# Efficacy and safety of zotarolimus-eluting stents compared with sirolimus-eluting stents in patients undergoing percutaneous coronary interventions — A meta-analysis of randomized controlled trials

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## ARTICLE INFO

## ABSTRACT

Background: Whether ZES can further improve angiographic and clinical outcomes compared to SES still remains uncertain.
Objectives: The aim of this study was to assess the efficacy and safety of zotarolimus-eluting stents (ZES) compared with sirolimus-eluting stents (SES) in patients undergoing percutaneous coronary interventions (PCI).
Methods: Major electronic information sources were explored for randomized controlled trials comparing ZES with SES among patients undergoing PCI during at least 9 months follow-up. The primary efficacy outcomes were target lesion revascularization (TLR), target vessel revascularization (TVR), and major adverse cardiac events (MACE); safety outcomes were stent thrombosis (ST), myocardial infarction (MI), and cardiac death.
Results: Seven comparative studies were identified (a total of 5983 patients). When compared with ZES at 12-month follow-up, SES significantly reduced risk of MACE (relative risk [RR]: 0.74, 95% confidence interval [CI]: 0.61 to 0.89, p = 0.002), and TLR (RR:0.39; 95% CI: 0.29 to 0.52; p<0.00001), without significant differences in terms of TVR (RR:0.68, 95% CI: 0.38 to 1.20; p = 0.18), ST (RR:0.71; 95% CI: 0.39 to 1.31; p = 0.28), cardiac death (RR:0.83; 95% CI: 0.49–1.42, p = 0.50) or MI (RR:1.08; 95%CI: 0.80 to 1.45; p = 0.62).
Conclusions: At 12-month follow-up, SES are superior to ZES in reducing the incidences of TLR and MACE in patients undergoing PCI, without significant differences in terms of TVR, ST, cardiac death, and MI.

## 1. Introduction

The first-generation drug-eluting stents (DES), coated with polymers to deliver anti-proliferative agents, such as sirolimus or paclitaxel, were introduced into clinical practice in 2003 on the basis of studies, demonstrating reduced angiographic late lumen loss and reduced need for repeat revascularization compared with bare-metal stents (BMS) in patients with coronary stenosis [1,2]. Although results of meta-analyses did not reveal significant differences in mortality and myocardial infarction (MI) between first-generation DES and BMS [1,3], late stent thrombosis (ST) has emerged as a major concern [4,5]. Although the precise mechanism is uncertain, both preclinical and selected clinical reports of ST described vascular hypersensitivity reactions and incomplete healing that may be mediated by polymer and/or drug incompatibility [6–8]. Therefore, next-generation DES is

being developed to increase the safety and biocompatibility by optimizing the three major components of DES: the stent platform, the polymer and the drug [9].

Zotarolimus is a synthetic analog of sirolimus and has a similar mechanism of action. The Endeavor zotarolimus-eluting stent (ZES), as one of the second-generation DES, combines a more rapid elution profile of the antiproliferative drug zotarolimus with a thinner, more biocompatible phosphorylcholine polymer placed on a cobalt alloy thin-strut stent [9]. The ZES has been shown to decrease the need for repeat revascularization compared to BMS, but there were no differences in the incidence of death or MI between the 2 types of stent [10]. Several randomized controlled trials (RCTs) have evaluated primary efficacy and safety of ZES compared with sirolimus-eluting stents (SES) in patients undergoing percutaneous coronary interventions (PCI) presenting with various clinical and angiographic risk profiles; however, all of them have not enough power to detect the difference between the 2 stents with respect to clinical hard endpoints.

Therefore, whether the Endeavor ZES can further improve angiographic and clinical outcomes compared to SES still remains uncertain. Meta-analysis has the potential to increase power and summarize

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results from different, but comparable, individual studies. Hence, we performed a meta-analysis at study-level of randomized clinical trials aiming to assess the safety and efficacy of ZES vs. SES in patients undergoing PCI.

## 2. Methods

### 2.1. Study search strategy

We searched Medline, Embase, the Cochrane Central Register of Controlled Trials (from 2004 through December 18, 2011), and relevant websites (www.acc.org, www.tctmd.com, www.theheart.org, www.clinicaltrialresults.org) for studies in any language. Relevant reviews and editorials from major medical journals published within the last year were identified and assessed for possible information on trials of interest. All RCTs involving head-to-head comparisons of ZES and SES in patients with coronary stenosis were examined using the following key words: "randomized trial", "sirolimus-eluting stent" (or SES), "zotarolimus-eluting stent" (or ZES).

### 2.2. Study selection

To be selected for this meta-analysis, studies had to include patients with symptoms or objective signs of myocardial ischemia due to native CAD who were assigned to treatment with ZES or SES in a randomized fashion. All studies had to report the outcomes of interest during a follow-up period of at least 9 months after the index procedure. No restriction criteria were imposed with regard to the form of study publication. Two investigators (Fan JQ, Du HA) independently performed study selection and data abstraction. Differences were resolved by discussion. Those meeting inclusion criteria were selected for further analysis.

### 2.3. Study outcomes

The primary efficacy endpoint of this meta-analysis was the need of clinically driven reintervention (target lesion revascularization [TLR] and/or target vessel revascularization [TVR]), as well as major adverse cardiac events (MACE), in-segment late luminal loss (ISLLL), and in-segment restenosis (ISR). The safety endpoint of this meta-analysis was definite ST, as well as all-cause death, cardiac death, and recurrent MI. MACE was defined as the composite of death, recurrent MI, or clinically driven TLR or TVR. Event definitions for each trial are listed in Table 2.

### 2.4. Data extraction and assessment of quality

We extracted pre-specified data elements from each trial, including study design, stent type, sample characteristics, sample size, glycoprotein IIb/IIIa inhibitors therapy, angiographic results, outcome measures, primary end point, and other study characteristics.

The quality of studies was scored using the Cochrane Collaborations tool for assessing risk of bias for RCTs [11]. The Silber score [12], another method of assessing the quality of clinical trials, including RCTs with DES, evaluates various factors that constitute a well-designed RCT, including adequate power, being multicenter, having an independent events committee, and having a primary clinical end point. High scores (closer to 10) suggest a stronger basis for making an evidence-based decision, whereas low scores (closer to 0) provide hypotheses rather than confirmatory evidence. A Silber score was assigned to all of the RCTs.

### 2.5. Statistical analysis

The review was conducted according to the Quality of Reports of Meta-Analyses of Randomized Clinical Trials (QUOROM) recommendations [13]. All analyses were performed based on the intention-to-treat principle. Relative risks (RR) with 95% confidence intervals (CI) were used as summary statistics. The pooled RR was calculated with the Mantel–Haenszel method for fixed effects [14] and the DerSimonian and Laird method for random effects [15]. We calculated the $I^2$ statistic by Cochran test to measure the consistency between trials with values of 25%, 50%, and 75% representing low, moderate, and high degrees of heterogeneity, respectively [16]. For the primary efficacy and safety endpoint, small-study effects were analyzed by constructing a funnel plot, in which the standard error of the logRR was plotted against RR. However, because graphical evaluation can be subjective, we performed both Harbord [17] and Peters tests [18], as formal statistical tests for publication bias. Sensitivity analysis for the primary outcome of interest was also performed; a $\geq 20\%$ modification of the overall effect by exclusion of a given study was considered significant [19]. $p < 0.05$ was used to indicate significance. Statistical analyses were performed with the RevMan 5.0 freeware package (Cochrane Collaboration, Software Update, Oxford, United Kingdom) and Stata 10.0 statistical software (STATA Corp, College Station, Texas, USA).

## 3. Results

### 3.1. Literature search and quality assessment

Fig. 1 shows the flow chart selected studies, providing a description of publication screening and reasons for exclusion. Seven RCTs were finally selected for data extraction. Agreement between investigators regarding quality assessment was complete in RCTs (kappa = 1.00). The Silber score of the 7 trials included ranged from 5 to 9, as shown in Table 1.

### 3.2. Characteristics of the studies and patients included

The main characteristics of these trials are listed in Table 2. A total of 7 randomized trials [20–26], including 5983 patients, were analyzed. The primary end point in 4 trials [20–22] was MACE (the combined incidence of death, MI, and clinically driven TLR/TVR), and in the remaining 3 trials [23,24], in-segment late lumen loss and binary angiographic restenosis, respectively. The mean duration of clinical follow-up ranged from 9 to12 months. Besides the SORT OUT III trial, other 6 trials completed quantitative angiographic analysis (QCA) during follow-up. The CATOS trial [26] exclusively recruited patients with total coronary occlusion. Two studies [21,25] exclusively recruited patients with ST segment elevation myocardial infarction (STEMI), and another 3 trials [20,22,24] enrolled all-comer patients.

Baseline characteristics of enrolled patients in individual trials are shown in Table 3. There were no significant differences between patients treated with ZES and SES regarding main clinical and angiographic characteristics. The mean age of participants in individual trials varied from 57.8 to 67.2 years. The frequency of diabetes mellitus ranged from 14.5% to 29.2%; the overall proportion of men was 66.8%.

### 3.3. Clinical and angiographic efficacy: TLR/TVR, ISR, ISLLL, and MACE
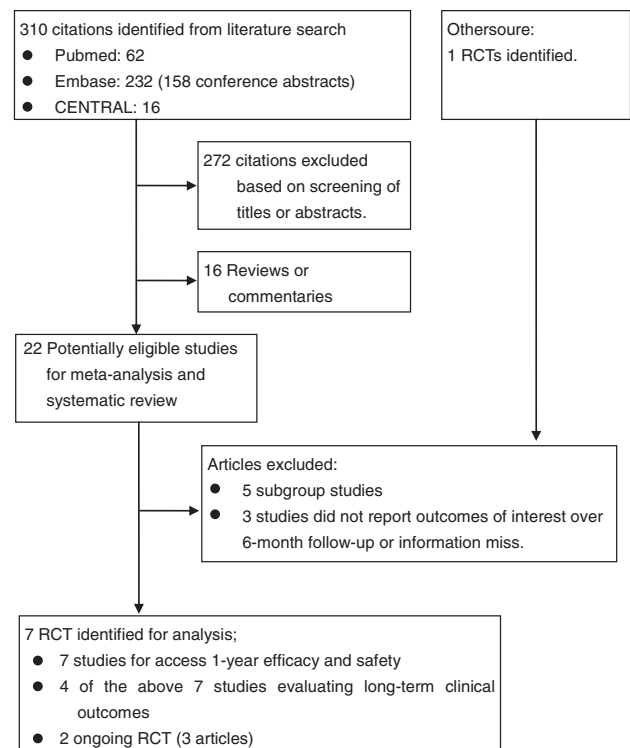
### 3.3.1. TLR/TVR



**Fig. 1.** Flowchart of selected studies.