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Safety and efficacy of degradable vs. permanent polymer drug-eluting stents: A meta-analysis of 18,395 patients from randomized trials

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ABSTRACT

Background: Degradable polymer drug-eluting stents (DP-DES) represent a promising strategy to improve the delayed healing and hypersensitive reaction in the vessel. However, the efficacy and safety of DP-DES vs. permanent polymer drug-eluting stents (PP-DES) are less well defined. The aim of this meta-analysis was to compare the total, short (<30 days), mid (30 days–1 year) and long (>1 year) term outcomes of DP-DES vs. PP-DES.
Methods: PubMed, Embase, and Cochrane Central Register of Controlled Trials (CENTRAL) were searched for randomized clinical trials to compare any of approved DP- and PP-DES. Efficacy endpoints were target-lesion revascularization (TLR) and in-stent late loss (ISLL). Safety endpoints were death, myocardial infarction (MI), and composite of definite and probable stent thrombosis (ST).
Results: The meta-analysis included 19 RCTs (n = 18,395) with interesting results. As compared with DES, there was a significantly reduced very late ST (OR [95% CI] = 0.42 [0.24–0.77], p = 0.852) and ISLL (OR [95% CI] = −0.07 [−0.12–0.02], p = 0.000) in DP-DES patients. However, there were no differences between DP-DES and PP-DES for other safety and efficiency outcomes, except that the stratified analysis showed a significant decreased TLR with DP-DES as compared to paclitaxel-eluting stent (OR [95% CI] = 0.41 [0.20–0.81], p = 0.457).
Conclusions: DP-DES are more effective in reducing very late ST and ISLL, as well as comparable to PP-DES with regard to death, TLR and MI. Further large RCTs with long-term follow-up are warranted to better define the relative merits of DP-DES.

1. Introduction

Permanent polymer drug-eluting stents (PP-DES) are currently widely used to reduce restenosis and the need for repeat revascularization, representing a major advance for percutaneous coronary intervention [1]. However, the presence of a polymer is a potential cause of stent thrombosis (ST) and a late catch-up phenomenon, as a consequence of delayed healing and hypersensitive reaction [2,3]. Therefore, great efforts have been prompted to develop alternative stents with degradable polymers (DP) for drug delivery, which degrade over time, and therefore may eliminate the problems of polymer-induced late phases of inflammation.

However, uncertainty exists regarding the relative performance of DP- versus PP-DES in percutaneous coronary intervention (PCI). The aim of this meta-analysis is to compare total-, short-, mid- and long term safety and efficacy of DP- vs. PP-DES.

2. Methods

Established methods [4] were used in compliance with the PRISMA statement for reporting systematic reviews and meta-analyses in health care interventions [5].

2.1. Search strategy

We searched Embase, PubMed, and Cochrane Central Register of Controlled Trials (CENTRAL) for studies on DP-DES until November 2013. The search strategy was formulated as the AND-combination of terms 1) polymer 2) stent in randomized controlled trials. There was no language restriction for the search.

References of meta-analyses, review articles, and original studies identified by the electronic searches were manually checked for additional trials. For studies that did not report outcomes of interest, efforts to contact authors were performed to obtain further details. Internet-based sources of information on the results of clinical trials in cardiology (www.theheart.org, www.cardiosource.com/clinicaltrials, www.clinicaltrialresults.com, and www.tctmd.com) were also searched. In addition, we searched conference abstracts

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of the following societies: American College of Cardiology, Transcatheter Cardiovascular Therapeutics, American Heart Association, European Society of Cardiology, Society of Cardiovascular Angiography and Intervention and Euro-PCR.

2.2. Selection criteria

Inclusion criteria were: 1. human studies, 2. randomized controlled studies (RCTs), 3. enrollment of at least 100 patients, 4. PP-DES as control, and 5. ability to report the outcomes of interest. Exclusion criteria were: 1. non-RCTs, 2. sub-study of the RCTs, and 3. studies dedicated to specific lesion subsets including bifurcation lesions, left main, chronic total occlusions, long lesions and venous grafts. Two authors (Yuqing Wang and Yuanlin Luo) independently assessed trial bias risk and extracted data.

2.3. Data extraction and synthesis

Based on the time point of eluting drug release, short (<30 days), mid (30 days–1 year) and long-term (>1 year) efficacy and safety outcomes were evaluated. For mid-term outcomes, the outcomes closest to 1 year were abstracted. For total outcomes, the longest reported follow-up events, including short and mid-term outcomes, were abstracted.

2.4. Definitions

Efficacy outcomes were target-lesion revascularization (TLR) and in-stent late loss (ISLL). Safety outcomes were death, myocardial infarction (MI) and stent thrombosis (ST). Stent thrombosis was defined by the Academic Research Consortium (ARC) as "definite" or "probable" stent thrombosis [6]. TLR was defined as any revascularization procedure involving the target lesion owing to luminal re-narrowing in the presence of symptoms or objective signs of ischemia.

2.5. Statistical analyses

The chi-square test was used to examine differences in categorical variables, such as the frequencies. A p value less than .05 was considered statistically significant. Summary estimate includes odds ratio (OR), relative risk (RR), and weighted mean difference (WMD) and its 95% confidence intervals (CI) were used as summary statistics in forest plot. Heterogeneity was assessed by Cochran's Q test, with a 2-tailed $p \geq 0.1$. The statistical inconsistency test (I^2) {$[(Q - df) / Q] \times 100\%$, where Q is the chi-squared statistic and df is degrees of freedom} was also employed to overcome the low statistical power of Cochran's Q test. Pooled ORs were calculated using a fixed effect model with the Mantel–Haenszel method. The DerSimonian and Laird random effects model was used in case of significant heterogeneity and/or moderate or significant inconsistency ($p < 0.1$ or $I^2 > 50\%$) across studies. Potential publication bias was examined by Egger's test, in which $p < 0.05$ indicated that there was significant publication bias. We conducted a sensitivity analysis in which one study was removed and the rest were analyzed to evaluate whether the results were affected statistically significantly. Review Manager (RevMan) 5.2.6 (The Nordic Cochrane Center, Copenhagen, Denmark) and Stata 12.0 (College Station, Texas, USA) were used for statistical analysis.

3. Results

3.1. Study selection

We identified 19 randomized clinical trials (28 published studies) that satisfied our inclusion criteria (Fig. 1) [7–34]. Additional follow-up data on safety and efficacy were available for ISAR-TEST-3, ISAR TEST-4, NEVO RES-I and LEADERS [12,27,28,31].

Altogether, 19 trials (n = 18,395) with results of interest were finally analyzed to compare the clinical outcomes with 9849 and 8546 allocated to the DP- and PP-DES, respectively. Eleven trials (n = 5828) were used for angiography evaluation with 2977 and 2851 allocated to the DP- and PP-DES as well.

There are four 3-arm trials. For ISAR TEST-4, data was abstracted to compare DP- to PP-DES (sirolimus + everolimus) [28,29]. We included the standard everolimus DP-DES as opposed to the half-dose everolimus DP-DES arm of the EVOLVE trial because standard everolimus DP-DES are the currently used stent type [15]. For GENESIS trial, we included the pimecrolimus DES as opposed to the paclitaxel/pimecrolimus DES arm as the control group [11]. The ISAR TEST-3 trial data included were the DP-DES and PP-DES arms only, with the polymer free arm of the trial excluded [16,27].

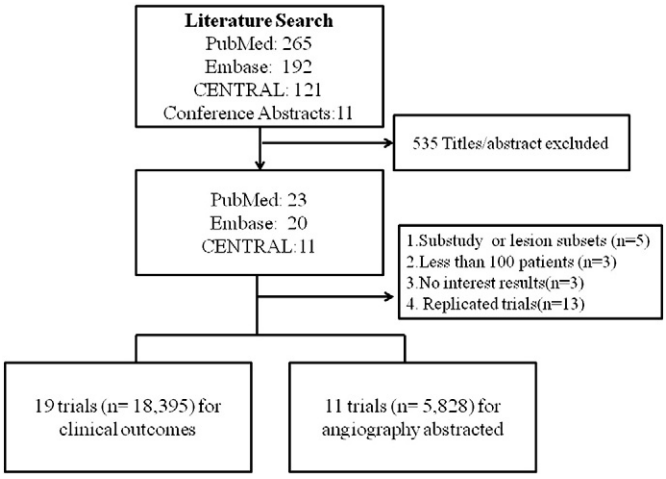

Fig. 1. Flow diagram of the review process.

3.2. Baseline characteristics

The baseline characteristics and quality analysis are described in Table 1. Mean lesion length was 15.2 mm in the DP-DES group as compared to 14.6 mm in the PP-DES group. Mean vessel size was 2.85 mm in DP-DES and 2.86 mm in PP-DES. Mean age was similar in the two groups (63.5 vs. 62.9). Men represented 73.3% of the DP-DES and 74.3% of the PP-DES population. There were 25.1% patients with diabetes in the DP-DES group and 24.7% in the PP-DES group. Protocols of dual anti-platelet therapy (DAPT) in our meta-analysis are summarized in Table 2. Mean dual anti-platelet duration was 8 months.

3.3. Safety endpoints

3.3.1. Death

There was no significant difference in the rate of death with DP-DES as compared with PP-DES: 2.78% (274/9849) in the DP-DES group and 3.14% (269 of 8546) in the PP-DES group (OR [95% CI] = 0.96 [0.81–1.14], p = 0.891) (Fig. 2). Subgroup analysis of short-, mid- and long term of death between DP-DES and PP-DES didn't show any difference (Supplement 1).

3.3.2. Myocardial infarction

There was no significant difference in the rate of MI with DP-DES as compared with PP-DES: 3.51% (346/9849) in the DP-DES group and 3.35% (286/8546) in the PP-DES group (OR [95% CI] = 1.08 [0.92–1.27], p = 0.932) (Fig. 3). Subgroup analysis of short-, mid- and long term of MI between DP-DES and PP-DES didn't show any difference (Supplement 2).

3.3.3. Stent thrombosis

There was no significant difference in the rate of total ST with DP-DES as compared with PP-DES: 0.92% (91/9849) in the DP-DES group and 1.21% (103/8546) in the PP-DES group (OR [95% CI] = 0.82 [0.61–1.09], p = 0.308) (Supplement 3). Subgroup analysis of early and late (30 days–1 year) ST between DP-DES and PP-DES didn't show any difference (Fig. 4A and B).

Seven studies (6206 patients) with a mean follow-up of 30 months were included to compare the outcome of very late ST between DP- and PP-DES. The meta-analysis showed a significant decreased very late ST in patients treated with DP-DES (0.45%,14/3107) as compared to patients receiving PP-DES (1.12%, 35/3099) (OR [95% CI] = 0.42 [0.24–0.77], p = 0.852) (Fig. 4C).