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Cilostazol added to aspirin and clopidogrel reduces revascularization without increases in major adverse events in patients with drug-eluting stents: A meta-analysis of randomized controlled trials ☆

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ABSTRACT

Background: The effects of cilostazol added to aspirin and clopidogrel (triple antiplatelet therapy: TAT) on clinical outcomes after drug-eluting stent (DES) implantation are unknown.
Methods: We conducted a meta-analysis of randomized controlled trials (RCTs) comparing TAT with aspirin and clopidogrel (dual antiplatelet therapy: DAT) in DES patients. Clinical end points were target lesion (TLR) and/or vessel (TVR) revascularization, death, myocardial infarction (MI), stent thrombosis (ST), bleeding, rash, gastrointestinal (GI) side effects, and drug discontinuation. We calculated the pooled estimate based on a fixed-effects model using Peto odds ratio (OR) for rare events. If heterogeneity was observed across an individual RCT, an analysis based on a random-effects model was performed.
Results: Eight RCTs were included in this meta-analysis, involving 3590 patients (TAT:DAT = 1800:1790). Up to 24 months, TAT showed a significant reduction in TLR (OR: 0.58, 95% confidence interval (CI): 0.43 to 0.78, $p<0.001$) and TVR (OR: 0.58, 95% CI: 0.40 to 0.83, $p=0.003$) compared with DAT. The incidence of death, MI, ST, or overall or major bleeding was comparable between the 2 groups, whereas the proportion of rash (OR: 2.50, 95% CI: 1.52 to 4.10, $p<0.001$), GI side effects (OR: 3.14, 95% CI: 1.79 to 5.50, $p<0.001$), or drug discontinuation (OR: 6.81, 95% CI: 2.12 to 21.86, $p<0.001$) was higher in TAT than DAT.
Conclusions: In this meta-analysis, TAT was associated with significantly effective outcomes for TLR and TVR without any increase in major adverse events but was associated with tolerance issues compared with DAT after DES implantation.

1. Introduction

Although restenosis after percutaneous coronary intervention (PCI) has been drastically reduced by drug-eluting stents (DESs) compared to bare metal stents (BMSs) [1–3], it still remains at approximately 10% [4], thus, efforts to further reduce restenosis continue.

Cilostazol, a selective inhibitor of phosphodiesterase (PDE) III, has been shown to inhibit neointimal hyperplasia after balloon injury or stenting [5,6], which is the primary cause of in-stent restenosis [7,8]. On the other hand, while cilostazol has an antiplatelet activity, it does not increase the risk of bleeding when administered in addition to aspirin and clopidogrel [9]. Currently, dual antiplatelet therapy (DAT) with aspirin and clopidogrel is recommended for at least 12 months after DES deployment [10]. Based on the favorable attributes of cilostazol, perhaps triple antiplatelet therapy (TAT), that is cilostazol administration adding to DAT, may further reduce angiographic or clinically driven restenosis without an increase in bleeding.

Recently, several meta-analyses of randomized controlled trials (RCTs) have reported a reduction in angiographic restenosis, target lesion (TLR), or vessel (TVR) revascularization without an increase in adverse events in administration of cilostazol [11–15]. However, most of them included RCTs that had not compared TAT with DAT [12,14,15], and all of them included RCTs of BMSs as well as those of DESs. To investigate the effects of TAT as compared to DAT on clinical outcomes in patients undergoing DES deployment, we conducted a meta-analysis of RCTs.

2. Materials and methods

An electronic search was performed for articles in any language using MEDLINE, EMBASE, the Cochrane Library, and Web of Knowledge. Search terms included "aspirin", "clopidogrel", "cilostazol", "drug", "eluting", "stent", and "randomized". The

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same terms or relevant trials were also searched on the website including the U.S. National Institute of Health (including clinicaltrials.gov), TCTMD.com, crtonline.org, escardio.org, and pcronline.com. The final search was run in March, 2012. The clinical end points of interest in terms of efficacy and safety were all-cause death, myocardial infarction (MI), stent thrombosis (ST), TLR, TVR, overall and major bleeding, rash, gastrointestinal (GI) side effects, and drug discontinuation. The eligibility criteria of studies for this meta-analysis were as follows: 1) RCTs comparing TAT with DAT in patients undergoing PCI using DESs; and 2) reporting the number of all-cause death, MI, ST, TLR, TVR, overall bleeding, major bleeding, rash, GI side effects, or drug discontinuation. Only RCTs were included in this meta-analysis to increase internal validity. When multiple follow-up outcomes were reported in the same study, those from the latest follow up were abstracted.

Data regarding study characteristics, baseline demographics of participants, procedural information, and outcome measures were extracted from each eligible RCT. From this information, the adequacy of randomization, double-blinding and reasons for lost to follow-up were checked, and Jadad score was calculated to assess the quality of each RCT [16]. At least 2 authors performed this process independently, and disagreements were resolved by discussion.

The pooled estimate was calculated by averaging the odds ratio (OR) of each study based on a fixed-effects model using Peto OR for rare events [17,18]. To assess heterogeneity across an individual RCT, the I^2 statistics and the Cochran's Q test were performed [19]. If these results rejected the null hypothesis of homogeneity, an analysis based on a random-effects model would be performed. If the pooled estimate for the outcomes was statistically significant, the pooled risk difference was calculated to estimate the number needed to treat, defined as 1/absolute risk difference.

The possibility of publication bias was assessed visually by a funnel plot for asymmetry plotting of the standard error of log OR against the log OR. In addition, Begg's rank correlation test [20] and Egger's linear regression test [21] were conducted as formal statistical tests for publication bias. If publication bias seemed to be present through this process, the Duval and Tweedie's trim and fill procedure was planned to be performed to estimate the possible impact of unpublished studies on the pooled estimate.

Two-sided p values of <0.05 were considered to be statistically significant. In the tests for assessment of heterogeneity or publication bias, however, the threshold for statistical significance was defined as a p value of 0.10 [22]. Analyses were conducted using STATA 11.2 (Stata Corp., College Station, Texas, USA). This study was conducted in accordance with the Preferred Reporting Items for Systematic reviews and Meta-Analyses (PRISMA) [23].

3. Results

Fig. 1 shows a flow diagram of study selection in this meta-analysis. Two studies were excluded because of BMS patients in the sample [24,25], and 3 studies (including abstracts of scientific sessions) due to the existence of other reports at longer-term follow up in the same studies, respectively. During additional web searches of the U.S. National Institute of Health, TCTMD.com, crtonline.org, escardio.org, and pcronline.com, we excluded 1 RCT using BMS [26], 3 studies that were already included through the first process, and 5 studies that had been registered at clinicaltrials.gov (U.S. National Institute of Health) but have not yet been reported. As a result, the most recent reports in 8 RCTs were included in this study, involving 3590 patients (TAT = 1800, DAT = 1790) [27–34].

Table 1 shows the characteristics of each RCT. All RCTs were conducted in South Korea, and LONG-DES II, DECLARE-DIABETES and -LONG, CILON-T, and DECLARE-LONG II were conducted as multicenter trials. The duration of follow up ranged from 1 to 24 months. Although the results at several follow-up periods were reported in some RCTs, only the most recent follow-up results were selected for comparison. The proportion of follow up was 100% in all but 2 RCTs, and the overall proportion of follow up in all 8 RCTs was 96.6% (3590 out of 3716). Most of the RCTs except DECLARE-LONG II (ZES) and the RCT conducted by Ahn et al. (SES) included more than 1 DES. Cilostazol was administered at least 6 months in all but 2 RCTs. However, the duration of baseline DAT was 6 months in both groups in 1 of the 2 RCTs [30]. Data analysis was conducted according to the intention-to-treat principle in 5 RCTs, which guaranteed the appropriateness of randomization and decision-making strategy in real world clinical settings.

The method of randomization was described in DECLARE-DIABETES and -LONG, and DECLARE-LONG II. Only DECLARE-LONG II was performed in a double-blinded fashion. Reasons for withdrawals or dropouts were described in all but 1 RCT. Accordingly, Jadad score ranged from 1 to 5.

Fig. 2 shows the clinical outcomes of the 8 RCTs up to 2 years. In the pooled analysis, TAT showed a significant reduction in proportion of TLR (OR: 0.58, 95% confidence interval (CI): 0.43 to 0.78, $p<0.001$) and TVR (OR: 0.58, 95% CI: 0.40 to 0.83, $p=0.003$) compared with DAT. The proportion of all-cause death (OR: 0.85, 95% CI: 0.45 to 1.61, $p=0.625$), MI (OR: 1.12, 95% CI: 0.57 to 2.20, $p=0.743$), ST (OR: 0.77, 95% CI: 0.39 to 1.55, $p=0.472$), overall bleeding (OR: 1.02, 95% CI: 0.63 to 1.65, $p=0.931$), or major bleeding (OR: 1.97, 95% CI: 0.71 to 5.45, $p=0.194$) was comparable between the 2 groups. In contrast, the proportion of rash (OR: 2.50, 95% CI: 1.52 to 4.10, $p<0.001$), GI side effects (OR: 3.14, 95% CI: 1.79 to 5.50, $p<0.001$), or drug discontinuation (OR: 6.81, 95% CI: 2.12 to 21.86, $p<0.001$) was much higher in TAT than in DAT. An analysis based on a random-effects model was performed only for drug discontinuation

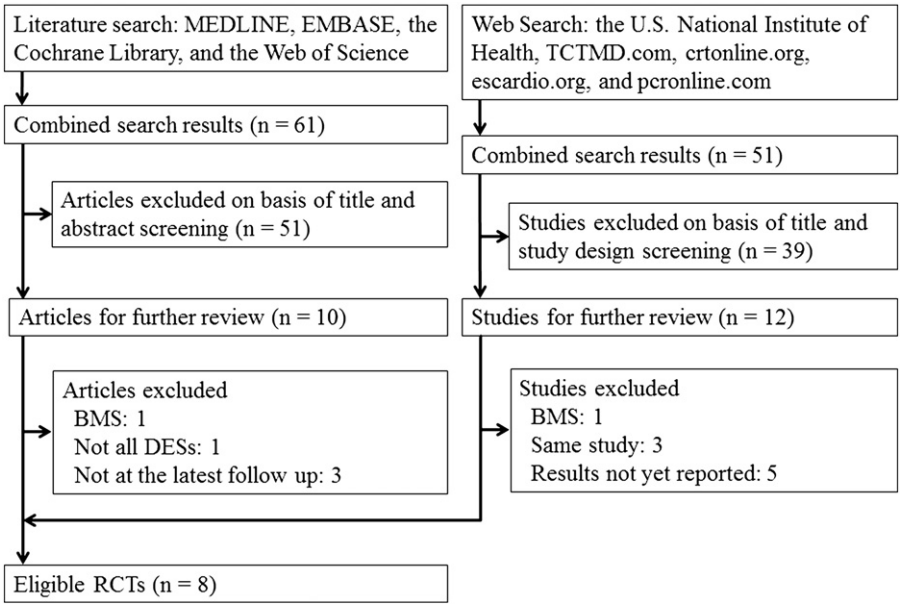

Fig. 1. Flow chart of study selection. BMS = bare metal stent; DES = drug-eluting stent; RCT = randomized controlled trial.