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Original article

Drug-eluting balloons versus drug-eluting stents for the management of in-stent restenosis: A meta-analysis of randomized and observational studies

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ABSTRACT

Objectives: The aim of this study was to evaluate the efficacy of drug-eluting balloons (DEB) with drug-eluting stents (DES) in patients with in-stent restenosis (ISR).
Background: DES implantation and DEB were available strategies in percutaneous coronary intervention (PCI) for ISR, but the optimal management for ISR lesions remains controversial.
Methods: Electronic databases were searched for randomized controlled trials and observational cohort studies which reported the clinical outcomes of using DEB comparing with DES implantation in patients with ISR. Clinical endpoints such as major adverse cardiovascular events (MACE), death, and myocardial infarction were assessed.
Results: Five randomized controlled trials and five observational cohort studies with 962 patients in the DEB group and 908 patients in the DES group met inclusion criteria. There was no significant difference between DEB and DES in major clinical outcomes, such as MACE (OR 1.01; 95% CI: 0.64–1.58; $p = 0.97$; $I^2 = 0\%$), all-cause death (OR 1.04; 95% CI: 0.54–1.98; $p = 0.91$; $I^2 = 0\%$), cardiovascular death (OR 1.44; 95% CI: 0.57–3.65; $p = 0.44$; $I^2 = 0\%$), stent thrombosis (OR 0.61; 95% CI: 0.16–2.33; $p = 0.47$; $I^2 = 0\%$), and myocardial infarction (OR 1.02; 95% CI: 0.53–1.94; $p = 0.96$; $I^2 = 0\%$). DEB was associated with a significant increase in target lesion revascularization (OR 1.54; 95% CI: 1.10–2.15; $p = 0.01$; $I^2 = 57\%$).
Conclusion: Treatment of ISR using DEB led to comparable clinical outcomes with DES implantation.

Introduction

In-stent restenosis (ISR) is one of the most important limitations leading to late stent failure [1]. The mechanism of ISR has been widely studied. The increased acute vessel injury at the time of percutaneous coronary intervention (PCI) with stent implantation and an enhanced healing response leading to varying degrees of neointimal proliferation may be the main reason contributing to ISR [2]. ISR has been characterized as a distinct pathophysiological process of post-intervention atherosclerosis [3]. A recent study also demonstrated neoatherosclerosis as a mechanism for this process [4].

Drug-eluting stents (DES) were widely used to treat ischemic coronary artery disease. Even very low doses of drug have exhibited a sustained anti-proliferative effect on vascular smooth muscle cells. Compared with plain old balloon angioplasty (POBA) or bare metal stent (BMS) implantation, PCI with DES dramatically reduced the rate of ISR [5]. On the other hand, DES restenosis was no longer an uncommon phenomenon because of increasing use of DES in complicated settings. In previous studies, it had been confirmed that repeated DES implantation was superior to conventional balloon angioplasty [6,7]. Nevertheless, repeated stenting for restenosis was associated with a high risk of treatment failure [8]. As DES implantation for ISR was associated with higher

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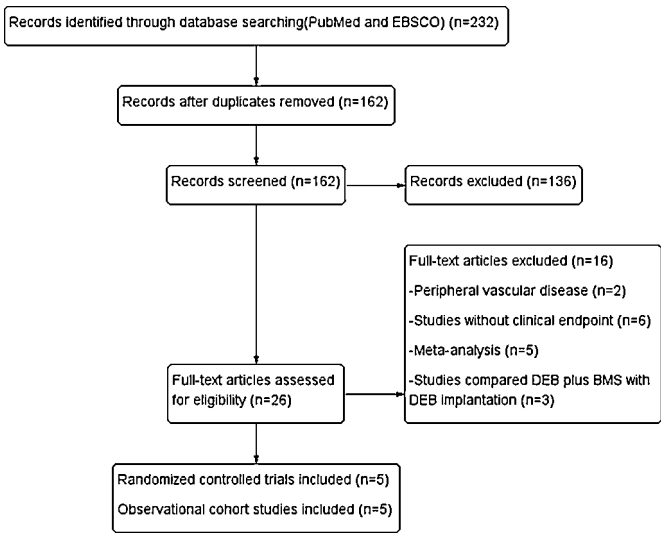

Fig. 1. Flowchart of study selection. BMS, bare metal stent; DEB, drug-eluting balloon; DES, drug-eluting stent.

rates of recurrent restenosis and recurrent target lesion revascularization (TLR) than de novo coronary interventions [9], the optimal management for ISR lesions was not currently established. The drug-eluting balloons (DEB) may be an attractive option in the management of ISR lesions, which had been proven effective in patients with both BMS-ISR and DES-ISR [10], and showed superior to conventional balloon angioplasty [11–13]. However, the relative efficacy of DES versus DEB in patients with ISR remains controversial.

Our study was designed to analyze the clinical outcome following the index procedure with either DEBs or with DESs in the treatment of ISR.

Methods

Study selection

PubMed and EBSCO were searched for relevant articles published between January 2005 and May 2016. Language was restricted to English. The key words we used included the following terms: "Drug Eluting Balloon", "DEB", "drug coated balloon", "DCB", "eluting stent", "DES", "in-stent restenosis," and "ISR". The references of relevant studies and reviews, editorials, and letters, together with related abstracts were also searched.

The main criteria for inclusion in this analysis was trials aiming to compare DEB to DES in patients with clinical evidence of stable or unstable angina or evidence of ischemia, and exhibiting ISR in coronary arteries. ISR was defined as >50% diameter stenosis on visual assessment, and any type of ISR was eligible. Randomized clinical trials or observational studies assessment of ≥1 of the following outcomes: death, myocardial infarction, cardiovascular death, target vessel revascularization (TVR), and TLR. Studies only comparing the angiographic results between two strategies without clinical endpoints were excluded. Studies aiming to compare DEB with BMS were also excluded.

Study endpoints

The endpoints of the analysis included: (a) major adverse cardiovascular events (MACE), (b) death from any cause, (c) cardiovascular death, (d) definite/probable stent thrombosis (ST), (e) myocardial infarction (MI), (f) target lesion revascularization (TLR), and (g) target vessel revascularization (TVR). MACE in this study was defined as death, myocardial infarction, and stent thrombus. Other endpoints were defined according to the study definition.

Data abstraction and analysis

Two investigators independently assessed reports for eligibility at title and/or at abstract level, with divergences resolved with a third reviewer; studies that met inclusion criteria were selected for further analysis. The risk of bias was evaluated by the same two reviewer authors, in accordance with The Cochrane Collaboration methods [14]. The Newcastle-Ottawa tool was used for quality assessment of prospective cohort studies [15].

Statistical analysis

Meta-analysis was performed using the Review Manager 5.3 statistical software. Reported event frequencies were used to calculate odds ratios (OR) with 95% confidence intervals (CI). We used the fixed-effects model in this analysis. Heterogeneity of the trial results was quantified with the Chi^2 heterogeneity statistic, inconsistency was assessed by means of I^2. Results were reported as the p-value of the Chi^2 test ($p < 0.05$ for heterogeneous results) and percent of the I^2. Interpretation of the latter was made by assigning attributes of low, moderate, and high in case of 0–25%, 50–75%, and more than 75%, respectively. We used a random effects or a fixed effect model based on associated heterogeneity. The random effects model results in wider confidence intervals and provides more conservative and robust results and it was used when $I^2 > 50\%$. To study the relevance of such publication bias, funnel plots were constructed plotting the trial results against their precision.

Results

After deduplication, screening of titles and abstracts, and full text review based on inclusion and exclusion criteria, 10 studies involving 1870 patients qualified for the analysis (Fig. 1). Including

Table 1
Interventions and characteristics of individual studies.

Author	Acronym	Date	Design	Location	Follow-up	Previous stent	DEB type	DES type
Almalla		2014	OS	Germany	1 year	DES		EES
Basavarajaiah		2015	OS	Italy	1 year	DES	PEB	2nd-generation
Kang		2015	OS	Korea	2 years	DES		2nd-generation
Kawamoto		2015	OS	Italy	2 years	DES		2nd-generation
Oh		2016	OS	Korea	16 month	BMS/DES	PEB	
Byrne	ISAR-DESIRE 3	2013	RCT	Germany	1 year	DES	PEB	PES
Unverdorben	PEPCAD II ISR	2014	RCT	Germany	3 years	BMS	PEB	PES
Alfonso	RIBS V	2014	RCT	Spain	1 year	BMS	PEB	EES
Alfonso	RIBS IV	2015	RCT	Spain	1 year	DES		EES
Pleva		2016	RCT	Czech Republic	1 year	BMS	PEB	EES

RCT, randomized controlled trial; OS, observational study; PEB, paclitaxel-eluting balloon; EES, everolimus-eluting stent; BMS, bare metal stents; DES, drug-eluting stent.

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