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Drug-Eluting Stents Versus Bare-Metal Stents in Saphenous Vein Graft Interventions

A Systematic Review and Meta-Analysis

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Objectives We sought to review the published data and perform a meta-analysis to reach robust conclusions in the comparison between bare-metal stents (BMS) and drug-eluting stents (DES) in saphenous vein graft (SVG) percutaneous coronary interventions (PCIs).

Background Drug-eluting stents are superior to BMS in reducing major adverse cardiac events (MACE) after PCI in native coronary arteries. However, studies comparing BMS with DES in PCI of SVG have had mixed results, probably due to smaller numbers and the nonrandomized nature of most of them.

Methods The published reports search identified 4 randomized controlled trials and 19 cohort studies comparing BMS with DES in SVG interventions. Clinical end point data were abstracted and analyzed in aggregate and in subgroup analyses with random-effects model.

Results Patients receiving DES had a lower risk of mortality (odds ratio [OR]: 0.75; confidence interval [CI]: 0.59 to 0.96), target lesion revascularization (TLR) (OR: 0.57; CI: 0.40 to 0.82), target vessel revascularization (TVR) (OR: 0.56; CI: 0.40 to 0.77), and MACE (OR: 0.61; CI: 0.42 to 0.79). Drug-eluting stent use resulted in a significant absolute risk reduction in TLR (−0.07; CI: −0.11 to −0.03), TVR (−0.10; CI: −0.15 to −0.05), and MACE (−0.12; CI: −0.18 to −0.06). There was no significant difference between the groups in recurrent myocardial infarction (OR: 0.99; CI: 0.65 to 1.51) or stent thrombosis (OR: 0.78; CI: 0.40 to 1.52).

Conclusions In this meta-analysis comparing DES with BMS use in PCI of SVG lesions, DES use was associated with improved mortality, MACE, TLR, and TVR. There was no evidence of increased risk of myocardial infarction or stent thrombosis. (J Am Coll Cardiol Intv 2010;3:1262–73) © 2010 by the American College of Cardiology Foundation

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Percutaneous revascularization procedures of saphenous vein graft (SVG) lesions are associated with a higher risk of complications (1), despite major advances in pharmacological and device therapy. Compared with balloon angioplasty alone, use of bare-metal stents (BMS) for treatment of SVG lesions resulted in significant reduction in major adverse events, including need for repeat revascularization (2). Embolism protection devices have significantly reduced acute morbidity and mortality (3,4). Nonetheless, restenosis at the target lesion as well as development of new lesions underlie the higher rates of long-term graft failure after percutaneous coronary intervention (PCI) (5–8).

Drug-eluting stents (DES) have decreased the restenosis rates after native coronary interventions and, although not approved for such indications, have been widely used for treatment of SVG lesions (9–11). However, the superiority of DES over BMS in SVG lesions has not been clearly established. Data emerging from comparative studies have been mixed. Most such comparisons were retrospective in nature and included a relatively small number of patients. In this meta-analysis, we report the compilation of the clinical outcomes data that exists from both randomized controlled trials (RCTs) and retrospective comparative studies looking at the differences between BMS and DES in the treatment of SVG obstructive lesions.

Methods

Review question and study protocol. The review sought to answer the following question: Does the use of DES in SVG interventions reduce periprocedural and long-term clinical events when compared with use of BMS? We report this protocol-driven systematic review according to the MOOSE (Meta-analysis Of Observational Studies in Epidemiology) (12) and QUOROM (Quality of Reporting of Meta-analysis) (13) statements.

Eligibility criteria. Two reviewers (M.E.W. and A.A.L.) judged eligibility of studies in duplicate and independently. Eligible studies were RCTs and cohort studies examining the use of DES versus BMS during SVG interventions. We included studies that used historic controls, but we performed a subgroup analysis to identify the significance of this methodology, because this traditionally favors new therapies (14). We excluded studies that reported only intravascular ultrasound and quantitative coronary angiography data and did not discern the clinical outcomes examined in the meta-analysis. Similarly, studies that did not include a control arm were excluded.

Search strategy. We searched MEDLINE (January 1980 to December 2009), the Cochrane databases (December 2009), EMBASE (January 1980 to December 2009), CINAHL (January 1982 to December 2009), the U.S. Food and Drug Administration website, and BIOSIS Previews (January 1980 to December 2009) with database-appropriate MESH terms for the following: percutaneous coronary intervention, balloon angioplasty, stenting, saphenous venous grafts, coronary artery bypass graft, and clinical outcomes. We sought additional studies by reviewing the reference lists of eligible studies and relevant review articles. The complete search strategy is available upon request from the authors.

Data abstraction. Two reviewers (M.E.W. and A.A.L.) working in duplicate and independently used a standardized form to abstract the data from each study. The author K.M.Z. solved disagreements that could not be solved by consensus. When necessary, major adverse cardiac events (MACE) were calculated by summing the reported individual end points if MACE was not specifically reported in the published report.

Quality assessment. We used the criteria by Juni et al. (15) to ascertain the methodological quality of included randomized trials and a modified Newcastle-Ottawa scale (16) to assess the quality of cohort studies (details included in Online Appendix).

Data analysis. META-ANALYSES. The main outcomes of our review were all-cause mortality, target lesion revascularization (TLR), target vessel revascularization (TVR), MACE, myocardial infarction (MI), and stent thrombosis (ST). We used the abstracted MACE as defined by the authors; however, the definition varied among studies. For mortality, some studies used all-cause mortality (17–27), whereas others used cardiac mortality (28–32). Some studies used TVR (20–22,24–27,29,32–35), whereas others used TLR (28,30,31,36) or both (18–20,24,37) in their composite MACE end point. When MACE was not specified in the original article, we calculated MACE as the sum of all-cause mortality, nonfatal MI, and TVR/TLR. Given the observed heterogeneity in the methodologies of the studies and the types of stents used, we conducted random-effects meta-analyses to pool these outcomes across included studies, estimating the odds ratios (ORs) of the pre-specified clinical end points between DES- and BMS-treated patients and their

Abbreviations and Acronyms

ARR = absolute risk reduction
BMS = bare metal stent(s)
CI = confidence interval
DES = drug-eluting stent(s)
EPD = embolism protection device
MACE = major adverse cardiac events
MI = myocardial infarction
NNT = numbers needed to treat
OR = odds ratio
PCI = percutaneous coronary intervention
RCT = randomized controlled trial
ST = stent thrombosis
SVG = saphenous vein graft
TLR = target lesion revascularization
TVR = target vessel revascularization

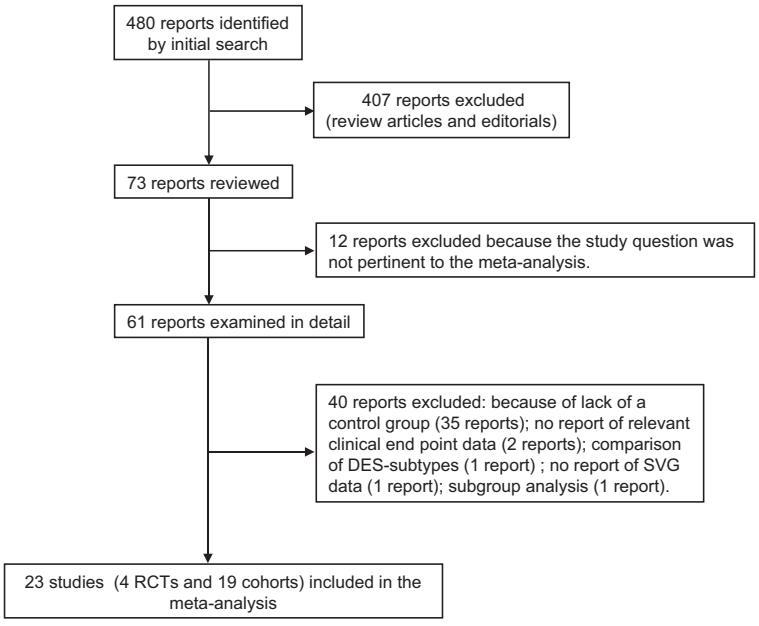

Figure 1. Selection of Trials for Inclusion in Meta-Analysis

Selection of trials for inclusion in meta-analysis. The initial search identified 480 articles, of which, 23 studies (4 randomized controlled and 19 cohorts) were included in the final analysis. DES = drug-eluting stent(s); RCT = randomized controlled trial; SVG = saphenous vein graft.

associated 95% confidence interval (CI). The OR is a way of comparing whether the probability of death, TLR, TVR, MACE, recurrent MI, or ST is the same between DES-treated patients and BMS-treated patients. We also calculated the absolute risk reduction (ARR) (i.e., risk difference) and the "numbers needed to treat" (NNT) to assess the clinical significance of the outcome. The ARR signifies the absolute difference in outcome rates between the DES-treated and BMS-treated groups. The ORs from separate studies were combined according to random-effects model (Mantel-Haenszel method) (38,39). The NNT is the reciprocal of the ARR and denotes the number of patients that would need to be treated with DES to prevent 1 adverse outcome. We reported the outcomes from RCTs and cohort studies separately as well as the combined outcomes from all the included studies. We estimated the proportion of between-study inconsistency due to true differences between studies (rather than differences due to random error or chance) with the I^2 statistic (40), with values of 25%, 50%, and 75% considered low, moderate, and high, respectively. Funnel plots graphically explored publication bias. The Review Manager software (RevMan version 4.3. Copenhagen, The Nordic Cochrane Centre, The Cochrane Collaboration, 2006) was used for the analysis.

SUBGROUP ANALYSES. We conducted planned subgroup analyses and tested for treatment–subgroup interactions. Planned subgroups comprised the types of study design (RCTs vs. cohort studies); the use of historical versus concurrent controls; and the frequency of distal embolic protection device (EPD) use (above and below the median).

Results

Search results. Of 480 articles retrieved during the initial search (Fig. 1), 407 articles were not reports of original investigations (review articles and editorials), 12 studies were not pertinent to the study question (studies of EPDs, covered stents, and brachytherapy), and 40 other studies were further excluded (35 were either case reports or case series without a control group, 2 studies did not report relevant clinical end point data pre-specified in our inclusion criteria, 1 study compared DES sub-types, 1 did not include SVG data, and 1 study was a subgroup analysis). Twenty-three studies (4 RCTs, 19 cohort studies) with a total of 5,324 patients (2,805 received DES and 2,519 received BMS) were eligible for review. The inter-reviewer agreement on study eligibility was 100%.

Study characteristics. Table 1 summarizes the clinical characteristics, and Table 2 summarizes the angiographic/procedural characteristics of the included studies (41–44). Target vessel diameter and lesion length were not specified in every study, but stent diameter and stent

Table 1. Clinical Characteristics of Included Studies

	Study Design	Study Period	Controls	Sample Size	Average Patient Age (yrs)	Length of Follow-Up (Months)	Mandated Angiographic Follow-Up (Y/N)
RCTs							
Brilakis et al. (29)	RCT	2005–2007	Contemporary	BMS 39 DES 41	BMS 67 ± 9 DES 66 ± 9	18	Y
Jeger et al. (32)	RCT	2003–2004	Contemporary	BMS 13 DES 34	71 ± 8	18	N
Vermeersch et al. (26)	RCT	2003–2004	Contemporary	BMS 37 DES 38	BMS 72 ± 8 DES 73 ± 7	6	Y
Vermeersch et al. (41)	RCT	2003–2006	Contemporary	BMS 37 DES 38	BMS 72 ± 8 DES 73 ± 7	BMS 32 DES 31	N
Cohort nonrandomized trials							
Assali et al. (33)	Cohort	2003–2005	Historical	BMS 43 DES 68	BMS 71 ± 9 DES 70 ± 8	NR	N
Bansal et al. (28)	Cohort	2003–2005	Contemporary	BMS 72 DES 37	BMS 64.9 ± 1.1 DES 68.0 ± 1.6	33	N
Brodie et al. (17)	Cohort	2003–2006	Contemporary	BMS 343 DES 785	BMS 68.8 ± 10.2 DES 67.5 ± 10.3	24	N
Chu et al. (18)	Cohort	2001–2004	Historical	BMS 57 DES 48	BMS 71.4 ± 9.9 DES 68.6 ± 10.2	12	N
Ellis et al. (42)	Cohort	2000–2003	Historical	BMS 175 DES 175	BMS 68.5 ± 10.0 DES 69.8 ± 9.0	NR	N
Ge et al. (43)	Cohort	2002–2004	Historical	BMS 89 DES 61	BMS 67 ± 8 DES 67 ± 8	6	Y
Gioia et al. (30)	Cohort	2002–2006	Contemporary	BMS 119 DES 106	BMS 70 ± 7 DES 71 ± 8	BMS 16 DES 16	N
Goswami et al. (31)	Cohort	2003–2007	Contemporary	BMS 95 DES 284	BMS 69.5 ± 10.4 DES 70.7 ± 9.7	30	N
Hoffman et al. (19)	Cohort	2002–2004	Contemporary	BMS 60 DES 60	BMS 67 ± 7 DES 67 ± 11	6	Y
Kaplan et al. (20)	Cohort	2003–2006	Contemporary	BMS 33 DES 37	BMS 70.5 ± 8.7 DES 72.3 ± 9.0	NR	N
Lee et al. (21)	Cohort	2003–2004	Contemporary	BMS 84 DES 139	BMS 69.4 ± 11.2 DES 68.6 ± 10.5	NR	Y
Lozano et al. (44)	Cohort	NR	Historical	BMS 114 DES 98	BMS 66.4 ± 9 DES 70.6 ± 8.9	30	N
Minutello et al. (22)	Cohort	2003–2005	Historical	BMS 50 DES 59	BMS 69.4 ± 11.0 DES 70.8 ± 12.7	BMS 20 ± 16 DES 20 ± 12	N
Okabe et al. (23)	Cohort	2000–2006	Historical and contemporary	BMS 334 DES 138	BMS 70 ± 11 DES 70 ± 11	12	N
Ramana et al. (24)	Cohort	2003–2007	Contemporary	BMS 170 DES 141	BMS 69.1 DES 70.0	BMS 36.2 DES 31.0	N
Shishehbor et al. (36)	Cohort	2000–2007	Historical and contemporary	BMS pre-2003: 239 BMS post-2003: 110 DES: 217	BMS pre-2003: 69 ± 9 BMS post-2003: 68 ± 10 DES: 70 ± 10	35	N
van Twisk et al. (25)	Cohort	2000–2005	Historical	BMS 128 DES 122	BMS 69.3 DES 68.3	48	N
Vignali et al. (35)	Cohort	2003–2006	Contemporary	BMS 288 DES 72	BMS 71.4 ± 8.6 DES 72.5 ± 7.8	14	N
Wohrle et al. (27)	Cohort	2005–2005	Historical	BMS 26 DES 13	BMS 69.6 ± 6.4 DES 70.7 ± 4.1	NR	Y

BMS = bare metal stent(s); DES = drug-eluting stent(s); NR = not reported; RCT = randomized controlled trial.

length were reported. Notably, the sample size in each study was relatively small (range 39 to 482 patients; median 113 patients), and the follow-up duration ranged from 6 to 48 months (median 18 months). There was considerable heterogeneity in the use of EPD, which ranged widely from 1.6% to 100% (median 43%). The average age of the graft reflected the clinical practice (range 7.5 to 12.4 years; median 11 years).

Study quality. Online Table 1 describes the methodological quality of the RCTs, and Online Table 2 describes

Table 2. Angiographic/Procedural Characteristics of Included Studies

	Type of DES Used	EPD Use (%)	Average Stent Length (mm)	Average Vessel or Stent Diameter (mm)	Average Graft Age (yrs)
RCTs					
Brilakis et al. (29)	Paclitaxel	54	BMS 29 ± 16 DES 28 ± 17	BMS 3.17 ± 0.42 DES 3.14 ± 0.35	BMS 12 ± 6 DES 11 ± 6
Jeger et al. (32)	Sirolimus and paclitaxel	NR	BMS 46 ± 30 DES 41 ± 25	BMS 17% ≥3.5 DES 29% ≥3.5	NR
Vermeersch et al. (26)	Sirolimus	BMS 84 DES 79	BMS 33.4 ± 18.2 SES 36.9 ± 17.6	BMS 3.36 ± 0.26 DES 3.41 ± 0.19	BMS 12.6 ± 5.9 DES 12.4 ± 4.6
Vermeersch et al. (41)	Sirolimus	BMS 84 DES 79	BMS 33 ± 18 DES 37 ± 18	BMS 3.36 ± 0.26 DES 3.41 ± 0.19	BMS 12.6 ± 5.9 DES 12.4 ± 4.6
Cohort nonrandomized trials					
Assali et al. (33)	Sirolimus and paclitaxel	BMS 48 DES 38	BMS 20.7 ± 13.1* DES 30.3 ± 18.5	BMS 3.6 ± 0.7* DES 3.3 ± 0.4	BMS 11.4 ± 4.5 DES 10.8 ± 5.1
Bansal et al. (28)	Sirolimus (95%)	BMS 27 DES 39	BMS 17.9 ± 0.76 DES 17.1 ± 1.0	BMS 3.8 ± 0.07* DES 3.0 ± 0.07	NR
Brodie et al. (17)	Sirolimus, paclitaxel	BMS 33.7 DES 37.3	BMS 22.0 ± 12.2 DES 25.0 ± 15.4	BMS 3.7 ± 0.8*† DES 3.3 ± 0.5	BMS 68.8 ± 10.2 DES 67.5 ± 10.6
Chu et al. (18)	Sirolimus	BMS 100 DES 100	BMS 23.1 ± 10.6 DES 20.8 ± 7.5	BMS 3.8 ± 0.8* DES 3.1 ± 0.4	BMS 9.4 ± 6.0 DES 10.1 ± 7.6
Ellis et al. (42)	Sirolimus	BMS 25.1* DES 35.1	BMS 21.6 ± 11.8 DES 20.6 ± 8.1	BMS 3.37 ± 0.37† DES 3.33 ± 0.34	BMS 9.8 ± 6.4 DES 10.0 ± 6.2
Ge et al. (43)	Sirolimus and paclitaxel	BMS 22.5 DES 31.1	BMS 20.4 ± 8.8* DES 29.4 ± 19.8	BMS 3.83 ± 0.58* DES 3.35 ± 0.39	BMS 9.2 ± 4.8 DES 9.7 ± 5.6
Gioia et al. (30)	Sirolimus, paclitaxel, tacrolimus	BMS 21 DES 26	BMS 24 ± 10 DES 21 ± 6	BMS 3.9 ± 0.5* DES 3.3 ± 0.4	BMS 11 ± 5 DES 11 ± 6
Goswami et al. (31)	Sirolimus, paclitaxel	NR	BMS 30.4 ± 22.2 DES 27.9 ± 16.3	BMS 4.4 ± 0.7* DES 3.3 ± 0.4	NR
Hoffman et al. (19)	Paclitaxel	BMS 47 DES 52	BMS 14.6 ± 4.4 DES 16.7 ± 3.7	BMS 3.06 ± 0.6† DES 3.05 ± 0.52	BMS 10.1 ± 4.5 DES 11.3 ± 5.7
Kaplan et al. (20)	NR	BMS 33.3 DES 27	BMS 15.6 ± 4.5* DES 18.9 ± 7.4	BMS 3.71 ± 0.54*† DES 3.42 ± 0.53	BMS 7.6 ± 1.3 DES 7.5 ± 1.3
Lee et al. (21)	Paclitaxel, sirolimus	BMS 19 DES 15	NR	BMS 2.96 ± 0.65† DES 2.94 ± 0.23	BMS 7.7 ± 2.8 DES 7.6 ± 3.8
Lozano et al. (44)	Paclitaxel, sirolimus, zotarolimus, other	BMS 5 DES 10	BMS 16 ± 5 DES 22.4 ± 13.5	BMS 3.45 ± 0.61* DES 3.28 ± 0.51	BMS 9.0 DES 10.1
Minutello et al. (22)	Sirolimus	BMS 48* DES 71.2	BMS 20.8 ± 9.9* DES 26.1 ± 16.5	BMS 3.43 ± 0.48* DES 3.12 ± 0.37	NR
Okabe et al. (23)	Sirolimus and paclitaxel	BMS 26 DES 21	BMS 19.8 ± 8.6 DES 20.3 ± 6.4	BMS 3.84 ± 2.07* DES 3.09 ± 0.37	BMS 9.7 ± 6.0 DES 1.04 ± 6.8
Ramana et al. (24)	Sirolimus	NR	BMS 29.3 DES 28.3	BMS 4.2* DES 3.3	BMS 12.9 DES 11.5
Shishehbor et al. (36)	Sirolimus and paclitaxel	BMS pre-2003: 16 BMS post-2003: 62 DES 56	NR	BMS pre-2003: 3.4 ± 0.8† BMS post-2003: 3.9 ± 0.8 DES 3.2 ± 0.5	BMS pre-2003: 9 ± 5 BMS post-2003: 10 ± 6 DES 10 ± 6
van Twisk et al. (25)	Sirolimus and paclitaxel	NR	BMS 31.9 IQR 18.0–40.3* DES 32.0 IQR 18.0–58.5	BMS 3.5 (IQR 3.3–4.0)* DES 3.1 (IQR 3.0–3.5)	NR
Vignali et al. (35)	Sirolimus, paclitaxel	NR	BMS 18.7 ± 6.2 DES 19.7 ± 6.4	BMS 3.5 ± 0.7* DES 3.0 ± 0.4	NR
Wohrle et al. (27)	Paclitaxel	BMS 54 DES 85	BMS 23.6 ± 14.1 DES 23 ± 12.4	BMS 3.28 ± 0.82† DES 3.06 ± 0.7	BMS 9.1 ± 5.1 DES 11.4 ± 7.4

*Statistical significant difference with $p < 0.05$. †Reference vessel diameter, not stent diameter.
EPD = embolic protection device; IQR = interquartile range; other abbreviations as in Table 1.

the quality of the cohort studies. All cohort studies and at least 1 RCT failed to blind participants and caregivers, and at least 1 RCTs and 11 cohort studies failed to blind outcome assessors. The follow-up was complete in all RCTs and 12 of the 16 cohorts. The inter-reviewer agreement on these quality domains was >90%.

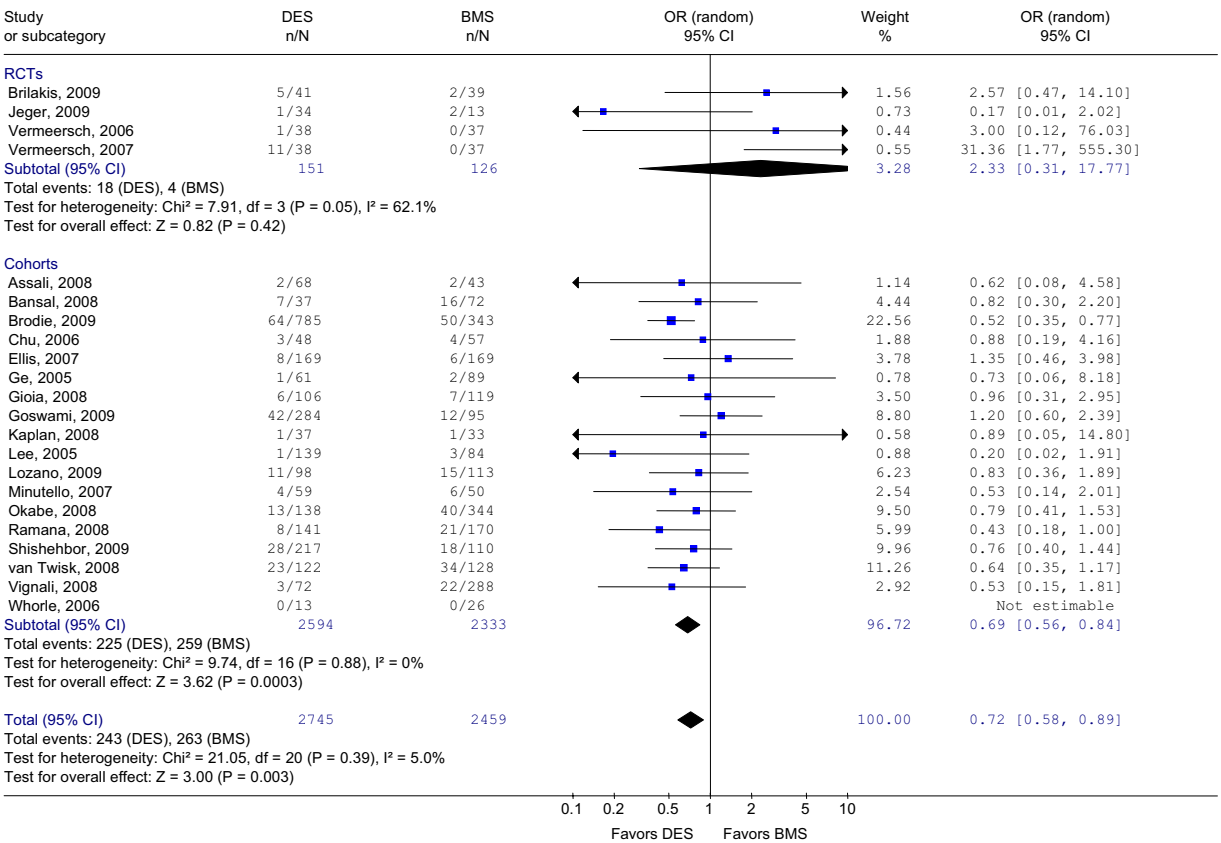

Figure 2. OR of All-Cause Mortality

Forest plot of unadjusted odds ratio (ORs) (with 95% confidence intervals [CIs]) for all-cause mortality in SVG intervention patients receiving DES compared with those receiving bare-metal stents (BMS). Significant reduction in all-cause mortality (OR: 0.72; CI: 0.58 to 0.89; p = 0.003) is noted with DES. Abbreviations as in Figure 1.

Meta-analyses. **EFFICACY.** Compared with BMS-treated patients, DES-treated patients had a lower incidence of the pre-specified clinical adverse events. This was demonstrated in the significant reduction in the OR of all-cause mortality (OR: 0.72; CI: 0.58 to 0.89), TLR (OR: 0.57; CI: 0.40 to 0.82), TVR (OR: 0.56; CI: 0.40 to 0.77), and MACE (OR: 0.61; CI: 0.47 to 0.79) (Figs. 2–5). Drug-eluting stent use resulted in a significant ARR in the incidence of TLR (ARR: −0.07; CI: −0.11 to −0.03; NNT: 14), TVR (ARR: −0.10; CI: −0.15 to −0.05; NNT: 10) and MACE (ARR: −0.12; CI: −0.18 to −0.06; NNT: 8) but not in the incidence of all-cause mortality, MI, or ST (Figs. 6 and 7). The results were consistent between the fixed and random effects models. We drew funnel plots to seek evidence of publication bias (Online Fig. 1): where inconsistency was high, the funnel plots were not interpretable; where inconsistency was low, the funnel plots were inconclusive.

HETEROGENEITY ANALYSIS. Tests for heterogeneity were done for each of the clinical end points with the I^2 statistic. There was significant heterogeneity (I^2 = 62.1%) noted in the all-cause mortality for the RCTs; however, the overall I^2 statistic was 5%, suggesting that the OR of 0.72 for DES compared with BMS had little heterogeneity effect. Overall, however, TVR had a high I^2 statistic (= 67.4%), suggesting that most of the variability across the studies here was due to heterogeneity rather than chance. Target lesion revascularization and MACE had relatively high I^2 statistics as well (52.8% and 68.4%, respectively).

SUBGROUP ANALYSES. The treatment effect of DES use was comparable in all subgroup analyses examined. We did not find any treatment–subgroup interaction through any of our planned subgroup analyses (Online Table 3). However, due to the significant heterogeneity in the study designs, some of the comparison arms were unbalanced. Of note, all-cause mortality was higher among RCTs, and this is largely influenced by the results of the DELAYED RRISC (Death and Events at Long-term follow-up AnalYsis: Extended Duration of the Reduction

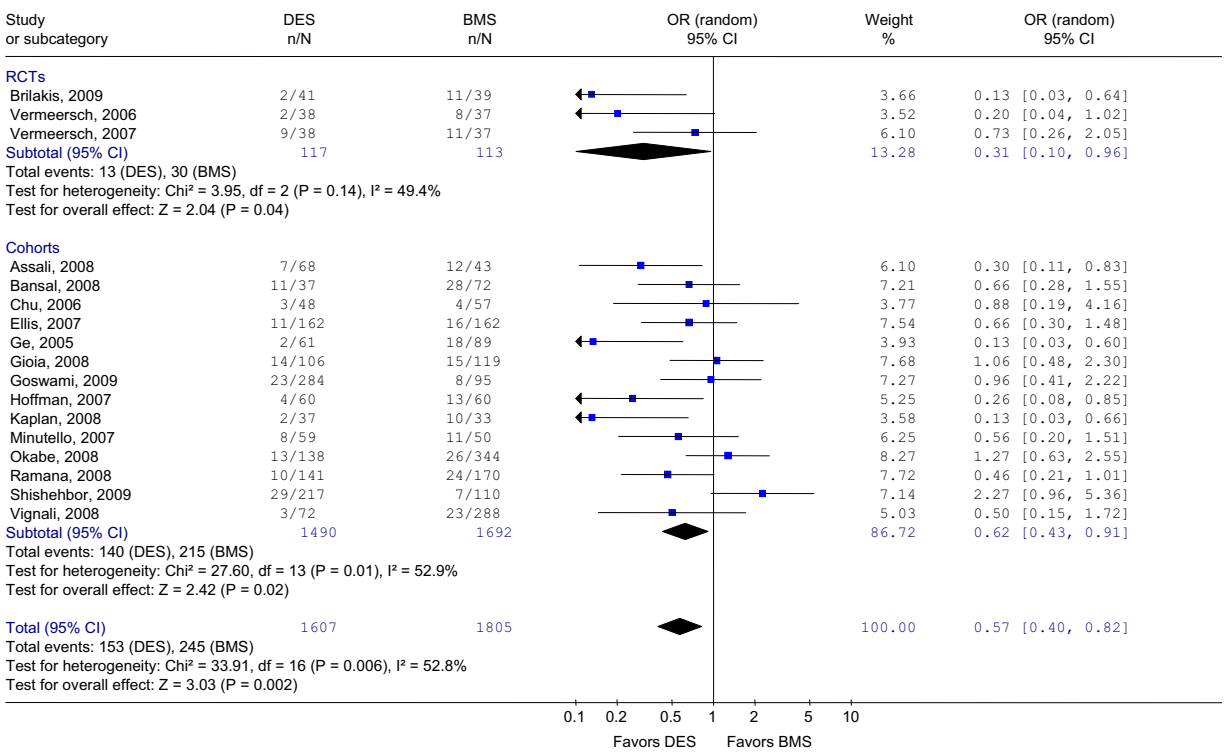

Figure 3. OR of TLR

Forest plot of unadjusted OR (with 95% CIs) for target lesion revascularization (TLR) in SVG intervention patients receiving DES compared with those receiving BMS. Significant reduction in TLR (OR: 0.57; CI: 0.40 to 0.82; p = 0.002) is noted with DES. Abbreviations as in Figures 1 and 2.

of restenosis in saphenous vein Grafts with Cypher) study. This difference was minimized by excluding this study. However, this difference is not statistically significant, whether we included or excluded the DELAYED RRISC study. The studies included were a mixture of RCTs and nonrandomized cohorts. Although the RCTs demonstrated higher overall all-cause mortality than cohort studies, there were no appreciable differences in the other outcomes tested.

SAFETY. The use of DES in treatment of SVG lesions was safe and was not associated with increased complications. Notably, none of the studies that reported the incidence of ST demonstrated significant differences between DES- and BMS-treated patients.

Discussion

Despite the general agreement on the superiority of DES over BMS in reducing clinical end points such as TVR, TLR, and MACE after native vessel PCI, studies comparing DES with BMS in SVG interventions have yielded conflicting results. This systematic review and comprehensive meta-analysis of the available studies demonstrates that DES use is associated with a significant reduction in adverse clinical end points (TVR, TLR, MACE, and all-cause mortality). Reassuringly, this improvement has not come with any compromise in safety; there is no signal of increased MI or ST associated with DES use.

Currently, the DES has become the mainstay of native vessel PCI, due to the established superiority over BMS in reducing MACE, primarily by reducing restenosis and need for TLR or TVR (45–48). However, studies examining DES use in SVG interventions were hampered by the nonrandomized nature and the small numbers in most cases. This resulted in conflicting conclusions and a degree of uncertainty as to whether DES should be used in SVG interventions. Although many of the early RCTs showed trends toward improved outcomes with DES over BMS in SVGs, the results from the RRISC study raised concerns regarding the potential association with increased mortality in the DES group and attrition of the improvement in restenosis after 3 years (41). However, it is important to note that the small number of patients in this study did not provide sufficient power to detect true effects on morbidity and mortality. In addition, most fatal adverse outcomes were noncardiac or procedure related,

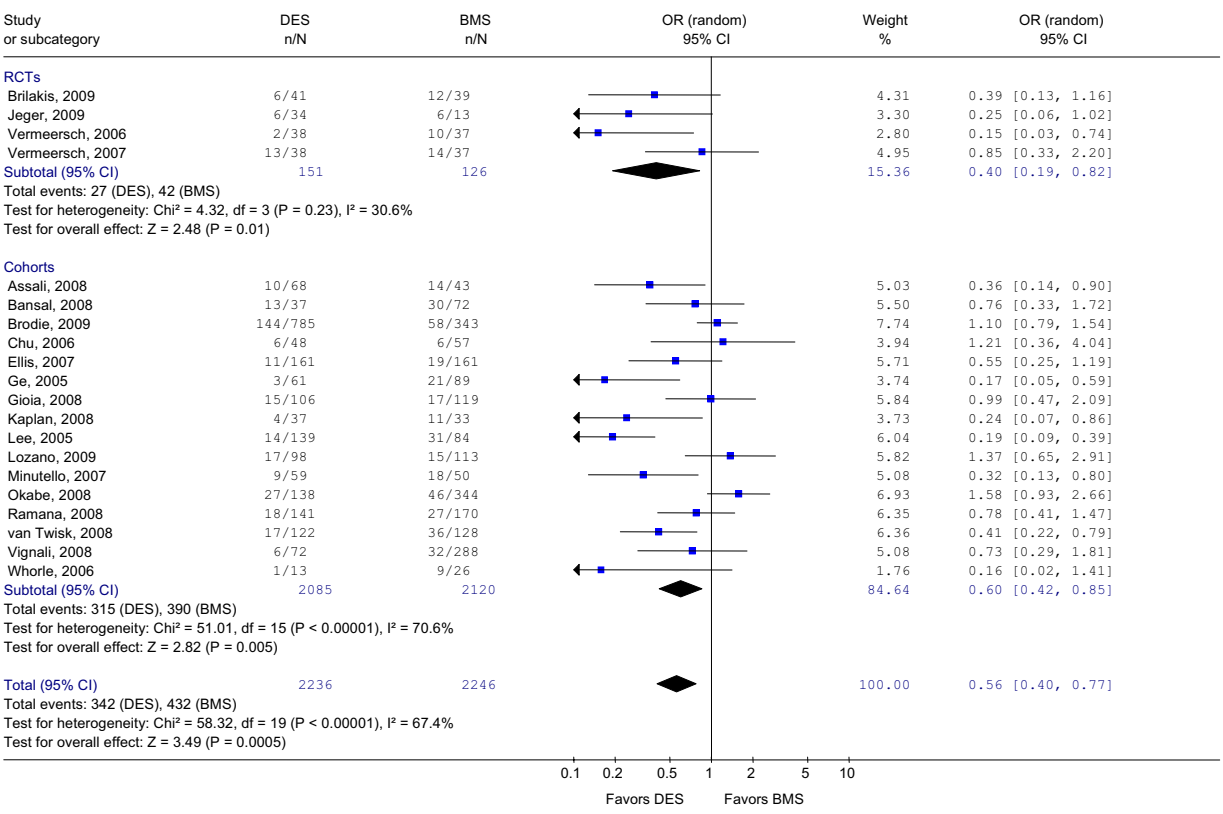

Figure 4. OR of TVR

Forest plot of unadjusted OR (with 95% CIs) for target vessel revascularization (TVR) in SVG intervention patients receiving DES compared with those receiving BMS. Significant reduction in TVR (OR: 0.56; CI: 0.40 to 0.77; p = 0.0005) is noted with DES. Abbreviations as in Figures 1, 2, and 3.

again emphasizing the limitations of small sample size. Moreover, this mortality difference was not replicated in any of the other published RCT or cohort studies. Most published reports in this field (DES in SVG interventions) have similar concerns caused by small sample size. Of note, 11 of the 19 studies included in the analysis included <150 patients.

The overall mortality rates observed in our analysis (8% to 10%) are similar to those reported in the SVG PCI published data (49). Our analysis demonstrated slight albeit statistically significant reduction in mortality among DES-treated patients. This reduction was not seen in the analysis of the RCTs (even with the exclusion of the DELAYED RRISC study) but was evident in the cohort studies. Such difference is likely due to selection bias in cohort studies. The systematic review by Shishehbor et al. (36) reaches similar conclusions with regard to potential selection bias in the current era. In that analysis and in comparison with BMS use, DES use in SVG interventions was associated with reduced mortality in the era of routine use of DES (after 2003), but when compared with BMS before 2003 (when DES was not available) that difference was not observed.

Our stratified analyses demonstrated a reduction in the benefits observed with DES in longer follow-up trials, which is noted on the visual inspection of the forest plots (Online Figs. 2 to 5). Although this reduction is not consistent in all the outcomes measured and did not achieve statistical significance, it is a plausible clinical course. Development of significant focal lesions in SVG usually indicates a progressive degenerative process that is not necessarily stopped by a very focal or segmental therapy such as stenting. Therefore, future large randomized trials with longer follow-up will be required to assess the durability of the beneficial effects of DES in SVG grafts.

The use of historical controls in some of the included studies (18,22,25,27,33,42) might have influenced the results, because this has been shown to favor new treatments (14). However, stratified analysis excluding studies using historical controls showed persistence in the significant reduction in TLR, TVR, and MACE (Online Table 3). By contrast, the reduction in mortality observed in our analysis is rather small and is probably multifactorial. The use of DES in native coronaries did not show

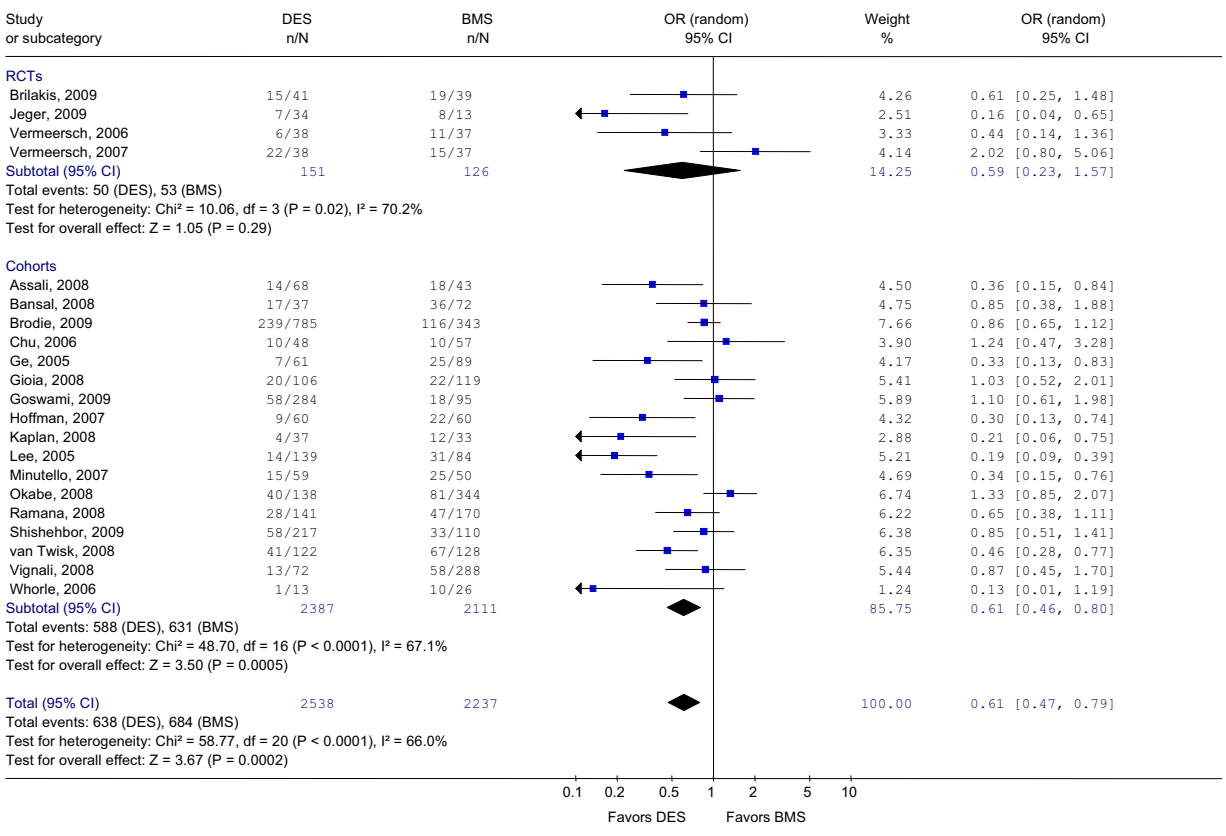

Figure 5. OR of MACE

Forest plot of unadjusted OR (with 95% CIs) for major adverse cardiac events (MACE) in SVG intervention patients receiving DES compared with those receiving BMS. Significant reduction in MACE (OR: 0.61; CI: 0.47 to 0.79; p = 0.0002) is noted with DES. Abbreviations as in Figures 1, 2, 3, and 4.

significant reduction in mortality (47,48), and the benefit observed in our analysis can be explained at least in part by the longer duration of dual antiplatelet therapy (50,51). Moreover, selection bias could have contributed to the reduction in mortality in cohort nonrandomized studies (Fig. 2, Online Table 3)

Traditionally, studies that mandate angiographic follow-up have reported higher TVR and TLR than those that do not, due to the "occulostenotic reflex" (52). We did not observe significant differences between those studies and those that did not mandate the angiographic follow-up or the unstratified analysis in the rates of TVR, TLR, or MACE. However, because these are post hoc analyses of published data rather than individual patient data, and because the influence of performance bias on the interaction cannot be entirely excluded, larger double-blind RCTs specifically designed to address this question will be necessary.

The use of EPDs was low (median of 38%) in the studies we reviewed. This finding is rather concerning, because the utility of EPD has been well-documented in the published data (53) and supported by the guidelines (54). However, we did not observe significant interaction in the rate of MI or MACE among studies with EPD use above or below the median of 38%. This again highlights the potential of selection bias among the nonrandomized cohort studies.

The risk of late ST after discontinuation of dual antiplatelet therapy has been a major concern about DES use (48). We did not find higher rates of ST in our analysis, which actually trended toward lower ST in the DES-treated patients. This might be explained by prolonged dual antiplatelet therapy in DES-treated patients, selection bias in the cohort studies, and relatively short follow-up duration in some of the included studies. Nonetheless, "real world" data suggest that with appropriate patient selection, the use of DES in SVG interventions is not associated with higher risk of ST.

Study limitations. Study quality, reliance on retrospective nonrandomized studies, short follow-up duration in most studies, and lack of data with the new generation of DES might have limited the inferences of this review. As

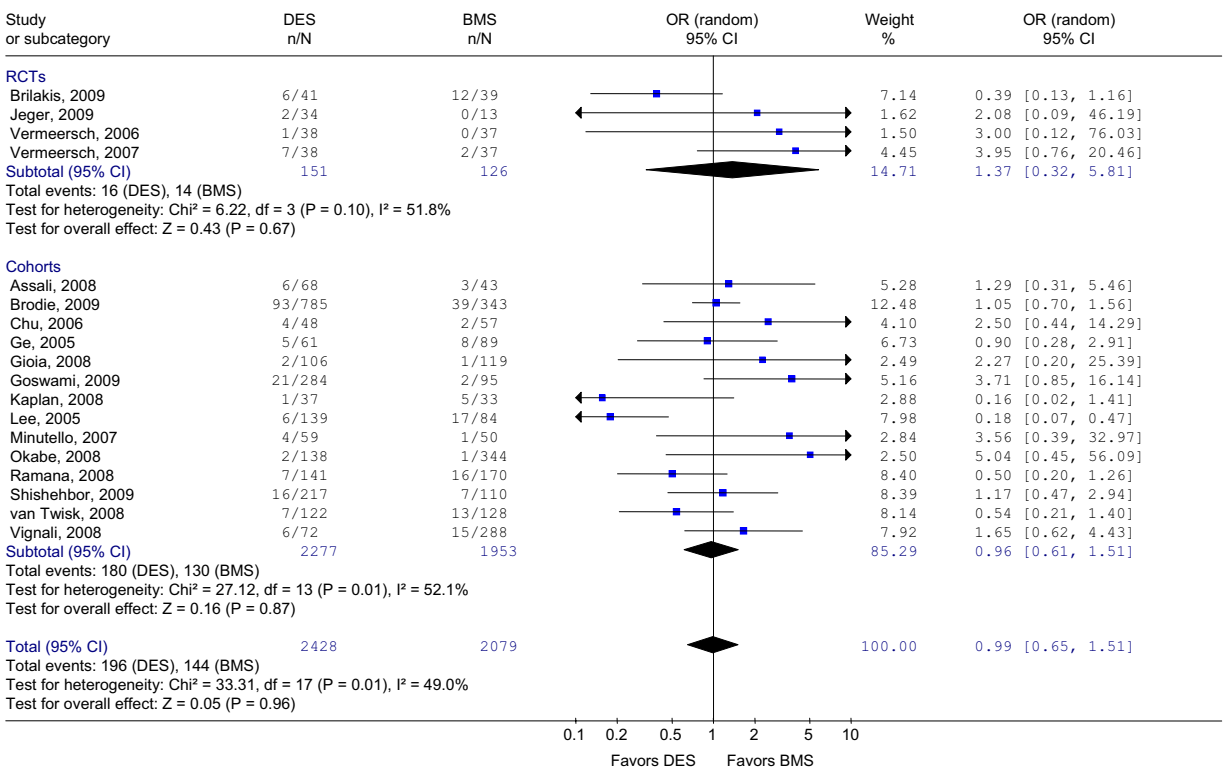

Figure 6. OR of Recurrent MI

Forest plot of unadjusted OR (with 95% CIs) for recurrent myocardial infarction (MI) in SVG intervention patients receiving DES compared with those receiving BMS. No significant difference is observed between the 2 groups. Abbreviations as in Figures 1, 2, 3, 4, and 5.

previously mentioned, the definition of MACE varied among the included studies, which led to heterogeneity reaching significant levels with some end points. Despite that heterogeneity, our analyses effectively summarize the current practice and provide important insights regarding the use of DES in SVG interventions. We purposefully relied on hard clinical end points rather than surrogate markers to ensure consistency of the measured outcomes and support the validity of our conclusions. Nonetheless, this heterogeneity might influence the generalizability of our results. Therefore, large well-designed randomized studies are still needed to answer this important question.

In cohort studies, the type of stent selected for PCI might have been influenced by the diameter of the target vessel, because DES might not have been available in larger sizes. However, the mean vessel diameter in the included studies is within the available stent diameter range in both DES and BMS. Although not identical, stent diameter (which was included in the analysis) is generally similar to vessel diameter, and that did not influence the overall conclusions of the analyses regarding TLR or TVR.

Conclusions

Our meta-analysis demonstrates the efficacy and safety of DES use in SVG interventions. Drug-eluting stent use was associated with lower rates of TLR, TVR, and MACE in general, with no evidence of an increased risk of ST. These results are no substitute for well-designed, appropriately powered, randomized trials with long follow-up to critically evaluate the long-term outcomes of DES in SVG interventions.

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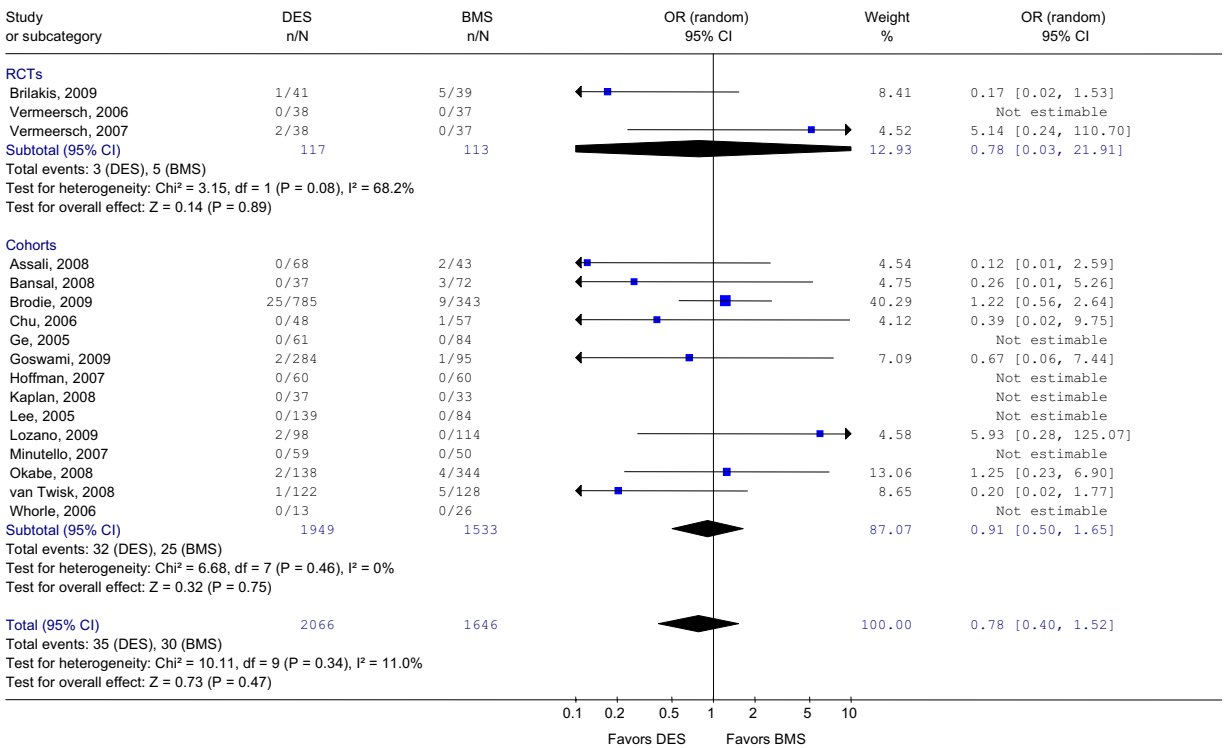

Figure 7. OR of ST

Forest plot of unadjusted OR (with 95% CIs) for major reported adverse effects, namely, stent thrombosis (ST) in SVG intervention patients receiving DES compared with those receiving BMS. No significant difference is observed between the 2 groups. Other abbreviations as in Figures 1, 2, 3, 4, 5, and 6.

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Key Words: bare-metal stent(s) ■ drug-eluting stent(s) ■ meta-analysis ■ percutaneous coronary intervention ■ saphenous vein graft.

APPENDIX

For supplementary material and tables, please see the online version of this article.