochrane Central Register of Controlled Trials (CENTRAL) and China National Knowledge Internet (CNKI) database to identify relevant randomized clinical trials published up to March 3, 2016. We also screened the ClinicalTrials. gov. The following search terms were used: "randomized controlled trial", "random", "placebo", "random allocation", "single-blind", "double-blind", "triple-blind", "DES", "drug- eluting stent", "DAPT", "dual antiplatelet therapy", "aspirin", "ASA", "acetylsalicylic acid", "clopidogrel", "Plavix", "prasugrel", "Effient", "ticagrelor", "Brilinta", "thienopyridine", "short term", "short duration", "3-month", and "6-month". Manually searching for additional relevant studies was done until no further citations were available. Searches were restricted to trials of human participants with full text published in English or Chinese.

Inclusion and exclusion criteria

We selected all randomized controlled trials that analyzed the efficacy of ≤6 months DAPT *vs.* ≥12 months after implantation of second-generation DESs. Two investigators (Peisen Huang and Yuan Yu) independently assessed all potentially relevant studies to identify studies that satisfied the following criteria: 1) human subjects underwent implantation of the second-generation DESs to treat coronary artery disease, 2) participants were randomly assigned to receive either short-term DAPT, defined as management with aspirin and a P2Y12 receptor inhibitor (clopidogrel, prasugrel, or ticagrelor) for no more than 6 months, or standard duration DAPT, defined as DAPT treatment given for at least 12 months after index PCI, and 3) follow up for at least 12 months. Exclusion criteria were: 1) a non-randomized controlled design, editorial comments, reviews, and conference abstracts, 2) a repeated report on the same study population or duplicated data. Discrepancies between the two reviewers in study selection were resolved by a third independent investigator.

Data collection and assessment of risk of bias

Two investigators (Peisen Huang and Yuan Yu) independently reviewed the full text of included trials and did the data collection. Efficacy endpoint (all-cause death, myocardial infarction, cerebrovascular accidents, and definite or probable stent thrombosis) and safety endpoint (major bleeding) were analyzed. In trials where participants were