Journal of Cardiology 64 (2014) 185–193

Contents lists available at ScienceDirect

Journal of Cardiology

journal homepage: www.elsevier.com/locate/jjcc

Original article

The impact of everolimus versus other rapamycin derivative-eluting stents on clinical outcomes in patients with coronary artery disease: A meta-analysis of 16 randomized trials

Yao-Jun Zhang (MD, PhD)[a,b,1], Lin-Lin Zhu (MD)[a,1], Christos V. Bourantas (MD, PhD)[b], Javaid Iqbal (MRCP, PhD)[b,c], Sheng-Jie Dong (MD)[d], Carlos M. Campos (MD)[b,e], Ming-Hui Li (MD)[a], Fei Ye (MD)[a], Nai-Liang Tian (MD)[a], Hector M. Garcia-Garcia (MD)[b], Patrick W. Serruys (MD, FESC)[b], Shao-Liang Chen (MD, FACC)[a,*]

[a] *Nanjing First Hospital, Nanjing Medical University, Nanjing, China*
[b] *Erasmus Medical Center, Rotterdam, The Netherlands*
[c] *Department of Cardiovascular Science, University of Sheffield, United Kingdom*
[d] *Soochow University, Suzhou, China*
[e] *Heart Institute (InCor), University of São Paulo Medical School, Sao Paulo, Brazil*

ARTICLE INFO

Article history:
Received 22 August 2013
Received in revised form
20 November 2013
Accepted 6 January 2014
Available online 20 February 2014

Keywords:
Everolimus-eluting stent
Biolimus-eluting stent
Zotarolimus-eluting stent
Sirolimus-eluting stent
Meta-analysis

ABSTRACT

Background: Everolimus-eluting stent (EES) are considered to have better clinical outcomes than other rapamycin derivative-eluting stents; however, the individual trials may not have sufficient power to prove it. This meta-analysis aimed to compare clinical outcomes of EES against other rapamycin derivative-eluting stents.

Methods: We searched Medline, the Cochrane Library, and other internet sources, without language or date restrictions for articles comparing clinical outcomes between EES and other rapamycin derivative-eluting stents. Safety endpoints were stent thrombosis (ST), mortality, cardiac death, and myocardial infarction (MI). Efficacy endpoints were major adverse cardiac events (MACE), target lesion revascularization (TLR), and target vessel revascularization (TVR).

Results: We identified 16 randomized controlled trials with 23,481 patients and a weighted mean follow-up of 18 months. Compared with other rapamycin derivative-eluting stents, EES were associated with a significant reduction in definite ST [relative risk (RR): 0.45; 95% confidence interval (CI): 0.30–0.69; $p < 0.001$] and TLR (RR: 0.87; 95% CI: 0.77–0.99; $p = 0.03$). EES also showed a non-significant trend toward reduction in definite/probable ST (RR: 0.75; 95% CI: 0.56–1.01; $p = 0.06$). However, both groups had similar rates of mortality (RR: 0.95; 95% CI: 0.82–1.09; $p = 0.45$), MI (RR: 0.95; 95% CI: 0.82–1.10; $p = 0.43$), and MACE (RR: 0.94; 95% CI: 0.87–1.02; $p = 0.35$). The stratified analysis of the included trials showed that EES was associated with significantly lower rate of definite ST compared with either zotarolimus-eluting stent ($p = 0.012$) or sirolimus-eluting stent ($p = 0.006$), but not biolimus-eluting stent ($p = 0.16$). In longer follow-up (>1 year) stratification, EES was associated with a significant reduction in risk of definite ST ($p < 0.001$).

Conclusions: EES is associated with a significant reduction in definite ST and TLR for treating patients with coronary artery disease, compared with a pooled group of other rapamycin derivative-eluting stents. Biolimus-eluting stent had similar safety and efficacy for treating patients with coronary artery disease, compared with the EES.

Introduction

Drug-eluting stents (DES) with controlled release of antiproliferative drugs significantly reduce the incidence of restenosis after percutaneous coronary intervention (PCI), compared with bare metal stents (BMS) [1–3]. Two different classes of highly lipophilic drugs have been employed on DES platforms in order to inhibit smooth muscle cell proliferation: drugs of the "limus"

* Corresponding author at: Department of Cardiology, Nanjing First Hospital, Nanjing Medical University, No. 68 Changle Road, 210006, Nanjing City, Jiangsu Province, China. Tel.: +86 25 52208048; fax: +86 25 52208048.
E-mail address: chmengx126@gmail.com (S.-L. Chen).
[1] These authors equally contributed to this work.

0914-5087/$ – see front matter © 2014 Japanese College of Cardiology. Published by Elsevier Ltd. All rights reserved.
http://dx.doi.org/10.1016/j.jjcc.2014.01.007

family and paclitaxel [4–8]. Recently, paclitaxel-eluting stents (PES, Taxus, Boston Scientific, Natick, MA, USA) has been withdrawn from clinical practice due to its higher incidences of stent thrombosis (ST) and repeat revascularization, compared with rapamycin derivative-eluting stents [9].

In contemporary practice, limus-eluting DES, including those eluting everolimus, biolimus A9, zotarolimus, and sirolimus, are used worldwide and have been shown to effectively inhibit neointimal hyperplasia after stent implantation [10–15]. However, data from experimental studies have suggested that different limus drugs may have differential effects on re-endothelialization and subsequently on vascular healing [16,17]. Indeed, a preclinical study has shown more rapid endothelialization with everolimus-eluting stent (EES) compared with sirolimus-eluting stent (SES) [16].

Apart from SES, several clinical trials reported that biolimus A9-eluting stent (BES) and zotarolimus-eluting stent (ZES) were non-inferior to EES in treating patients with obstructive coronary disease [15,18]. In a large overview of comparative trials, treatment with EES significantly reduced the risk of repeat revascularization and definite ST compared with SES [19]. However, an updated meta-analysis demonstrated that the use of EES versus SES was associated with similar incidence of overall clinical events [20]. In a previous meta-analysis, Baber et al. also demonstrated an inconsistent benefit with EES using stratified analysis, and detected differences in the treatment effect across control non-EES strata, showing reductions in clinical outcomes were substantial in trials versus PES, intermediate versus ZES, and smallest against SES [21]. Therefore, whether EES has favorable clinical outcomes compared with other rapamycin derivative-eluting stents remains unsettled.

The aim of the present study is to compare the clinical performance of EES and other limus DZS (namely, BES, ZES, and SES), using data from randomized controlled trials (RCTs).

Methods

Data sources and search strategy

We performed a computerized search of Medline, the Cochrane Library, and internet sources for clinical RCTs from January 2002 to July 2013 using the medical subject heading terms "everolimus-eluting stent," as well as a combination of the terms "biolimus-eluting stent," "zotarolimus-eluting stent," and "sirolimus-eluting stent". We used the Science Citation Index as a cross reference to identify trials that met the search criteria. Medline was searched using the method described by Biondi-Zoccai et al. [22,23]. Additional searches for potential trials included the references of previous meta-analyses, review articles, and the following congresses: scientific sessions of the American College of Cardiology, American Heart Association, Transcatheter Cardiovascular Therapeutics, EuroPCR, Chinese Interventional Therapeutics, and European Society of Cardiology.

Study identification and data extraction

Citations were screened at title/abstract level and retrieved as full articles. Criteria for inclusion in the meta-analysis were: (1) randomized trials between EES and comparator rapamycin derivative-eluting stents; (2) available clinical follow-up data. Studies of non-randomized data, sub-studies of randomized trials, and studies with comparison of BMS or polymer-free DES were excluded. Three independent investigators (LL Zhu, MH Li, and SJ Dong) extracted the data, which included the trials' name, dual antiplatelet therapy (DAPT) duration, follow-up duration, sample size, baseline characteristics, and clinical outcomes in EES and comparator rapamycin derivative-eluting stents. Internal validity, using the Cochrane Collaboration's tool [24] was assessed by 2 investigators (LL Zhu, SJ Dong) for the risk of bias, according to allocation sequence generation, allocation sequence concealment, participants' and personnel blinding, outcome assessment blinding, incomplete outcome data, selective outcome reporting, etc.

Clinical endpoints

The clinical endpoints in the present meta-analysis included: (1) ST (definite and definite/probable), defined by Academic Research Consortium (ARC) classification; (2) mortality; (3) cardiac death; (4) myocardial infarction (MI); (5) major adverse cardiac events (MACE, as defined by individual trials included in this meta-analysis); (6) target lesion revascularization (TLR); and (7) target vessel revascularization (TVR).

Statistical analysis

We calculated relative risk (RR) and 95% confidence interval (CI) from the extracted data. We considered both the fixed-effects model (based on the Mantel–Haenszel method) and the random-effects model (DerSimonian and Laird method) for the meta-analyses. Heterogeneity of the effect size across studies was tested using Q statistics at the $p = 0.10$ level of significance. I^2 test, a quantitative measure of inconsistency across studies was also calculated, where Q was the *chi*-squared statistic and df was its degree of freedom. Heterogeneity was classified as low with a value of $I^2 < 25\%$, moderate with 50%, and high with 75%. Forest plots were generated for graphical presentations of the clinical outcomes.

Stratified analyses were conducted to explore heterogeneity potentially caused by discrete factors. Potential publication bias was assessed by visual inspection of the contour-enhanced funnel plot, in which the logarithm RR was plotted against their inverse standard error with different significant contours. The Egger's linear regression test was employed to test for funnel plot asymmetry at the $p < 0.10$ level of significance [25]. A probability value of <0.05 was considered statistically significant. All analyses were performed using STATA 12.0 (Stata Corp., College Station, TX, USA).

Results

Eligible trials

Sixteen eligible RCTs were identified and included in the present meta-analysis (Fig. 1) [10,13–15,26,11,27–36]. Out of 16 RCTs, 2 trials compared EES with BES [14,15], 2 trials compared EES with ZES [11,27], and 12 trials compared EES with SES [10,13,26,28–36]. The majority of the included RCTs were assessed as being at low risk of bias across all domains of qualities according to the Cochrane Collaboration's tool (Supplement, Fig. 1).

Baseline characteristics

The characteristics of included trials are shown in Table 1. Data were analyzed from 11,107 (47.3%) patients who underwent EES implantation and 12,374 (52.7%) patients underwent comparator rapamycin derivative-eluting stent implantation (overall patient numbers, $n = 23{,}481$). Patients' follow-up ranged from 12 to 36 months, with a weighted mean follow-up time of 18 months. The RESET and NEXT trial from Japan had older patients (69 years) and higher prevalence of diabetes mellitus (45%, 46%) [14,32]. The XAMI trial studied the performance of EES and SES for patients with acute myocardial infarction [34].