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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

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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"

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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].

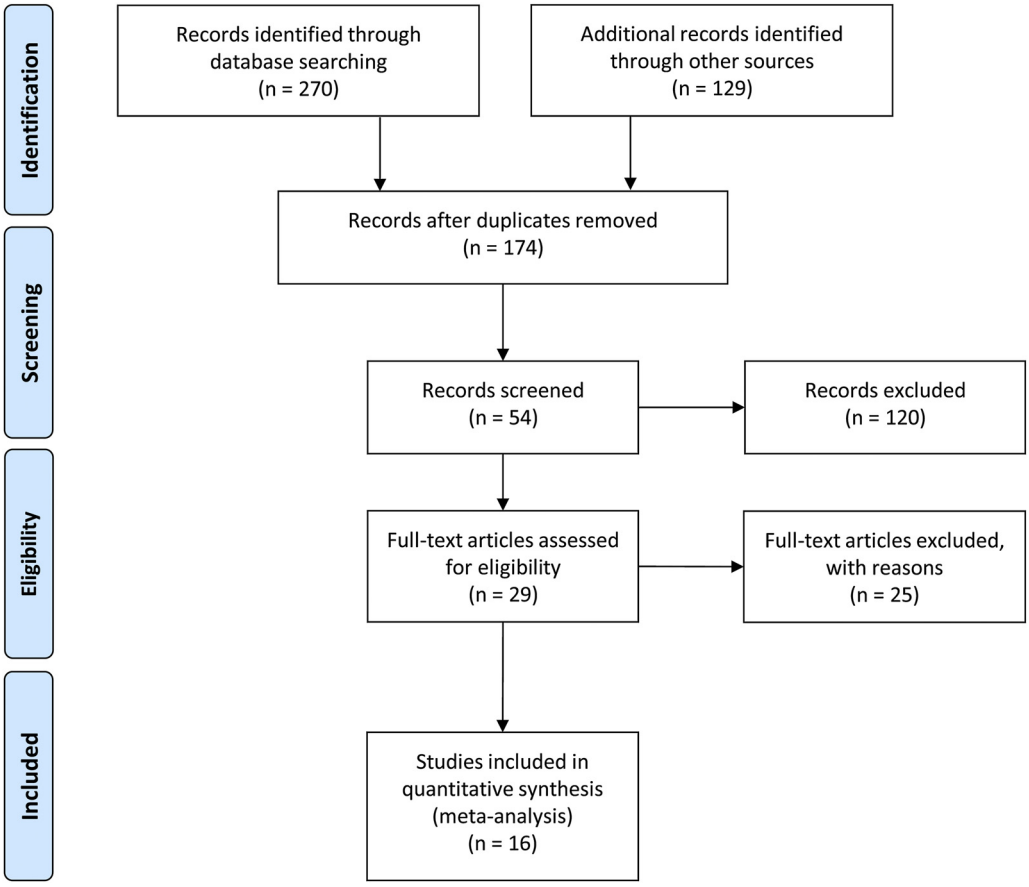


Fig. 1. Flow diagram of the meta-analysis. Sixteen randomized clinical trials were identified.

Stent thrombosis

All 16 RCTs contributed to the analysis of definite/probable ST according to ARC classification. Thirteen trials were included in the analysis for this endpoint, as 3 trials had no ST event. The frequency of definite ST was 0.27% (30/11,107) in the EES group, and 0.67% (83/12,374) in the comparator DES group. The meta-analysis showed a significant reduction in the risk of definite ST with the use of EES (RR: 0.45, 95% CI: 0.30–0.69; $p < 0.001$) (Fig. 2). Although the statistical significance was marginal, there was a trend toward low incidence of definite/probable ST in EES group (RR: 0.75, 95% CI: 0.56–1.01; $p = 0.06$). There was no evidence of statistical heterogeneity among these RCTs (p heterogeneity = 0.81 for definite ST; p heterogeneity = 0.71 for definite/probable ST).

Mortality and myocardial infarction

Mortality and MI were reported in all RCTs. The use of EES versus other rapamycin derivative-eluting stents resulted in a similar risk of mortality (RR: 0.95, 95% CI: 0.82–1.09; $p = 0.45$) and MI

Table 1
Features of randomized trials included after full-text inspection.

RCTs	Year published	EES	Comparator DES	FLU, months	DAPT, months	Sample size	Age, years	Male, %	DM, %	ACS, %
COMPARE II	2013	EES	BES	12	12	912/1795	63/63	74/74	22/22	58/58
NEXT	2013	EES	BES	12	3	1618/1617	69/69	77/77	46/46	16/17
RESOLUTE	2011	EES	ZES	24	6	1152/1140	64/64	77/77	23/24	53/54
TWENTE	2013	EES	ZES	24	12	694/697	65/64	73/73	21/23	51/52
ESSENCE DIABETES	2010	EES	SES	12	12	149/151	63/64	52/66	100/100	43/40
BASKET-PROVE	2010	EES	SES	12	12	774/775	66/66	76/74	15/18	65/65
EXCELLENT	2010	EES	SES	12	6	1079/364	63/63	65/63	37/41	53/48
Burzotta et al.	2011	EES	SES	12	12	75/75	64/65	85/75	25/33	49/39
LONG-DES III	2011	EES	SES	12	12	224/226	63/63	74/66	32/27	39/46
ISAR-TEST 4	2011	EES	SES	36	6	652/1951	67/67	77/75	29/29	40/42
RESET	2012	EES	SES	12	3	1597/1600	69/69	78/76	45/45	18/18
SORT OUT IV	2012	EES	SES	24	12	1390/1384	64/64	76/75	14/14	42/43
XAMI	2012	EES	SES	12	12	404/221	61/62	73/75	9/11	100/100
Sakakibara et al.	2012	EES	SES	12	12	50/50	64/76	67/65	33/37	NA/NA
CIBELES	2013	EES	SES	12	12	106/101	65/63	20/14	41/32	NA/NA
Target I	2013	EES	SES	12	12	231/227	60/59	68/69	17/14	72/71

ACS, acute coronary syndrome; BES, biolimus-eluting stent; DAPT, dual antiplatelet therapy; DES, drug-eluting stent; DM, diabetes mellitus; EES, everolimus-eluting stent; FLU, follow-up; NA, not available; RCTs, randomized controlled trials; SES, sirolimus-eluting stent; ZES, zotarolimus-eluting stent.

(RR: 0.95, 95% CI: 0.82–1.10; $p = 0.49$) (Fig. 3A). Heterogeneity was not significant among trials (p heterogeneity = 0.85 for mortality; p heterogeneity = 0.83 for MI) (Fig. 3B).

Target lesion revascularization and major adverse cardiac events

The pooled RR showed significant difference in risk of TLR between EES and non-EES groups (RR: 0.87, 95% CI: 0.77–0.99; $p = 0.03$) (Fig. 3C). In terms of MACE, the definition was described and reported in all 16 trials (Supplement, Table 1). The pooled RR for MACE was 0.94 (95% CI: 0.87–1.02; $p = 0.17$). There was no evidence of heterogeneity among the trials (p heterogeneity = 0.76 for TLR; p heterogeneity = 0.47 for MACE) (Fig. 3D). The pooled results for cardiac death and TVR showed there were no statistical differences between groups ($p = 0.13$ and $p = 0.86$, respectively) (Supplement, Fig. 2).

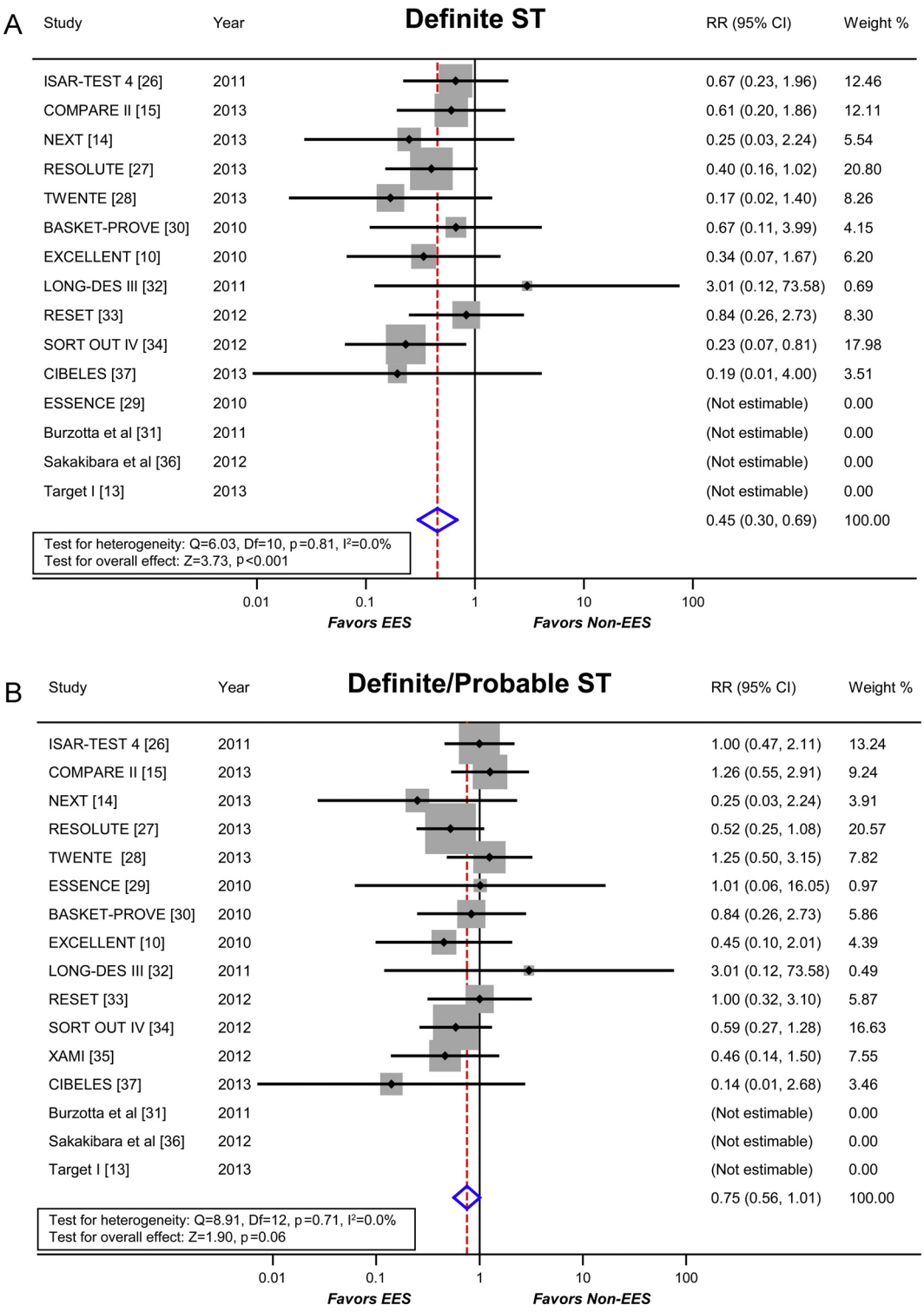


Fig. 2. Forest plots with relative ratios from the trials. Size of data markers indicates weight of each trial included in the meta-analysis: (A) definite ST and (B) definite/probable ST.
EES, everolimus-eluting stent; RR, relative risk; ST, stent thrombosis.

Stratified analyses for clinical outcomes

Stratified analyses were performed for definite ST and definite/probable ST to evaluate consistency of our main findings (Fig. 4). In longer follow-up (>1 year) stratification, EES was associated with a significant reduction in risk of definite ST ($p < 0.001$). In the different rapamycin derivative-eluting stent stratification, only BES presented a similar risk of definite ST compared with the EES. The stratified sub-analyses for other clinical outcomes are presented as supplementary material (Supplement, Figs. 3 and 4).

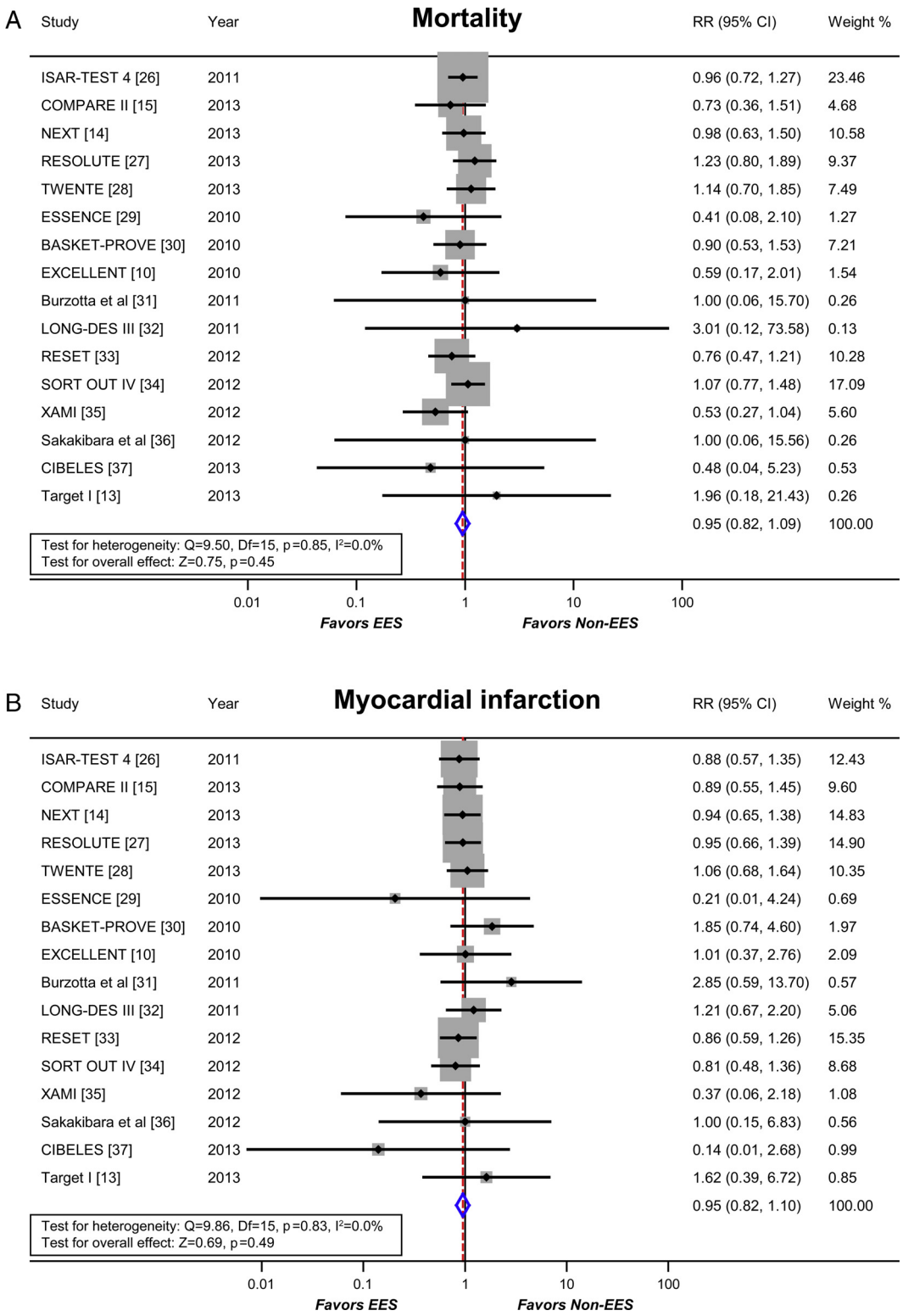
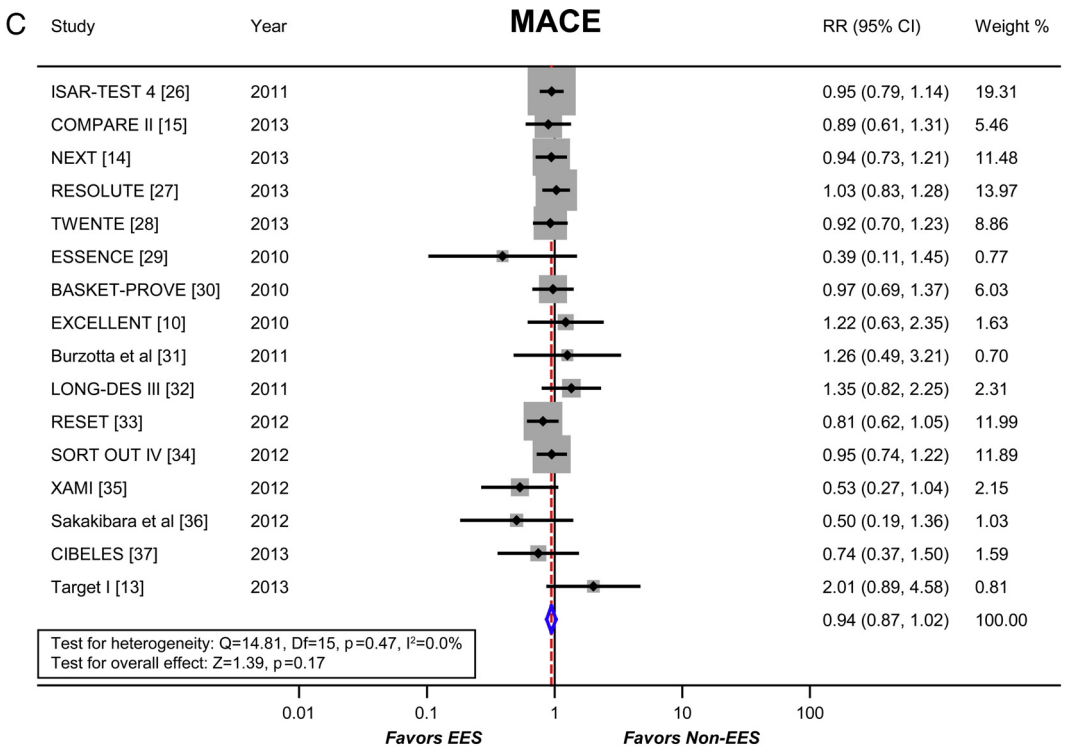


Fig. 3. Forest plots with relative ratios from the trials. Size of data markers indicates weight of each trial in the meta-analysis: (A) mortality, (B) myocardial infarction, (C) MACE, and (D) TLR.
EES, everolimus-eluting stent; MACE, major adverse cardiac event; RR, relative risk; ST, stent thrombosis; TLR, target lesion revascularization.



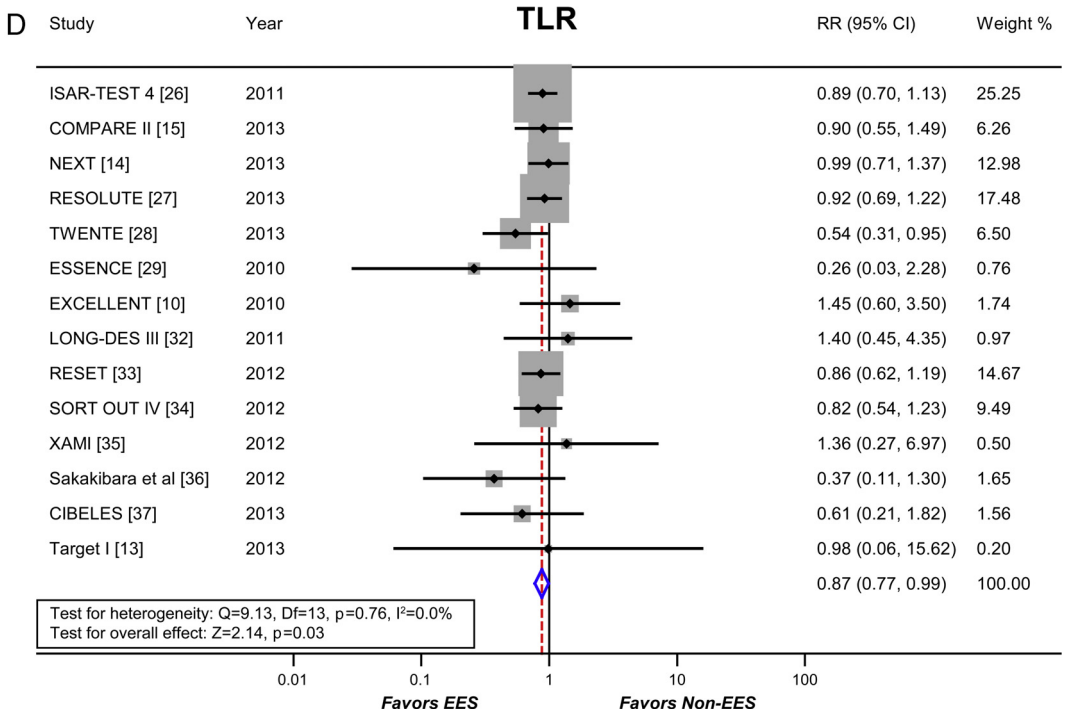


Fig. 3. *(Continued).*

Publication bias

The contour-enhanced funnel plots for the studied clinical endpoints did not reveal asymmetry. Assessment of publication bias using logarithm of relative risk demonstrated a symmetric funnel plot, showing no evidence of publication bias (Fig. 5). The Egger's regression tests were performed and confirmed no publication bias ($p = 0.72$ for definite ST, $p = 0.53$ for definite/probable ST, $p = 0.37$ for mortality, $p = 0.90$ for MI, $p = 0.45$ for TLR, and $p = 0.69$ for MACE).

Discussion

Our meta-analysis of 16 RCTs with 23,481 patients has shown that EES is associated with a significant reduction in definite ST and TLR, compared with other rapamycin derivative-eluting stents in a weighted mean follow-up of 18 months. There were no significant differences in the risk of mortality, MI, and MACE between the use of EES and non-EES stents. In the stratified analyses, the risk reduction with EES for definite ST was primarily against SES and ZES.

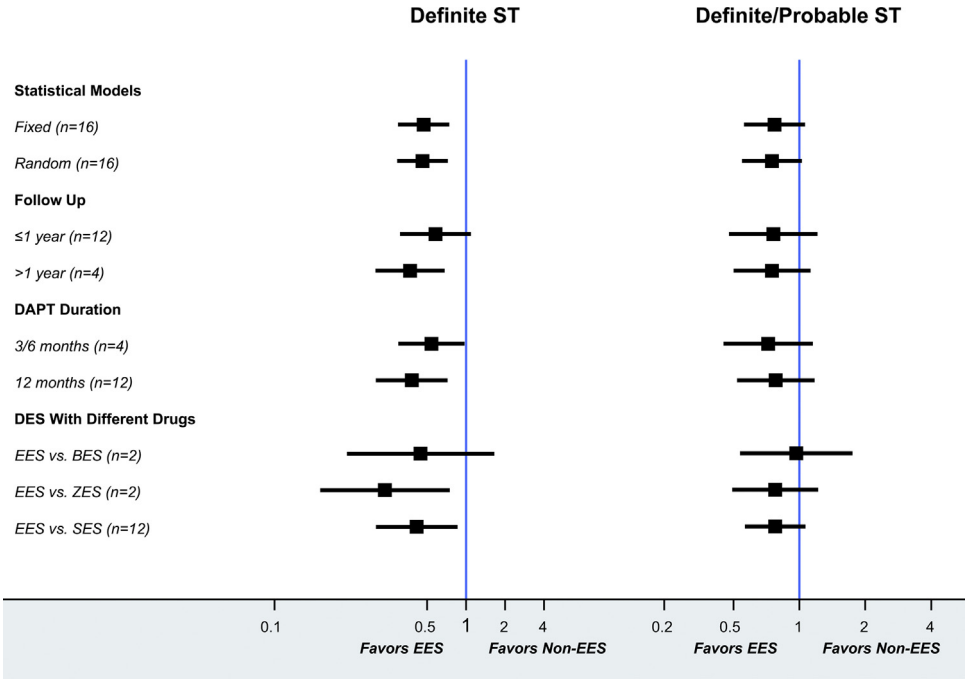


Fig. 4. Stratified sub-analyses of the randomized trials. The pooled estimates for definite ST, definite/probable ST are shown as relative risk. Boxes indicate point estimates and lines for 95% confidence intervals.
BES, biolimus-eluting stent; DES, drug-eluting stent; EES, everolimus-eluting stent; SES, sirolimus-eluting stent; ST, stent thrombosis; ZES, zotarolimus-eluting stent.

Several studies have evaluated the performance of EES against BMS or other DES [10,11,15,29,33,37–40]. A recent comprehensive meta-analysis has reported that EES reduces the incidence of ST compared with BMS [41]. Similarly, studies have shown that EES is associated with a significant reduction in clinical events compared with PES [37,38]. Although recent studies have suggested that EES has the most favorable safety and efficacy profile, the difference in clinical outcomes (including ST, TLR, and MACE) between EES and other limus-eluting stents remains to be proven conclusively. We, for the first time, have shown that EES has a significantly improved clinical performance compared with other limus-eluting stents.

ST incidence associated with devices is different between EES and other limus-eluting stents. Jensen et al. have shown that EES is associated with a lower incidence of ST compared with SES at 2-year follow-up, then concluded that the EES is non-inferior to the SES for both patient-related and device-related clinical outcomes [33]. Moreover, 2-year follow-up from the Resolute all-comers trial has shown similar safety and efficacy outcomes between EES and ZES, although there was a trend toward less ST in the EES group ($p = 0.077$) [11]. Additionally, in the COMPARE II trial, although no statistical difference existed in the incidence of definite ST between EES and BES ($p = 0.38$), numerically it appeared that EES had less incidence of ST at 1 year follow-up (4/912 in EES vs. 13/1795 in BES) [15]. Our study with pooled data from 16 RCTs has demonstrated that EES is associated with a significantly lower incidence of ST. The stratified analysis, however, confirmed that this benefit is largely against SES and ZES, not BES. Several ex vivo experimental studies have also demonstrated that various limus drugs may have a differential influence on re-endothelialization and delayed vascular healing, the biological precursor for ST [17,42].

Everolimus and other limus drugs are all inhibitors of the mammalian target of rapamycin, and have proven efficacy in inhibiting neointimal hyperplasia. However, several previous studies have proposed that everolimus may have more potent effect and EES implantation may lead to reduction in TLR [17,37]. Similarly, a meta-analysis of 11 RCTs (12,869 patients) has shown that EES is associated with a significantly reduced risk of repeat revascularization compared with SES (OR: 0.85, 95% CI: 0.71–1.00; $p = 0.047$) [43]. Unfortunately, the clinical outcomes of the APPENDIX-AMI trial with 977 patients in this meta-analysis have not been formally published yet. Conversely, another updated meta-analysis of 8 RCTs including 11,167 patients has shown no significant effect of EES on re-interventions as compared with SES (RR: 0.86, 95% CI: 0.72–1.04; $p = 0.12$) [20]. These conflicting results may be caused by insufficient power to achieve the statistical difference in the latter meta-analysis with only 8 trials identified during the last search in September 2011. In the present study, we have reported the largest number of patients who experienced EES implantation and shown a significantly lower incidence of TLR compared with all other rapamycin derivative-eluting stents. Presumably, the

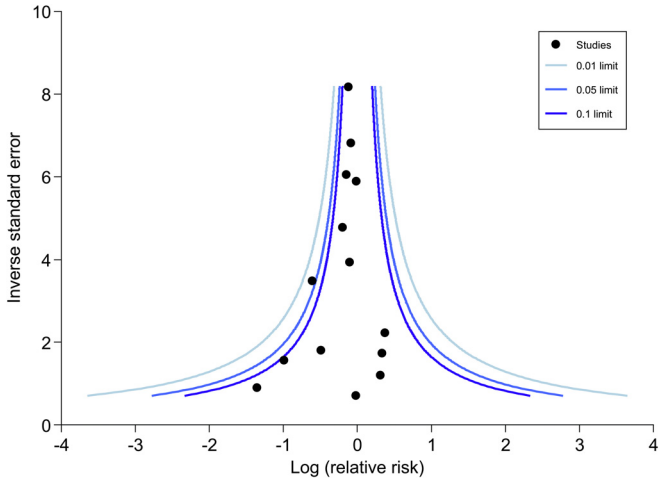


Fig. 5. Contour-enhanced funnel plot of the randomized trials for target lesion revascularization, suggesting no publication bias was found.

underlying mechanism of low TLR rate in the EES group is partially due to effective inhibition of neointimal hyperplasia in long-term follow-up [17].

Together with the antiproliferative drug, the stent platform and polymer with the varying stent designs may also play a major role in adverse events and ST [44]. In Target I trial, Gao et al. reported that SES with novel biodegradable polymer has similar safety and efficacy for the treatment of patients with de novo lesions compared with the EES [13]. In addition, ST can be also attributed to patient, procedural, and lesion factors [44]. Furthermore, recent meta-analyses have reported that the patients allocated to biodegradable polymer DES showed significantly less late/very late ST [45,46]. Although several DES in the comparator control group used biodegradable polymers in the present study, EES group still had lower incidence of definite ST. Therefore, our data support the notion that EES offers superior safety and efficacy compared with other limus-eluting stents.

Recently the concept of "novel rapamycin derivative drugs," "biodegradable polymers or polymer-free," and "new backbone materials" has been highlighted for DES design [47,48]. This is either safety considered, on the basis of decreasing most of the incidence of ST, or efficacy considered (on basis of reducing in-stent restenosis). The underlying principle is that, even if each component of DES is technically possible or achievable, this would not definitely improve clinical outcomes, given the unknown deficits in some components, especially at longer-term follow-up. Therefore, to make it possible, it is necessary to understand why different limus drugs react in a particular way, how individual DES perform in different clinical settings, at least to exert a synergistic effect of all components of DES to its safety and efficacy.

Limitations

Our study has several limitations. Firstly, the meta-analysis shares the limitations of the original trials, the results were based on the trial level. Secondly, the comparator DES groups include SES, ZES, BES together, which have different stent designs and polymers. However, we have employed several stratified analyses to distinguish the performance of different rapamycin derivative-eluting stents compared with EES. Thirdly, several studies only enrolled patients with specific clinical presentations (such as chronic total occlusion, hemodialysis), and this may have had invisible bias. Fourthly, although 4 trials have more than 1-year follow-up outcomes, it is preferable to address the clinical performance in the longer-term follow-up. Fifthly, the definitions (e.g. MACE and MI) used in each trial were different, which makes direct comparison less precise. Finally, whether the TLR was driven by clinical ischemia was not reported in several studies. However, despite these limitations, the large sample size of the present study ($n = 23{,}481$) provided sufficient power to evaluate the impact of EES on each clinical outcome.

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 in a mean weighted follow-up of 18 months. Longer-term follow-up is warranted to demonstrate persistent safety and efficacy benefits of EES. BES had similar safety and efficacy for treating patients with coronary artery disease, compared with the EES.

Appendix A. Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/j.jjcc.2014.01.007.

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