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The optimal discontinuation of dual antiplatelet therapy in patients undergoing percutaneous coronary intervention with drug-eluting stents: A meta-analysis of randomized trials

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ABSTRACT

Background: Current guidelines recommend prolonged dual antiplatelet therapy (DAPT) for patients with drug-eluting stents (DES) implantation. Nevertheless, optimal discontinuation of DAPT remains a controversy. We performed a meta-analysis of all randomized controlled trials (RCTs) that evaluate optimal discontinuation of DAPT in patients undergoing percutaneous coronary intervention (PCI) with DES.

Methods: We searched electronic databases including PubMed, Cochrane Library, EMBASE and ClinicalTrials.gov from database RCTs that reported different modes of discontinuation of DAPT in patients with DES. The primary endpoints were all-cause death, cardiovascular death, myocardial infarction (MI) and probably or definite stent thrombosis (ST). Secondary endpoints were repeat revascularization, stroke, major bleeding and net adverse clinical events (NACE).

Results: We included 13 RCTs meeting the criteria with a total of 36,749 patients. No significant difference was observed in all-cause death (RR [95% CI] = 0.87 [0.75, 1.01], $P = 0.07$, $I^2 = 0\%$), cardiovascular death (RR [95% CI] = 0.97 [0.79, 1.19], $P = 0.76$, $I^2 = 0\%$), repeat revascularization (RR [95% CI] = 1.07 [0.92, 1.25], $P = 0.36$, $I^2 = 0\%$), and stroke (RR [95% CI] = 1.01 [0.80, 1.28], $P = 0.94$, $I^2 = 0\%$). Compared with shorter DAPT, longer DAPT was associated with a significant reduction in MI (RR [95% CI] = 1.46 [1.26, 1.69], $P < 0.00001$, $I^2 = 28\%$) and ST (RR [95% CI] = 1.93 [1.45, 2.58], $P < 0.00001$, $I^2 = 32\%$), and a significant increase in major bleeding (RR [95% CI] = 0.60 [0.49, 0.74], $P < 0.00001$, $I^2 = 0\%$). However, there was no difference in NACE (RR [95% CI] = 1.03 [0.91, 1.17], $P = 0.63$, $I^2 = 0\%$). In subgroup analyses based on stent type, we demonstrated that longer DAPT was associated with a significant reduction in thrombotic events (MI and ST) after first-generation DES implantation (RR [95% CI] = 2.58 [1.85, 3.58], $I^2 = 0\%$) and everolimus-eluting stents (EES, RR [95% CI] = 1.54 [1.12, 2.11], $I^2 = 0\%$). Conversely, there was no difference in thrombotic events in patients with zotarolimus-eluting stents (ZES, RR [95% CI] = 1.17 [0.83, 1.63], $I^2 = 75\%$) and biodegradable polymer DES (BP-DES, RR [95% CI] = 1.15 [0.74, 1.79]).

Conclusions: 1) Compared with shorter DAPT, longer DAPT was associated with a significant reduction in thrombotic events (MI and ST) and a higher rate of major bleeding. 2) By the assessment of the trade-off between thrombotic and hemorrhagic events, shorter DAPT was non-inferior to longer DAPT. 3) The benefit of longer DAPT was significant in patients with first-generation DES and EES and weakened with other second-generation DES (ZES and BP-DES).

1. Introduction

With the rapid development of cardiac interventional technique, millions of coronary artery disease (CAD) patients worldwide undergo PCI with DES every year for the treatment of ischemic events [1]. Compared with bare metal stents (BMS), DES have been shown to cause a remarkable reduction in repeated revascularization [2,3]. However, several observational studies have confirmed that there remains the risk of death or myocardial infarction (MI) after DES implantation, resulting from late or very late ST [4,5]. Therefore, DAPT (a combination of aspirin and a P2Y12 inhibitor) has been regarded as a footstone for preventing thrombotic events.

Nevertheless, the optimal discontinuation of DAPT after DES implantation remains a controversy. Previous studies reported that [6,7] premature discontinuation of DAPT was the major determinant of ST after implantation of DES, and prolonged duration of DAPT was associated with a reduction of adverse events compared to shorter DAPT.

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Contrarily, the PARIS-2 registry found [8] that DAPT discontinuation was related to an apparent increase in major cardiovascular events (MACE) only for the first 7 days after PCI and then attenuated over time. In addition, some trials reported [9–14] an opposite result in hemorrhagic events after longer DAPT. Now regardless of the type of DES, current guidelines recommend [15,16] administration of DAPT for 6 to 12 months or more after DES implantation to prevent ischemia events.

Although several RCTs have been conducted to investigate the optimal discontinuation of DAPT after DES implantation, they were underpowered enough due to small sample size and lower event rates than expected. In this study, we did perform a meta-analysis of all RCTs that evaluated efficacy and safety of shorter and longer DAPTs in patients undergoing PCI with DES.

2. Methods

We regarded the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) as a guideline to perform our meta-analysis [17].

2.1. Data sources and searches

We systematically searched electronic databases including PubMed, Cochrane Library and EMBASE from database inception to May 2016, identifying randomized clinical trials that reported different modes of discontinuation of DAPT in patients undergoing PCI with DES. The ClinicalTrials.gov was also searched to identify additional eligible clinical trials. In addition, we manually searched reference lists of the eligible studies and recent reviews about this topic. Keywords were "percutaneous coronary intervention", "drug-eluting stent", "dual antiplatelet therapy", "platelet aggregation inhibitors", "aspirin", "clopidogrel", "prasugrel", and "thienopyridine". There is no limitation to language.

2.2. Study selection

Two investigators independently screened the records. Firstly, we browsed the titles and abstracts from the results of the electronic search to exclude irrelevant articles, and then further obtained and read the full text of each article to determine whether it could meet pre-specified inclusion criteria. We solved disagreements by discussion to reached agreement on final inclusion. The inclusion criteria were as follows: 1) patients undergoing PCI with DES or a mixture of BMS and DES; and 2) randomized controlled trials comparing different durations of DAPT (aspirin plus anyone of the following agents: clopidogrel or prasugrel or ticagrelor) after PCI. Exclusion criteria were: 1) non-randomized controlled trials; 2) RCTs comparing different stents or different antiplatelet agents; 3) irretrievable or duplicated data; and 4) ongoing trials.

2.3. Data extraction and study characteristics

The following data were independently extracted by two investigators, and disagreements were resolved by the third investigator. Main characteristics of patients and randomized trials enrolled in our meta-analysis were extracted using a standardized data extraction form including: the name of the first author, publication year, sample size, age, sex, stent type, the length of randomization and follow-up at the time of index PCI, DAPT regimen and length, etc. We managed to extract data for intention-to-treat (ITT).

Our primary endpoints were all-cause death, cardiovascular death, MI and ST. The secondary endpoints included repeat revascularization, stroke and NACE as effective measure, and major bleeding as safety measure.

2.4. Quality assessment

The quality of each RCT was evaluated by two investigators respectively according to the Cochrane Handbook, which was based on the following domains: random sequence generation, allocation concealment, blinding of participants and personnel, blinding of outcome assessment, incomplete outcome data, selective reporting and other bias. Furthermore, investigators used the Grading of Recommendations Assessment, Development and Evaluation (GRADE) system to assess the quality of each endpoint.

2.5. Data analysis

Statistical analysis was performed with the RevMan software [Review Manager (RevMan).Version 5.2, The Cochrane Collaboration, Copenhagen, Denmark] and the Stata 12.0 software (Statacorp LP, College Station, Texas, USA). The Mantel-Haenszel methods for a fixed-effect model were used to the calculate pooled estimate; however, if heterogeneity was evident, the random-effect model would be used. Risk ratios (RR) and 95% confidence intervals (95% CI) were used as summary statistics for the treatment group (shorter DAPT) versus the control group (longer DAPT), with two-sided *P* values

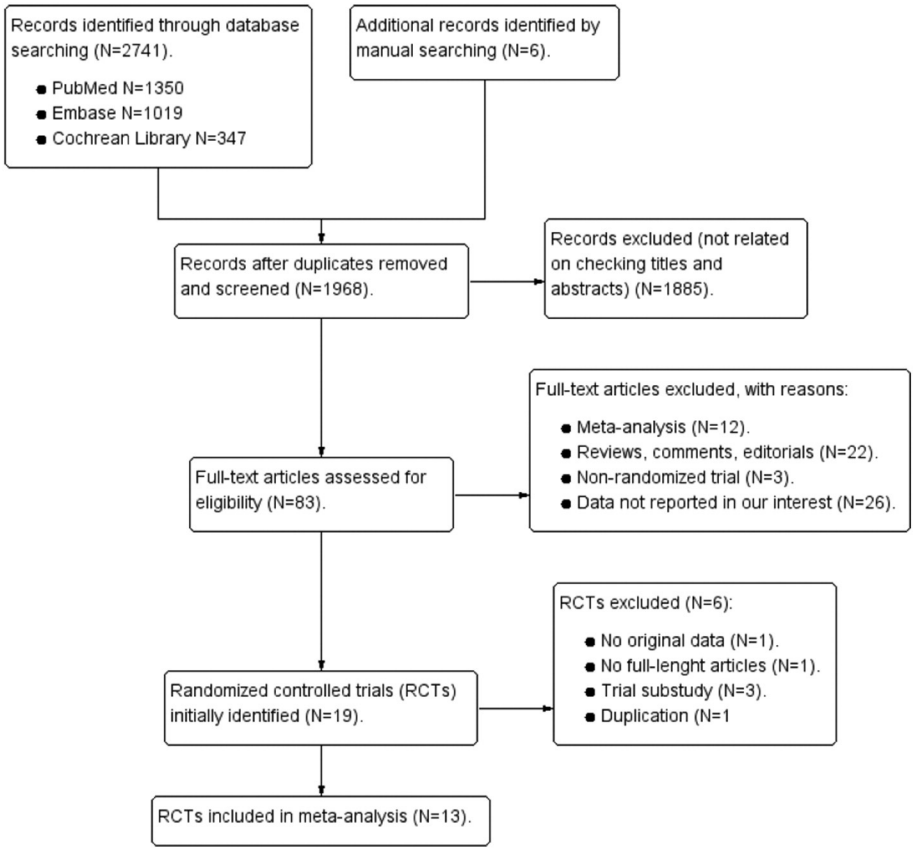

Fig. 1. Flow diagram of the literature search and study selection.

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