Journal of the American College of Cardiology
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Published by Elsevier Inc.

Vol. 58, No. 15, 2011
ISSN 0735-1097/$36.00
doi:10.1016/j.jacc.2011.06.049

Interventional Cardiology

Impact of the Everolimus-Eluting Stent on Stent Thrombosis

A Meta-Analysis of 13 Randomized Trials

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Objectives We evaluated the impact of the everolimus-eluting stent (EES) on the frequency of stent thrombosis (ST), target vessel revascularization (TVR), myocardial infarction (MI), and cardiac death in randomized controlled trials comparing the EES to non–everolimus-eluting drug-eluting stents (EE-DES).

Background Whether or not the unique properties of the EES translate into reductions in ST remains unknown.

Methods We searched MEDLINE, Scopus, the Cochrane Library, and Internet sources for articles comparing outcomes between EES and non–EE-DES without language or date restriction. Randomized controlled trials reporting the frequency of ST were included. Variables relating to patient and study characteristics and clinical endpoints were extracted.

Results We identified 13 randomized trials (n = 17,101) with a weighted mean follow-up of 21.7 months. Compared with non–EE-DES, the EES significantly reduced ST (relative risk [RR]: 0.55; 95% confidence interval [CI]: 0.38 to 0.78; p = 0.001), TVR (RR: 0.77; 95% CI: 0.64 to 0.92; p = 0.004), and MI (RR: 0.78; 95% CI: 0.64 to 0.96; p = 0.02). There was no difference in cardiac mortality between the groups (RR: 0.92; 95% CI: 0.74 to 1.16; p = 0.38). The treatment effect was consistent by different follow-up times and duration of clopidogrel use. The treatment effects increased with higher baseline risks of the respective control groups with the strongest correlation observed for ST (R^2 = 0.89, p < 0.001).

Conclusions Intracoronary implantation of the EES is associated with highly significant reductions in ST with concordant reductions in TVR and MI compared to non–EE-DES. Whether these effects apply to different patient subgroups and DES types merits further investigation. (J Am Coll Cardiol 2011;58:1569–77) © 2011 by the American College of Cardiology Foundation

Drug-eluting stents (DES) have greatly improved the percutaneous management of de novo coronary artery lesions by lowering the incidence of restenosis and risk of subsequent revascularization (1,2). These highly significant and durable results led to widespread DES adoption and use in many "off-label" indications after their introduction. Several reports of late and very late stent thrombosis (ST) associated with the first-generation sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES), particularly in the context of dual-antiplatelet therapy (DAPT) cessation, dampened early enthusiasm and suggested that prolonged DAPT might be necessary after DES intervention (3,4). Identification of possible differences among DES with respect to ST might have major implications regarding long-term safety of DES and DAPT duration.

The newer-generation DES, including the everolimus-eluting stent (EES), have been developed with the intent of improving the overall safety of earlier DES while maintaining anti-restenotic efficacy. Compared to earlier DES, the

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Manuscript received April 29, 2011; revised manuscript received June 20, 2011, accepted June 28, 2011.

Abbreviations and Acronyms

DAPT = dual-antiplatelet therapy
DES = drug-eluting stent(s)
EE = everolimus-eluting
EES = everolimus-eluting stent(s)
MI = myocardial infarction
PES = paclitaxel-eluting stent(s)
SES = sirolimus-eluting stent(s)
ST = stent thrombosis
TVR = target vessel revascularization
ZES = zotarolimus-eluting stent(s)

antiproliferative agent in the EES is released from a thin biocompatible fluoropolymer that is coated onto a low profile flexible cobalt chromium metallic stent platform (5). Experimental animal data have indicated that stent strut endothelialization was more rapid with the EES compared to other DES, which might yield a lower thrombotic risk (6). Similarly, several clinical trials suggest a reduction in both clinical and angiographic restenosis with EES implantation (7,8).

Despite the theoretical advantages of the EES on lowering thrombotic risk, the impact of the EES on ST remains unknown, as earlier studies were not sufficiently powered to detect differences in the frequency of this rare event. Although ST rates in EES versus non-EES patients were lower in some, but not all studies, overall event rates were too low to draw any definitive conclusions from any individual study. Accordingly, we conducted a meta-analysis of all randomized controlled trials to date comparing the EES to non-EES on the frequency of ST and other cardiac endpoints.

Methods

Study objectives. The primary aim of this meta-analysis was to compare the frequency of ST between EES and non–EE-DES in randomized controlled trials. The main outcome of interest included Academic Research Consortium (ARC) definite or probable ST (9). Additional endpoints included myocardial infarction (MI), target vessel revascularization (TVR), and cardiac mortality.

Study search strategy. We searched MEDLINE, Scopus, Cochrane Library, and Internet sources for abstracts, without language or date restrictions, using combinations of the following terms: "Xience V," "everolimus-eluting," "Promus," and "stent thrombosis." Two reviewers (U.B. and J.W.S.) identified articles eligible for further review after screening abstracts and titles. Additional searches of the following conference proceedings were also performed: Scientific Sessions of the American College of Cardiology, American Heart Association, Transcatheter Cardiovascular Therapeutics, and European Society of Cardiology. Web sites were also searched for relevant materials. References of review articles and earlier meta-analyses were also reviewed for potential studies. Principal investigators of trials were also contacted to provide missing data from presentations as Late Breaking Clinical Trials in the above conferences and still in press.

Study identification. We performed searches by the previously described data sources for studies that met the following criteria: 1) randomized comparison between EES and control DES (non-EES); 2) reporting of clinical outcomes; and 3) reporting the frequency of ST. We excluded comparisons of nonpermanent polymer DES (bioabsorbable or biodegradable). The final search yielded 13 randomized controlled trials comparing the EES to the PES, the SES, or the zotarolimus-eluting stent (ZES).

Data extraction. We extracted pre-specified data elements from each trial including comparator DES, sample size and characteristics, duration of clopidogrel therapy, outcome measures, and primary endpoints. Events in each trial were extracted on the basis of the intention-to-treat approach. Stent thrombosis was defined in all studies using the Academic Research Consortium (ARC) classification (9). Myocardial infarction, either spontaneous or periprocedural, was defined using the universal definition or ARC criteria in 5 trials (10–14) whereas the remaining studies used a protocol definition. Target lesion revascularization was substituted for TVR in 2 studies (15,16), and TVR was ischemia or clinically driven in 11 trials. Complex lesion morphology was defined according to the trial protocol.

Statistical analysis. We calculated both the relative risk (RR) and absolute risk difference (RD) from the abstracted data. The RR was calculated using the inverse variance method for each study outcome to allow for pooling of similar outcomes. A negative RD indicates an advantage for EES whereas a positive RD indicates a benefit for non-EES.

The average effects for the outcomes and 95% confidence intervals (CI) were obtained using a random effects model, as described by DerSimonian and Laird (17). Heterogeneity of RR and RD across trials was assessed using the Cochrane Q statistic (a p value $\leq$0.1 was considered significant) and the I^2 statistic. The presence of publication or reporting bias was assessed using the Begg and Mazumdar rank correlation and Egger's linear regression method (18,19).

We conducted sensitivity analyses to assess the effects of selected measures of study quality on ST, cardiac mortality, TVR, and MI. The influence of each study was estimated by deleting each in turn from the analysis and evaluating the change in the effect size and significance. A study was considered influential if its exclusion changed the effect estimate by at least 20%. All analyses were also repeated using a fixed-effects model.

Using linear regression, we also explored the relationship between baseline risk and treatment effect for ST, TVR, and MI. Baseline risk was defined as the event rate for each endpoint in the comparator DES group. The absolute risk difference was modeled as a weighted linear function of the event rate in the comparator DES group.

The p value threshold for significance was 0.05. All analyses were conducted using STATA 10.0 (Stata Corp., College Station, Texas). The study was performed in

accordance with the recommendations set forth by the Quality of Reporting of Meta-Analysis (QUOROM) (20).

With a control ST event rate of 1.5% and a sample size of 17,101, the present study had 80% and 90% power to detect relative risk reductions in ST with EES use of 32% and 37%, respectively.

Results

Eligible studies. Table 1 lists the study characteristics of the 13 randomized trials included in the present meta-analysis (10–16,21–26). A total of 7 trials were identified through Internet sources or major conference proceedings (10–12,15,21–23) (Fig. 1). Additional data relating to the specific endpoints of interest for our analysis that were not available in reports or presentations from our literature search were requested and provided by the principal investigators of 4 studies (11,12,22,23). There were a greater number of patients randomized to EES (n = 9,764) than to non-EES (n = 7,337), because certain studies employed an imbalanced randomization. The most frequent comparator DES types were either SES (n = 8 trials) or PES (n = 4 trials); 1 trial compared EES to ZES. The mean age ranged from 62 to 67 years with the majority of patients being male. The frequency of diabetes mellitus ranged from 14% to 100%. Follow-up ranged from 9 to 48 months; the weighted mean follow-up was 21.7 months. Duration of clopidogrel use in all trials ranged from 6 to 12 months.

Stent thrombosis. All 13 randomized trials reported rates of ARC definite or probable stent thrombosis. As there were no episodes of ST in 2 studies, 11 trials were included in the analysis for this endpoint. The frequency of ST in the EES groups was 0.7% (72 of 9,655), and the analogous rate in the comparator DES groups was 1.5% (112 of 7,230). The pooled RR for ST associated with EES versus non-EES use was 0.55 (95% CI: 0.38 to 0.78; p = 0.001) (Fig. 2). The pooled RD between the groups was −0.5%, favoring EES (95% CI: −1.0% to 0.0%, p = 0.04). There was no evidence of statistical heterogeneity among these studies (p heterogeneity = 0.26).

Myocardial infarction. MI was reported in all trials. The frequency of MI in the EES group was 2.9% (282 of 9,764), and the analogous rate in the comparator DES groups was 3.9% (289 of 7,337). The pooled RR for MI associated with EES versus non-EES use was 0.78 (RR: 0.78; 95% CI: 0.64 to 0.96; p = 0.02) (Fig. 2). The pooled RD between the groups was −0.7%, nonsignificantly in favor of EES (95% CI: −1.5% to 0.1%, p = 0.08). There was no evidence of heterogeneity (p heterogeneity = 0.18).

Target vessel revascularization. Among the 13 trials, the frequency of TVR in the EES group was 5.7% (559 of 9,764), and the analogous rate in the non-EES groups was 7.7% (563 of 7,337). The pooled RR for TVR associated with EES versus non-EES use was 0.77 (95% CI: 0.64 to 0.92; p = 0.004). The pooled RD between the groups was −1.5%, favoring EES (95% CI: −2.6% to −0.4%; p =

Table 1 Characteristics of Randomized Trials

Trial/First Author (Ref. #)	Year Published or Presented	Comparator DES	Sample Size (EES/non-EES)	Follow-Up, Months	Clopidogrel Duration, Months	Age, yrs	Male, %	DM, %	CL, %	AP, %	Primary Endpoint
SPIRIT II (16)	2007	PES	223/77	48	6	62	73	23	79	28	Cardiac death, MI, TLR
SPIRIT III (24)	2008	PES	669/332	36	6	63	73	29	NA	21	Cardiac death, MI, ID-TVR
BASKET-PROVE (25)	2010	SES	774/775	24	12	66	75	16	14	65	Cardiac death, nonfatal MI
COMPARE (26)	2010	PES	897/903	24	12	63	71	18	74	60	All-cause mortality, MI, TVR
ESSENCE DM (23)	2010	SES	149/151	12	NA	63	59	100	NA	42	In-segment late loss
EXCELLENT (11)	2010	SES	1,067/361	9	6	63	64	38	NA	50	In-segment late loss
ISAR-TEST-4 (22)	2009	SES	652/652	36	6	67	76	29	73	41	Cardiac death, MI, TLR
RESOLUTE All Comers (14)	2010	ZES	1,152/1,140	24	6	64	77	23	21	53	Cardiac death, MI, ID-TLR
SORT OUT IV (10)	2010	SES	1,390/1,384	9	12	64	75	14	57	42	MACE
SPIRIT IV (15)	2010	PES	2,458/1,229	24	12	63	68	32	11	28	TLF
Burzotta et al. (13)	2011	SES	75/75	18	12	65	80	29	100	44	Side branch trouble
LONG-DES III (12)	2011	SES	224/226	12	12	63	70	30	41	43	In-segment late loss
Park et al. (21)	2011	SES	34/32	9	12	61	50	29	100	41	In segment late loss

AP = acute presentation; BASKET-PROVE = Basel Stent Kosten Effektivitäts Trial–Prospective Validation Examination; CL = complex lesion; COMPARE = Comparison of the Everolimus-Eluting XIENCE-V Stent With the Paclitaxel-Eluting TAXUS LIBERTÉ Stent in All Comers; DES = drug-eluting stent(s); DM = diabetes mellitus; EES = everolimus-eluting stent(s); ESSENCE DM = Prospective Randomized Trial of Everolimus-Eluting Stents and Sirolimus-Eluting Stents in Patients With Diabetes Mellitus and Coronary Artery Disease; EXCELLENT = Efficacy of Xience/Promus versus Cypher to Reduce Late Loss In Stent; ID = ischemia driven; ISAR-TEST 4 = Intracoronary Stenting and Angiographic Results: Test Efficacy of 3 Limus-Eluting Stents; MACE = major adverse cardiovascular events; MI = myocardial infarction; NA = not available; PES = paclitaxel-eluting stent(s); SES = sirolimus-eluting stent(s); SORT OUT = Scandinavian Organization for Randomized Trials With Clinical Outcome; SPIRIT = Clinical Evaluation of the Xience V Everolimus-Eluting Coronary Stent System in the Treatment of Patients With De Novo Native Coronary Artery Lesions; TLF = target lesion failure; TLR = target lesion revascularization; ZES = zotarolimus-eluting stent(s).

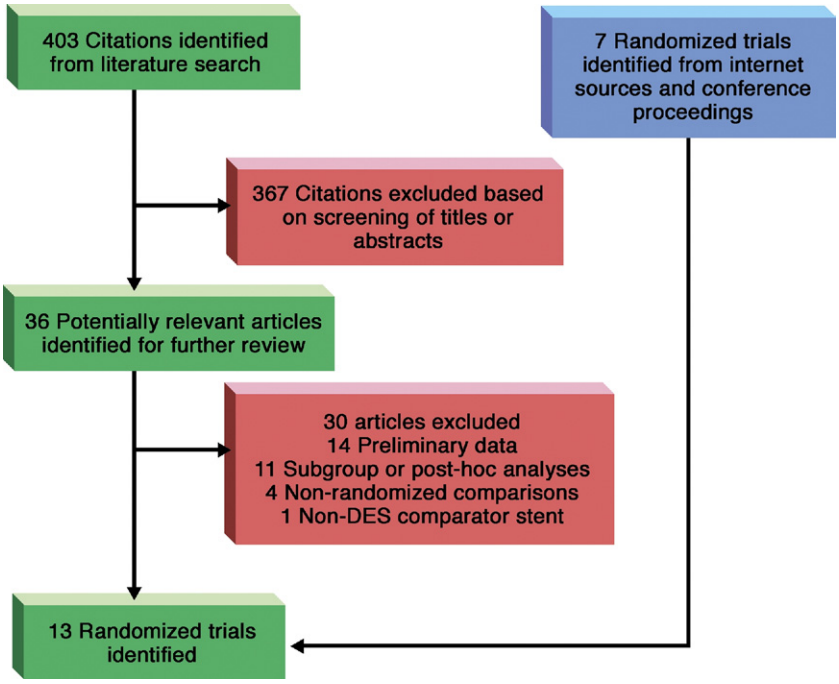

Figure 1 **Flow Diagram of Meta-Analysis**

After exclusions, 6 randomized controlled trials (RCTs) from the literature search and 7 RCTs identified through Internet sources were entered into the meta-analysis. DES = drug-eluting stent(s).

0.009). There was evidence of statistical heterogeneity for TVR across studies (p heterogeneity = 0.05). The study with the largest and most significant reduction in TVR was the COMPARE (Comparison of the Everolimus-Eluting XIENCE-V Stent With the Paclitaxel-Eluting TAXUS LIBERTÉ Stent in All-Comers) trial (26). Compared to other trials using the PES as a control DES, the proportion of patients presenting with ACS was greatest in the COMPARE trial. The analysis for this endpoint was repeated after removing the COMPARE trial, yielding a pooled RR for TVR of 0.83 (95% CI: 0.73 to 0.93; p = 0.001) without any further evidence of heterogeneity (p heterogeneity = 0.44).

Cardiac mortality. The frequency of cardiac death in the EES group was 1.6% (153 of 9,540), and the respective rate in the comparator DES groups was 1.9% (142 of 7,111). The pooled RR for cardiac mortality associated with EES versus non-EES use was 0.92 (95% CI: 0.74 to 1.16; p = 0.38) (Fig. 2). The pooled RD between the groups was −0.1% (95% CI: −0.5% to 0.2%; p = 0.41). There was no evidence of statistical heterogeneity among these studies (p heterogeneity = 0.78).

Sensitivity and influence analysis. We evaluated the consistency of our main findings by performing stratified analyses for ST, TVR, and MI. We did not perform a similar analysis for cardiac mortality as we did not detect a significant effect in the primary analysis including all studies. The overall treatment effect of the EES remained consistent for each endpoint using either a random or fixed effects model, 6 or 12 months' minimum clopidogrel use, and by different lengths of follow-up (≤1 year or cumulative beyond 1 year) (Fig. 3). Treatment effect, however, varied by comparator DES for ST (p heterogeneity = 0.03), TVR (p heterogeneity = 0.007), and MI (p heterogeneity = 0.006). In general, the risk reductions with EES for each endpoint were largest against PES, intermediate with ZES, and smallest in trials using SES as the control DES.

Because we included both published (n = 6) and unpublished study results (n = 7) in the present analysis, we repeated all analyses using published data alone. Results for each endpoint were consistent with our overall findings (data not shown). Of note, 4 of the 7 unpublished study results were verified by the study investigators (11,12,22,23) whereas the results of 1 other study are long-term findings of an existing publication (15).

We estimated the influence of each study by deleting each in turn from the analysis and found no significant change in the pooled treatment effect for ST, MI, TVR, or cardiac mortality.

Regression analysis. We explored the association between baseline risk for ST in each trial and treatment benefit with EES. Baseline risk was defined as the control (non–EE-DES) rate for ST in each trial. Using weighted linear regression, we found that the absolute benefit of the EES increased with greater baseline risk ($R^2 = 0.89$, $p < 0.001$) (Fig. 4). Similar associations of smaller magnitude were observed for MI and TVR (data not shown).

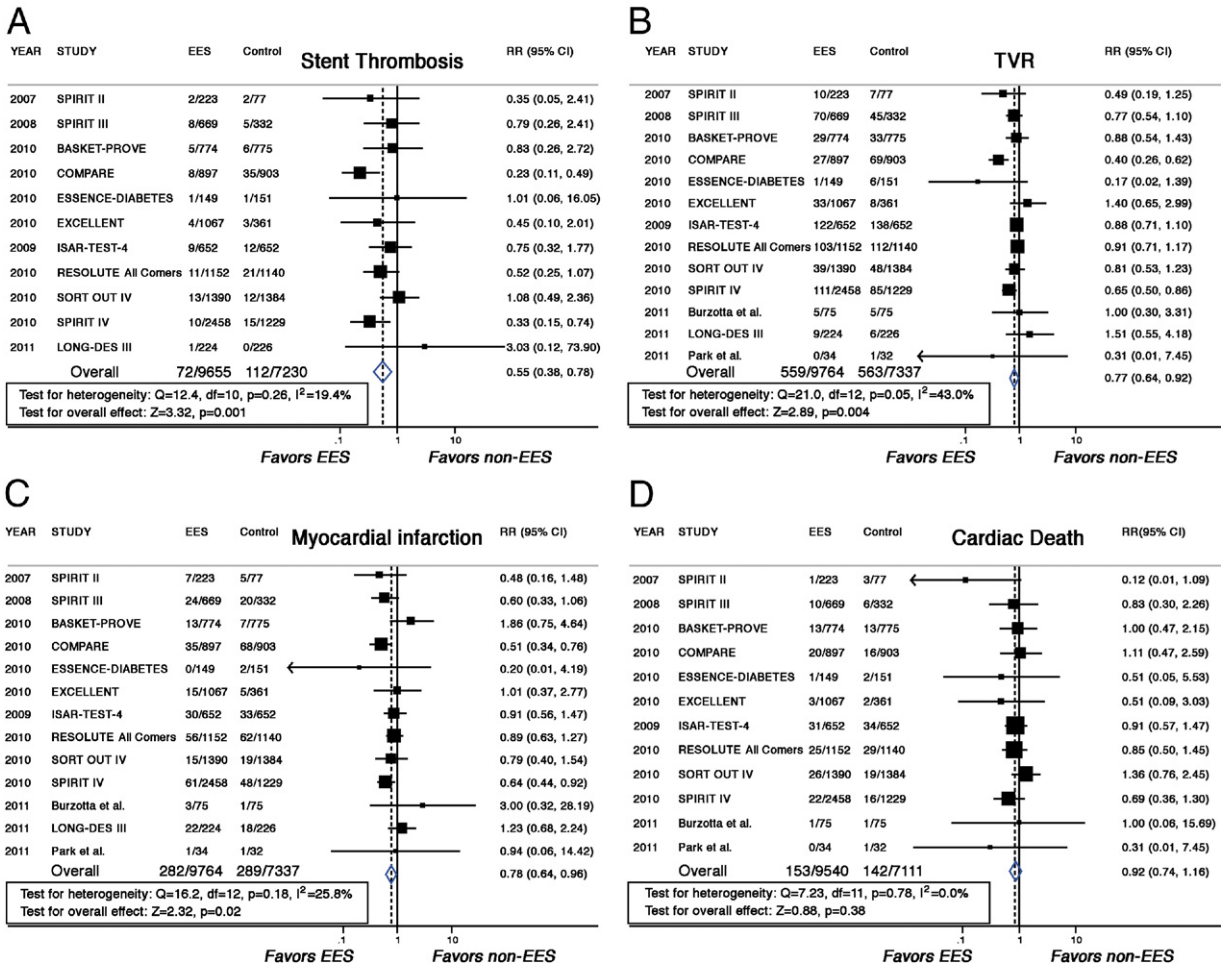

Figure 2 **Outcomes in Randomized Trials**

Size of data markers reflects weight of each study: **(A)** stent thrombosis, **(B)** target vessel revascularization, **(C)** myocardial infarction, and **(D)** cardiac mortality. CI = confidence interval; DES = drug-eluting stent(s); EES = everolimus-eluting stent(s); RR = relative risk.

Publication bias. As our analysis included published and unpublished reports, we assessed publication bias using standard statistical tools for the published studies (n = 6), and qualitatively assessed risk of bias for all studies (n = 13). The qualitative assessment was performed by evaluating various indicators of study quality, as previously described (27). Visual inspection of the funnel plots for ST did not reveal asymmetry. In support, there was no evidence of small study effects based on the Begg rank correlation and Egger's regression tests (p = 0.73 and p = 0.98, respectively). Similar results were obtained for TVR, MI, and cardiac mortality. Similarly, the majority of studies were classified as low risk of bias across all domains of study quality (Fig. 5).

Discussion

In the present meta-analysis comprising 13 randomized trials and including >17,000 patients and 184 ST events, we found that the EES was associated with a large and significant reduction in the frequency of ARC definite or probable ST compared to other, non-EES. We also detected analogous reductions in both MI and TVR with the EES whereas there were no differences in cardiac mortality between groups. The reduction in ST was graded, increasing in a dose-dependent fashion with increasing risk for ST. Given the relatively recent introduction of the EES into clinical practice, these data are the most comprehensive to date evaluating the comparative efficacy and safety of this novel second-generation DES to those of non-EES.

Previous studies. In contrast to earlier DES trials, DAPT was recommended for a minimum of 6 months and often for as long as 12 months in all studies included in the present meta-analysis. Moreover, contemporary DES trials often exclude patients who might not comply with DAPT (i.e., expected nonadherence and/or surgery) while similar exclusions were not routinely applied in first-generation DES studies (1,28). These distinctions are critical as pre-

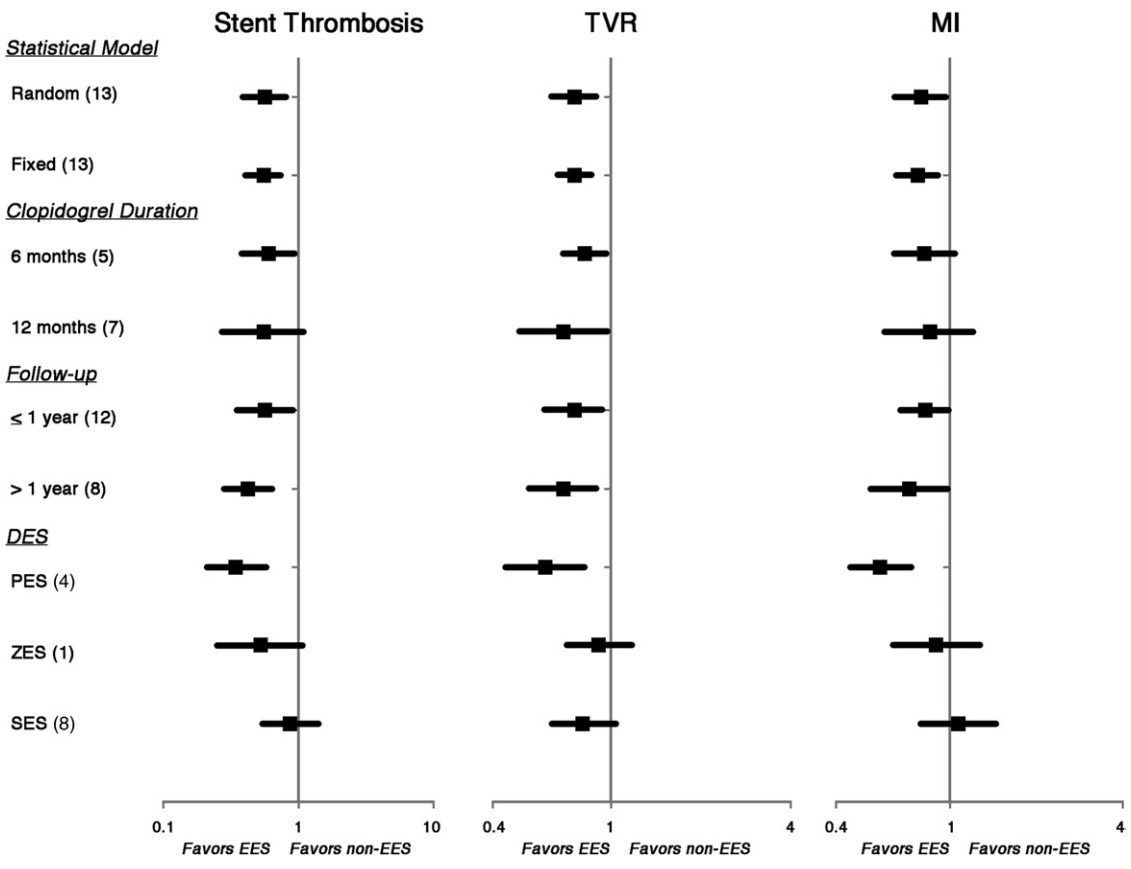

Figure 3 **Stratified Analyses of Randomized Trials**

The pooled estimates are reported as relative risk. The **values in parentheses** are the number of studies included in the analysis for each separate subgroup. **Boxes** represent point estimates and **lines** are 95% confidence intervals. MI = myocardial infarction; PES = paclitaxel-eluting stent(s); SES = sirolimus-eluting stent(s); TVR = target vessel revascularization; ZES = zotarolimus-eluting stent(s).

mature DAPT cessation is perhaps the strongest clinical predictor of ST (29), a link that was not fully appreciated when earlier DES trials were designed. Although we cannot fully exclude the contribution of DAPT cessation on the frequency of ST we observed, its contribution was likely minimal as all studies in the present meta-analysis were randomized, and there were no differences in the duration of DAPT in the treatment arms across trials. In addition, we did not detect any difference in the effect of the EES on ST in trials mandating 6 months versus 12 months of clopidogrel therapy (Fig. 3).

Earlier DES trials also often included patients considered to be at relatively low risk for subsequent thrombotic events (1,28,30). However, concerns regarding the long-term safety of DES (i.e., late and very late ST) from several post-marketing and observational reports (31) suggested that this increased risk was most apparent when DES were implanted in patients (e.g., diabetes mellitus, chronic renal failure, acute myocardial infarction) or lesions (e.g., bifurcation, ostial, small reference vessel diameter) that would have been otherwise excluded from these pivotal trials. In response to such concerns, subsequent DES trials that were included in the present meta-analysis were designed to include a much broader patient (and lesion) population. For example, the frequency of complex lesions and patients presenting with an acute coronary syndrome was substantial in most studies of this meta-analysis. This temporal evolution of DES trial design strengthens the generalizability of the results from the present meta-analysis to real-world DES practice patterns.

DES comparisons. Although the results of our stratified analysis suggest a consistent benefit with EES by clopidogrel duration and length of follow-up, we did detect differences in the treatment effect across control DES strata. In particular, reductions in ST, TVR, and MI were accentuated in trials versus PES, intermediate versus ZES, and smallest against SES. Our regression analysis provides further insight and a potential rationale for this heterogeneity. As the absolute benefit of the EES increased with higher baseline risk of the study population and overall control event rates were lowest in trials with SES compared to PES and ZES, our findings in different DES groups are

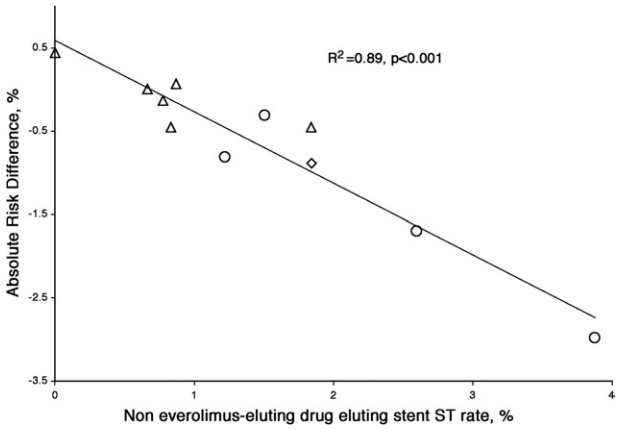

Figure 4 **Relationship Between Baseline Risk and Risk Difference for ST in RCTs**

The plot shows the regression of baseline risk on the risk difference for stent thrombosis (ST) in randomized controlled trials (RCTs). A negative risk difference favors EES, whereas a positive risk difference favors non–everolimus-eluting DES. **Open symbols** represent control DES (**circles** = PES, **triangles** = SES, and **diamonds** = ZES). Abbreviations as in Figures 2 and 3.

not entirely unexpected. Because of the inherent limitations of this approach (32), however, we cannot rule out the possibility that the variability in EES efficacy across control DES reflects a true attenuation of treatment effect rather than differences in baseline risk of study populations across studies. The latter explanation is supported by the observation that the PES was not found to be associated with increased stent thrombosis versus an identical bare metal stent in a recent large study (33). Finally, this heterogeneity may be due to the subdivision of our data into several smaller subgroups (only 1 study to date comparing EES to ZES).

Possible mechanisms of benefit. Although there are several well-established parameters that correlate with increased risk of ST and TVR, the influence of these parameters on the observed treatment effects were likely minimal as we only included randomized trials in the present meta-analysis. Assuming adequate randomization, therefore, the effects of the EES were most likely due to the unique features of this DES system compared to others. Any of the EES system components (metallic stent material, strut thickness, polymer, drug, elution properties, healing), or their combination could account for our results.

First, everolimus is a potent antiproliferative agent, reducing late loss and subsequent revascularization to a greater extent than paclitaxel (34,35). Angiographic follow-up of the recently completed RESOLUTE All Comers trial also demonstrated numerically less in-segment and in-stent late loss with EES compared to ZES (36). Our results of lower TVR with EES use are not unexpected, therefore, and are consistent with previous angiographic findings.

Second, the metallic stent properties of the EES system include a cobalt chromium platform that enables a thin strut configuration. Compared to thick struts, thin struts may minimize vascular injury and subsequent neointimal hyperplasia, thereby lowering clinical and angiographic restenosis (37,38). The metallic struts of the EES are the thinnest (81 μm) of all comparator DES included in the control group of this meta-analysis. Endothelialization may also be more rapid and complete in stents with thin versus thick struts. Simon et al. (39), for example, reported that endothelial cell migration and coverage was reduced at a distance >75 μm and was nonexistent at a distance of >250 μm. Similarly, Joner et al. (6) demonstrated that the extent of endothelial coverage at 14 days was significantly greater in EES versus non-EES in an animal model. As incomplete endothelialization is strongly linked with risk for ST (40), our findings of lower ST associated with EES use are consistent with and extend these earlier experimental observations to the clinical setting.

Important differences in the polymer coating of the EES compared to other DES might also contribute to lower adverse events. The permanent, nonerodable matrix in first-generation DES might provoke delayed-type hypersensitivity and inflammatory reactions, increasing risk for late ST (41). In contrast, the fluoropolymers used in the EES are associated with less thrombogenicity and inflammation and reduced platelet activation (29,42). The greater biocompatibility and hemocompatibility of this class of polymers has led to their use in other vascular territories as well (43,44).

Clinical implications. Although rare, ST has serious clinical consequences, usually presenting as MI or even cardiac death. Within this context, our findings, which suggest a markedly lower risk for ST with EES use, have important clinical implications. Our results indicated an absolute reduction in ST with EES use of 0.5%, translating into a

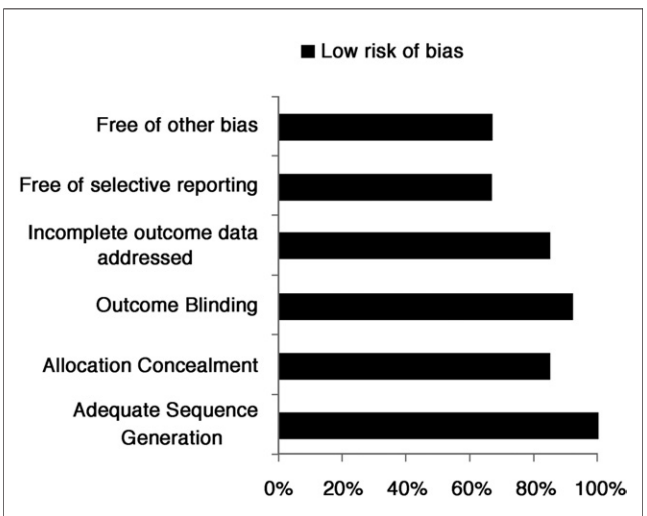

Figure 5 **Risk of Bias**

Proportion of studies classified as having low risk of bias across domains of study quality.

number needed to treat of 200 to prevent 1 episode of ST over a mean follow-up of 21.7 months. Moreover, the magnitude of risk reduction was increased to 1.0% (number needed to treat = 100) in patients at highest risk for ST. Although modest, this level of protection is consistent with other commonly performed cardiac interventions. In addition, the potential advantages of interventions that might yield a modest absolute benefit are more apparent at a population rather than at an individual patient level. This is particularly true of intracoronary interventions, which have been performed in millions of individuals worldwide, with DES being used much more commonly than bare metal stents.

Study limitations. A limitation of the present study is the lack of patient-level data, which precluded our ability to evaluate differences in the composite endpoint of cardiac death or MI and the timing of ST with respect to DAPT duration and/or cessation. The inclusion of such data would also permit more flexibility in subgroup analyses. In addition, we are unable to firmly extend our findings to other second-generation DES as only 1 trial used such a stent as the comparator DES; further investigation in this direction is required. Despite these limitations, the large sample size of our study provided us with sufficient power to assess the impact of the EES on ST. In addition, the definition of ST was uniform and standardized across all trials, minimizing bias. As we only included randomized trials, the possibility of confounders influencing our point estimates for various endpoints is less likely.

Conclusions

Our findings demonstrate a large and significant reduction in ST with EES use compared to non–EE-DES. Similar benefits of less magnitude are also present with TVR and MI. Longer follow-up of studies included in this meta-analysis will provide further insight on the durability of our results and extension to other patient populations.

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Key Words: drug-eluting stent ■ everolimus-eluting ■ stent thrombosis.