REVIEW ARTICLE

Drug-Eluting vs Bare-Metal Stents in Primary Angioplasty

A Pooled Patient-Level Meta-analysis of Randomized Trials

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Background: Concerns have emerged regarding a higher risk of stent thrombosis after drug-eluting stent (DES) implantation, especially in the setting of ST-segment elevation myocardial infarction (STEMI). Our objective was to perform a meta-analysis using individual patient data to evaluate the long-term safety and effectiveness of DES compared with bare-metal stents (BMS) in patients undergoing primary percutaneous coronary intervention for STEMI.

Data Sources: Formal searches of electronic databases (MEDLINE and CENTRAL) and scientific session presentations from January 2000 to June 2011.

Study Selection: We examined all completed randomized trials of DES for STEMI.

Data Extraction: Individual patient data.

Data Synthesis: Individual patient data were obtained from 11 of 13 trials identified, including a total of 6298 patients (3980 [63.2%] randomized to DES [99% sirolimus-eluting or paclitaxel-eluting stents] and 2318 [36.8%] randomized to BMS). At long-term follow-up (mean [SD], 1201 [440] days), DES implantation significantly reduced the occurrence of target-vessel revascularization (12.7% vs 20.1%; hazard ratio [95% CI], 0.57 [0.50-0.66]; $P < .001$, P value for heterogeneity, .20), without any significant difference in terms of mortality, reinfarction, and stent thrombosis. However, DES implantation was associated with an increased risk of very late stent thrombosis and reinfarction.

Conclusions: The present pooled patient-level meta-analysis demonstrates that among patients with STEMI undergoing primary percutaneous coronary intervention, sirolimus-eluting and paclitaxel-eluting stents compared with BMS are associated with a significant reduction in target-vessel revascularization at long-term follow-up. Although there were no differences in cumulative mortality, reinfarction, or stent thrombosis, the incidence of very late reinfarction and stent thrombosis was increased with these DES.

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THE EARLY ADMINISTRATION of pharmacological and/or mechanical reperfusion therapies[1,2] and improvements in antiplatelet and anticoagulation agents[3-6] have greatly contributed to the reduction in mortality achieved over the last 2 decades in patients with ST-segment elevation myocardial infarction (STEMI). In randomized trials, bare-metal stents (BMS) have been shown to reduce target-vessel revascularization (TVR) in STEMI, with rates of death and/or reinfarction comparable to balloon angioplasty.[7-9] However, these benefits may not be as profound in unselected patients with STEMI.[8]

Drug-eluting stents (DES) have shown a further significant reduction in restenosis and TVR in patients without acute coronary syndromes compared with BMS.[10-14] Initial meta-analyses showed the efficacy and safety of DES at short-term follow-up in the setting of STEMI,[15-17] with no safety issues. However, concerns have emerged regarding a potentially higher risk of stent thrombosis (ST) with DES[18,19] that might be even more pronounced among patients with STEMI, as suggested by a prospective registry.[20-22] Therefore, the aim of the Drug-Eluting Stents in Primary Angioplasty (DESERT) Cooperation was to perform a pooled patient-level meta-analysis of randomized trials to evaluate the risks and benefits of DES compared with BMS in patients undergoing primary percutaneous coronary intervention (PCI) for STEMI.

See Invited Commentary at end of article

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Group Information: The DESERT Cooperation members are listed in the byline.

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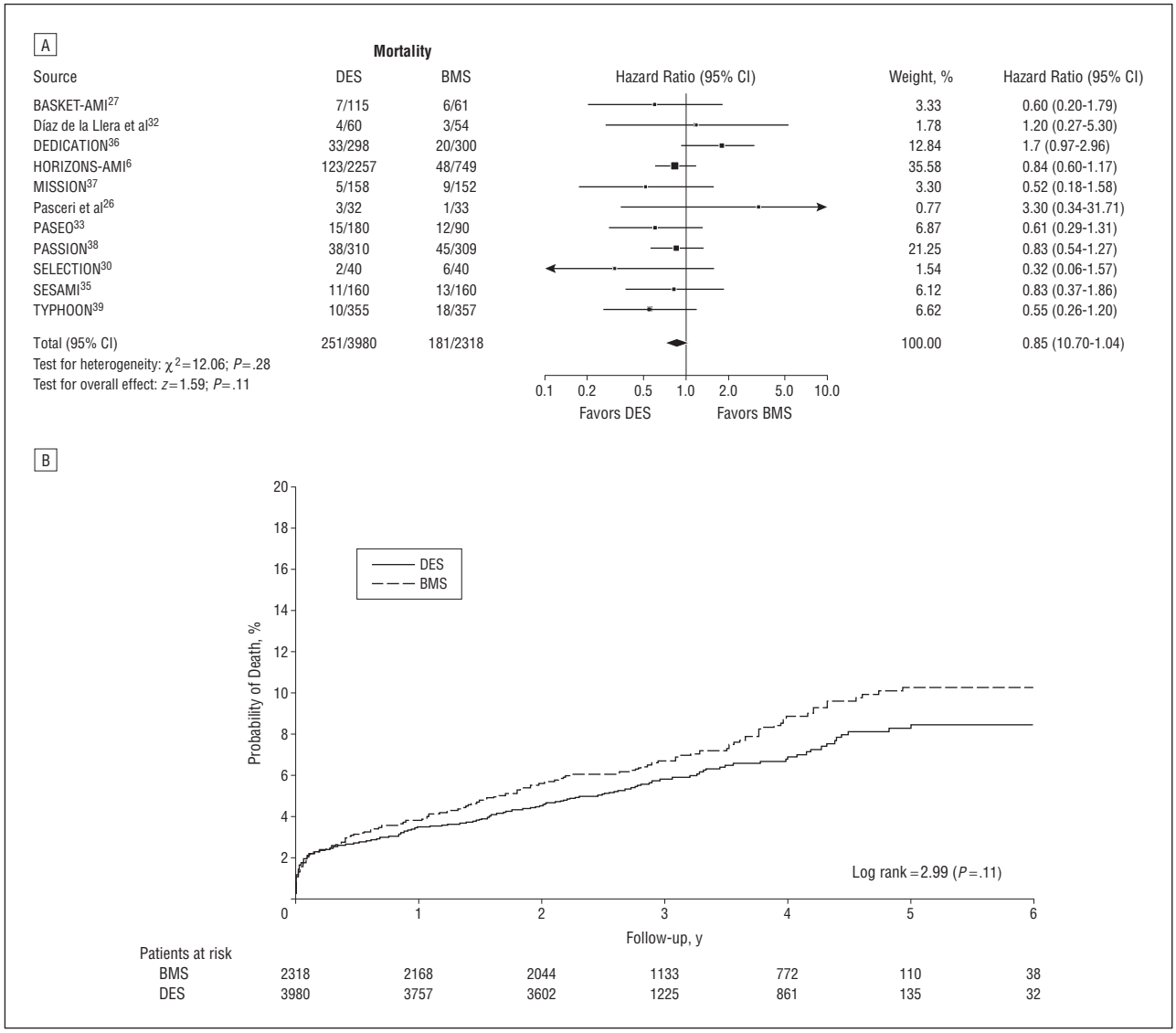

Figure 1. Drug-eluting stent (DES) and mortality at long-term follow-up. A, Absolute numbers of death and hazard ratios for this end point with DES vs bare-metal stent (BMS) for individual trials and the pooled population. Hazard ratios are shown on a logarithmic scale. The size of the square is proportional to the weight of the individual studies, measured as the inverse of the estimated variance of the log hazard ratio. B, Kaplan-Meier curves of probability of death in each of the stent groups for the pooled population. Trial name acronyms are spelled out in Table 1 footnote.

METHODS

ELIGIBILITY AND SEARCH STRATEGY

To identify all completed, randomized trials comparing DES vs BMS in primary PCI for STEMI, we scanned the literature by formal searches of electronic databases (MEDLINE and CENTRAL) and the scientific session abstracts in *Circulation*, *Journal of College of Cardiology*, *European Heart Journal*, and *American Journal of Cardiology* from January 2000 to June 2011. Furthermore, oral presentations and/or expert slide presentations were included (searched on the Transcatheter Cardiovascular Therapeutics (TCT) [http://www.tctmd.com], EuroPCR [http://www.europcr.com], American College of Cardiology (ACC) [http://www.acc.org], American Hospital Association (AHA) [http://www.aha.org], and European Society of Cardiology (ESC) [http://www.escardio.org] websites from January 2000 to June 2011). The following keywords were used: randomized trial, myocardial infarction, reperfusion, primary angioplasty, stenting, DES, BMS, sirolimus-eluting stent (SES), Cypher (Cordis Corporation), paclitaxel-eluting stent (PES), Taxus (Boston Scientific Corporation). Inclusion criteria were (1) randomized treatment allocation, (2) follow-up data of more than 1 year, and (3) availability of complete clinical data. Exclusion criteria were (1) follow-up data in less than 90% of patients, (2) ongoing studies or irretrievable data, (3) trials with overall small sample size (<50 patients), and (4) investigators' unwillingness to provide individual patient data. No language restrictions were enforced. All principal investigators were contacted and invited to provide individual patient data, which were transferred without patient identifiers to the Eastern Piedmont University, Novara, Italy. The dataset was checked for completeness and consistency and compared with the results from any publications. Queries were resolved by direct correspondence with the responsible study investigator. Data were managed according to the intention-to-treat principle.

OUTCOME

The primary end point for the present study was mortality, whereas secondary end points were reinfarction, TVR, and

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Table 1. Characteristics of the Randomized Trials Included in the Meta-analysis

Source	Period	Study Design (No. of Patients)	Stent Type	GP IIb/IIIa Inhibitors, %	Primary Study End Point	FU Available, y	Routine Angiographic FU, %	Dual Oral Antiplatelet Therapy
SELECTION[30]	2004	SES (n = 40) vs BMS (n = 40)	SES and Bx Velocity[a]	100	Percentage of the stent volume obstructed by NIH measured by IVUS at 7 (1) mo (mean [SD])	6	95	Aspirin indefinitely; clopidogrel for 9 mo
PASSION[38]	2003	DES (n = 310) vs BMS (n = 309)	PES vs Express2[b] or Libertè[b]	73.8	Combined death, ReMI, or TLR at 1 y	5	0	Aspirin indefinitely; clopidogrel for at least 6 mo
TYPHOON[39]	2003	DES (n = 355) vs BMS (n = 357)	SES or BMS[c]	71.5	Target-vessel failure at 1 y	4	24	Aspirin indefinitely; clopidogrel for at least 6 mo
SESAMI[35]	2003	DES (n = 160) vs BMS (n = 160)	SES or BMS[c]	74.9	Angiographic restenosis at 1-y follow-up	5	52	Aspirin indefinitely; clopidogrel for at least 12 mo
PASEO[33]	2003	DES (n = 180) vs BMS (n = 90)	SES, PES, BMS[c]	100	Combined death, ReMI, TVR, and stroke at 6 mo	5	0	Aspirin indefinitely; clopidogrel for at least 12 mo
BASKET-AMI[27]	2003	SES (n = 76) or PES (n = 67) vs BMS (n = 74)	SES, PES, Multi-Link Vision[d]	65	Combined death, ReMI, TVR, and stroke at 6 mo	3	0	Aspirin indefinitely; clopidogrel for at least 6 mo
HORIZONS-AMI[6]	2005	PES (n = 2257) vs BMS (n = 749)	PES, Express[b]	52	(1) 12-mo Ischemia-driven revascularization of the target lesion; (2) Composite (safety) end point of major adverse cardiovascular events, consisting of death, reinfarction, stroke, and stent thrombosis	3	40	Aspirin indefinitely; clopidogrel for at least 6 mo (1 y or longer was recommended)
MISSION[37]	2004	SES (n = 158) vs BMS (n = 152)	SES, BMS	80	Late loss at 9-mo follow-up	3	82	Aspirin indefinitely; clopidogrel for at least 12 mo
DEDICATION[36]	2005	DES (n = 313) vs BMS (n = 313)	DES: Cypher,[a] Taxus,[b] Endeavor[d]; BMS: Multi-Link Vision,[d] Express,[b] Libertè,[b] Driver[e]	96	Late loss at 8-mo follow-up	3	100	Aspirin indefinitely; clopidogrel for at least 12 mo
Díaz de la Llera et al[32]	2004	SES (n = 60) vs BMS (n = 54)	SES, BMS	100	Death, nonfatal MI, and recurrent myocardial ischemia at 1-y follow-up	6	100	Aspirin indefinitely; clopidogrel for 9 mo
Pasceri et al[26]	2002	DES (n = 32), BMS (n = 33)	Cypher[a] vs Bx Velocity[a]	89	Death, nonfatal MI, and recurrent myocardial ischemia at 1-y follow-up	6	100	Aspirin indefinitely; clopidogrel for 6 mo

Abbreviations: BASKET-AMI, Basel Stent Kosten-Effektivitäts in Acute Myocardial Infarction; BMS, bare-metal stent; DEDICATION, Drug Elution and Distal Protection in ST-Elevation Myocardial Infarction; DES, drug-eluting stent; FU, follow-up; GP, glycoprotein; HORIZONS-AMI, Harmonizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction; IVUS, intravascular ultrasound; MI, myocardial infarction; MISSION, MISSION! Intervention Study; NIH, neointimal hyperplasia; PASEO, Paclitaxel or Sirolimus-Eluting Stent vs Bare Metal Stent in Primary Angioplasty; PASSION, Paclitaxel-Eluting vs Conventional Stent in Myocardial Infarction with ST-Segment Elevation; PES, paclitaxel-eluting stent; ReMI, reinfarction; SELECTION, Single-Center Randomized Evaluation of Paclitaxel-Eluting Stent vs Conventional Stent in Acute Myocardial Infarction; SES, sirolimus-eluting stent; SESAMI, Sirolimus-Eluting Stent vs Bare-Metal Stent in Acute Myocardial Infarction; TLR, target-lesion revascularization; TVR, target-vessel revascularization; TYPHOON, Trial to Assess the Use of Cypher Stent in Acute Myocardial Infarction Treated With Balloon Angioplasty.

[a] Manufactured by Cordis Corporation.
[b] Manufactured by Boston Scientific Corporation.
[c] The choice of the stent was left to the discretion of the operator.
[d] Manufactured by Abbott Laboratories.
[e] Manufactured by Medtronic Inc.

ST (definite or probable according to Academic Research Consortium [ARC] definitions) at long-term follow-up.

DATA ANALYSIS

Statistical analysis was performed using the Review Manager 4.27 freeware package (Cochrane Collaboration), SPSS 15.0 statistical package (SPSS Inc), and the R statistical software (version 2.11.0; R Foundation for Statistical Computing). Continuous data were expressed as mean (SD) and categorical data as percentage. The pooled odds ratio for categorical variables was calculated by using the Mantel-Haenszel method, whereas a weighted mean difference was used for continuous variables.[23] Data were pooled by fixed-effect method with generic inverse variance weight. The weight of the individual studies was measured as the inverse of the estimated variance of the log hazard ratio (HR) obtained with Cox proportional hazard analysis. Heterogeneity across trials was assessed by the I^2 statistic. We additionally performed survival analyses with the use of Cox regression analysis stratified according to trial.[5] The proportionality hazards assumption in Cox regression models was

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Table 2. Patient Characteristics

Variables	DES (n = 3980)	BMS (n = 2318)	*P* Value
Age, mean (SD) y	60.5 (11.9)	60.9 (12.1)	.50
Sex, %	76.4	77.3	.48
Hypertension, %	44.5	42.1	.23
Diabetes, %	15.5	15.4	.70
Hypercholesterolemia, %	38.4	36.2	.41
Symptom onset to balloon time, mean (SD), min	266 (249)	255 (184)	.46
Preprocedural TIMI flow, %			
0-1	66.1	66.7	
2	14.2	14.6	.96
3	19.7	18.8	
Postprocedural TIMI 3 flow, %	89.7	92.1	.30
Type of DES, %			
Cypher[a]	26.7	0	
Taxus[b]	72.3	0	<.001
Endeavor[c]	1.0	0	
Glycoprotein IIa-IIIb inhibitors, %	67.6	74.4	.92
Infarct-related artery, %			
LM	0.2	0.1	
LAD	44.0	45.8	
Dg	0.1	0.2	.90
LCX	13.4	12.8	
RCA	42.2	41.1	
Graft	0.1	0.1	

Abbreviations: BMS, bare-metal stent; DES, drug-eluting stent; Dg, diagonal branch; LAD, left anterior descending artery; LCX, left circumflex artery; LM, left main; RCA, right coronary artery; TIMI, Thrombolysis in Myocardial Infarction.
[a]Manufactured by Cordis Corporation.
[b]Manufactured by Boston Scientific Corporation.
[c]Manufactured by Medtronic Inc.

Table 3. Percentage of Patients Receiving Dual Antiplatelet Therapy at Follow-up

	Group, %		
Follow-up, mo	DES (n = 3965)	BMS (n = 2305)	*P* Value
6	94.0	88.3	<.001
12	64.1	58.9	.002
24	21.8	10.6	.004
36	16.6	7.6	.004

Abbreviations: BMS, bare-metal stent; DES, drug-eluting stent.

tested by using the Score test and Schoenfeld residuals. In case the proportionality assumption was not met, we used a Cox model with time-varying regression coefficients (piecewise time-constant coefficients).[24] This means that the entire study period was split in a certain number of time intervals, and the effect of DES (HR) estimated within each of these intervals. The choice of the time intervals was based on estimates of fully time-dependent regression. Kaplan-Meier survival curves are presented with event rates reported as estimated probabilities. Results were considered statistically significant at $P<.05$ (2-sided), and Bonferroni correction was used to adjust for multiple testing. The study was performed in compliance with the Quality of Reporting of Meta-analyses (QUOROM) guidelines.[25]

RESULTS

ELIGIBLE STUDIES AND BASELINE CHARACTERISTICS

A total of 16 randomized trials[6,26-40] were initially identified. Two trials were excluded because of inclusion of both STEMI and non-STEMI patients.[29,31] Three other trials were excluded because of small sample size[28] or investigator unwillingness to provide individual patient data[34,40] (**Figure 1**). Therefore 11 trials were finally included in the meta-analysis, in which 6298 patients were randomized, including 3980 patients (63.2%) assigned to the DES group and 2318 patients (36.8%) assigned to the BMS group. Characteristics of the included trials are given in **Table 1**. The length of clinical follow-up varied between 3 and 6 years.

In the Paclitaxel or Sirolimus-Eluting Stent vs Bare Metal Stent in Primary Angioplasty (PASEO)[33] and Basel Stent Kosten-Effektivitäts in Acute Myocardial Infarction (BASKET-AMI)[27] trials, patients were randomized at a ratio of 1:1:1 to BMS, SES, or PES. Routine angiographic follow-up was performed in the randomized study of Sirolimus-Eluting Stent vs Conventional Stent in Acute Myocardial Infarction (SESAMI),[35] the prospective randomized controlled trial to evaluate the efficacy of drug-eluting stents vs bare-metal stents for the treatment of acute myocardial infarction (MISSION! Intervention Study),[37] and the Drug Elution and Distal Protection in ST-Elevation Myocardial Infarction (DEDICATION) study,[36] as well as in a subgroup of patients in the Trial to Assess the Use of Cypher Stent in Acute Myocardial Infarction Treated With Balloon Angioplasty (TYPHOON).[39] In the Har-

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monizing Outcomes With Revascularization and Stents in Acute Myocardial Infarction (HORIZONS-AMI) trial,[6] patients underwent both a pharmacology randomization (bivalirudin or unfractionated heparin plus a glycoprotein IIb-IIIa inhibitor, with a 1:1 randomization ratio) and a stent randomization (Taxus vs Express [Boston Scientific Corporation], with a 3:1 randomization ratio). Baseline characteristics are reported in **Table 2**; there were no significant differences observed between the 2 groups.

The DES used were SES in 26.7%, PES in 72.3%, and zotarolimus-eluting stents (Endeavor; Medtronic) in 1.0% of patients. No significant differences in baseline characteristics were observed between the 2 groups (Table 2). However, a significantly higher percentage of patients in the DES group were receiving dual antiplatelet therapy (aspirin and clopidogrel) during 3-year follow-up compared with the BMS group (**Table 3**).

STUDY END POINTS

Mortality

At long-term follow-up (mean [SD], 1201 [440] days), a total of 432 patients had died. No significant difference in mortality was observed with DES compared with BMS implantation (8.5% vs 10.2%, respectively; HR, 0.85 [95% CI, 0.70-1.04]; $P = .11$, P value for heterogeneity, .28) (Figure 1). Similar results were observed with Cox regression analysis stratified according to trial, where the proportionality of hazards was met ($P = .46$). There were no differences in cardiac mortality between DES and BMS implantation (data available from 9 trials including 5846 patients) (5.7% vs 6.8%, respectively; HR, 0.84 [95% CI, 0.65-1.09]; $P = .19$, P value for heterogeneity, .20).

Reinfarction

Reinfarction was observed in a total of 350 patients. As shown in **Figure 2**, no significant difference in reinfarction was observed between DES and BMS implantation (9.4% vs 5.9%, respectively; HR, 1.12 [95% CI, 0.88-1.41]; $P = .36$, P value for heterogeneity, .37). However, the assumption of proportionality of hazards was not met ($P = .01$), and therefore we additionally used a Cox model with time-varying regression coefficients (piecewise time-constant coefficients). In fact, as given in **Table 4**, the HR changed across time, suggesting that at long-term follow-up (after 2 years from the beginning of the study) the reinfarction rate increased significantly for the DES group compared with the BMS group (HR, 2.06 [95% CI, 1.22-3.49]; $P = .03$).

Table 4. Results of Cox Models With Piecewise Time-Constant Regression Coefficients

Outcome	Coefficient	SE (Coef)	HR (95% CI)[a]	*P* Value
Death 0-1 y	−0.075	0.14	0.93 (0.70-1.22)	.14
Death 1-2 y	−0.535	0.23	0.58 (0.37-0.93)	.23
Death >2 y	−0.07	0.18	0.93 (0.65-1.33)	.18
ReMI 0-1 y	−0.1579	0.1572	0.85 (0.63-1.16)	.31
ReMI 1-2 y	0.2970	0.2588	1.34 (0.81-2.23)	.25
ReMI >2 y	0.7262	0.2676	2.06 (1.22-3.49)	.03
ST 0-1 y	−0.1009	0.159	0.90 (0.66-1.23)	.52
ST 1-2 y	0.3216	0.346	1.38 (0.70-2.71)	.35
ST >2 y	1.0362	0.401	2.81 (1.28-6.19)	.04
TVR 0-1 y	−0.72205	0.091	0.48 (0.41-0.58)	<.001
TVR 1-2 y	−0.42056	0.145	0.66 (0.49-0.87)	.01
TVR >2 y	−0.07401	0.20	0.93 (0.62-1.38)	.71

Abbreviations: HR, hazard ratio; ReMI, reinfarction; ST, stent thrombosis; SE (Coef), standard error coefficient; TVR, target-vessel revascularization.
[a] Hazards ratios refer to effect of bare-metal stents vs drug-eluting stents.

Stent Thrombosis

Stent thrombosis, according to the ARC definition, was observed in a total of 267 patients (219 definite and 48 probable). As shown in **Figure 3**, the long-term rate of ST was not significantly different between DES and BMS implantation (5.8% vs 4.3% respectively; HR, 1.13 [95% CI, 0.86-1.47]; $P = .38$, P value for heterogeneity, .94). However, the assumption of proportionality of hazards was not met ($P = .04$), and therefore we additionally used a Cox model with time-varying regression coefficients (piecewise time-constant coefficients). In fact, as given in Table 4, the HR changed across time, suggesting that at long-term follow-up (after 2 years from the beginning of the study), the rate of ST increased significantly for the DES group compared with the BMS group (HR, 2.81 [95% CI, 1.28-6.19]; $P = .04$).

Target-Vessel Revascularization

A total of 837 patients underwent a repeated intervention of the target vessel. As shown in **Figure 4**, DES use significantly reduced the occurrence of TVR compared with BMS use (12.7% vs 20.1%, respectively; HR, 0.57 [95% CI, 0.50-0.66]; $P < .001$, P value for heterogeneity, .20) (number needed to treat = 12.2 [95% CI, 10.3-15.4]. Similar results were observed with Cox regression analysis stratified according to trial, where the proportionality of hazards was met ($P = .07$). Similar findings were observed in terms of target lesion revascularization (data available in 5072 patients from 7 trials) (10.1% [DES] vs 17.9% [BMS]; HR, 0.54 [95% CI, 0.45-0.64]; $P < .001$, P value for heterogeneity, .10) (number needed to treat, 11.7 [95% CI, 10.1-15.2]).

COMMENT

The present study represents, to our knowledge, the first meta-analysis reporting on long-term clinical outcome (mean [SD], 3.3 [1.2] years) of DES in the setting of primary PCI for STEMI based on individual patient-level data. The principal finding from our study is that among patients with STEMI undergoing primary PCI, compared with BMS, SES and PES are associated with significant and sustained reductions in TVR, without significant differences in ST, reinfarction, or death. Reductions in TVR were noted with

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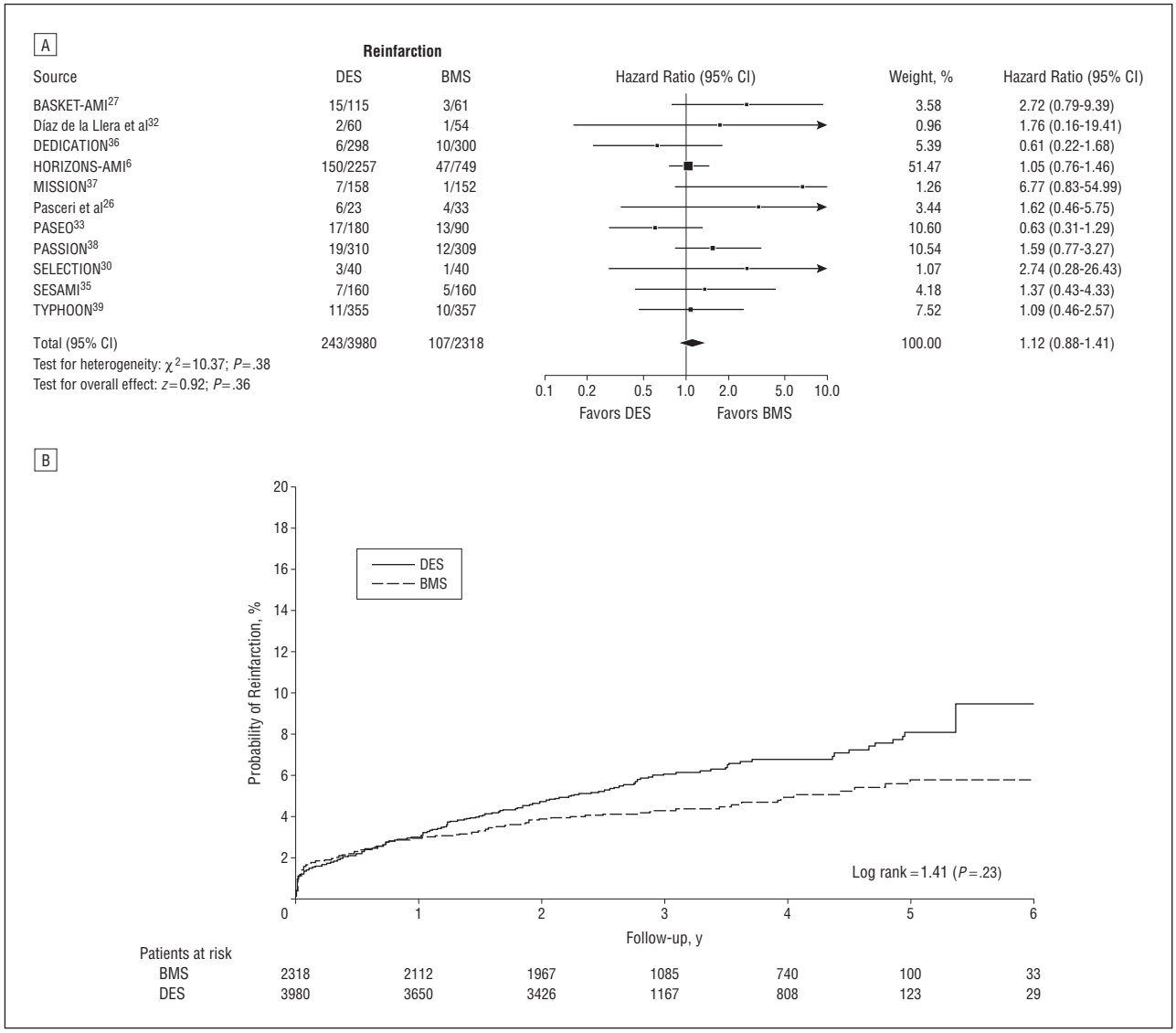

Figure 2. Drug-eluting stent (DES) and reinfarction at long-term follow-up. A, Absolute numbers of reinfarction and hazard ratios for this end point with DES vs bare-metal stent (BMS) for individual trials and the pooled population (fixed-effect model). Hazard ratios are shown on a logarithmic scale. The size of the square is proportional to the weight of the individual studies, measured as the inverse of the estimated variance of the log hazard ratio. B, Kaplan-Meier curves of probability of reinfarction in each of the stent groups for the pooled population. Trial name acronyms are spelled out in Table 1 footnote.

DES in both the early and very late periods. However, we observed a significantly higher occurrence of very late reinfarction and ST with these DES compared with BMS.

Early after its introduction, stenting had been avoided in the setting of STEMI because of concerns that implantation of a metallic device within a thrombotic environment such as that of a plaque disruption resulting in myocardial infarction might predispose to ST with resultant vessel occlusion. Vigorous anticoagulation—necessary to avoid ST—exposed the patient to the risks of bleeding and vascular complications.[41] However, following improvements in stent deployment techniques and advances in antiplatelet therapy,[4-6,42,43] numerous studies and randomized trials demonstrated the safety and efficacy of BMS in the setting of STEMI.[7-9,44-46] Previous meta-analyses in patients undergoing primary PCI have shown the benefits of stenting compared with balloon angioplasty alone in terms of reducing TVR, though no definite impact on death or reinfarction was present.[9] However, restenosis rates after BMS implantation, in patients with STEMI are still high, especially in unselected patients with complex lesion morphology.[47] Several initial randomized trials have shown that, among patients without acute coronary syndromes, DES implantation is associated with a significant reduction in restenosis and TVR.[10-14] However, concerns emerged regarding an increased risk of very late ST associated with DES implantation.[18-22] As most episodes of ST result in myocardial infarction, the increased rate of very late ST with DES implantation may have an impact on mortality, particularly after primary PCI in STEMI, since reinfarction is a major determinant of mortality.[47,48]

In a recent prospective multicenter primary PCI registry (PREMIER [Prospective Registry Evaluating Myocardial Infarction: Events and Recovery]), the use of DES rather than BMS was associated with a high risk of mortality within the first 6 months (presumably due to ST) in cases of early

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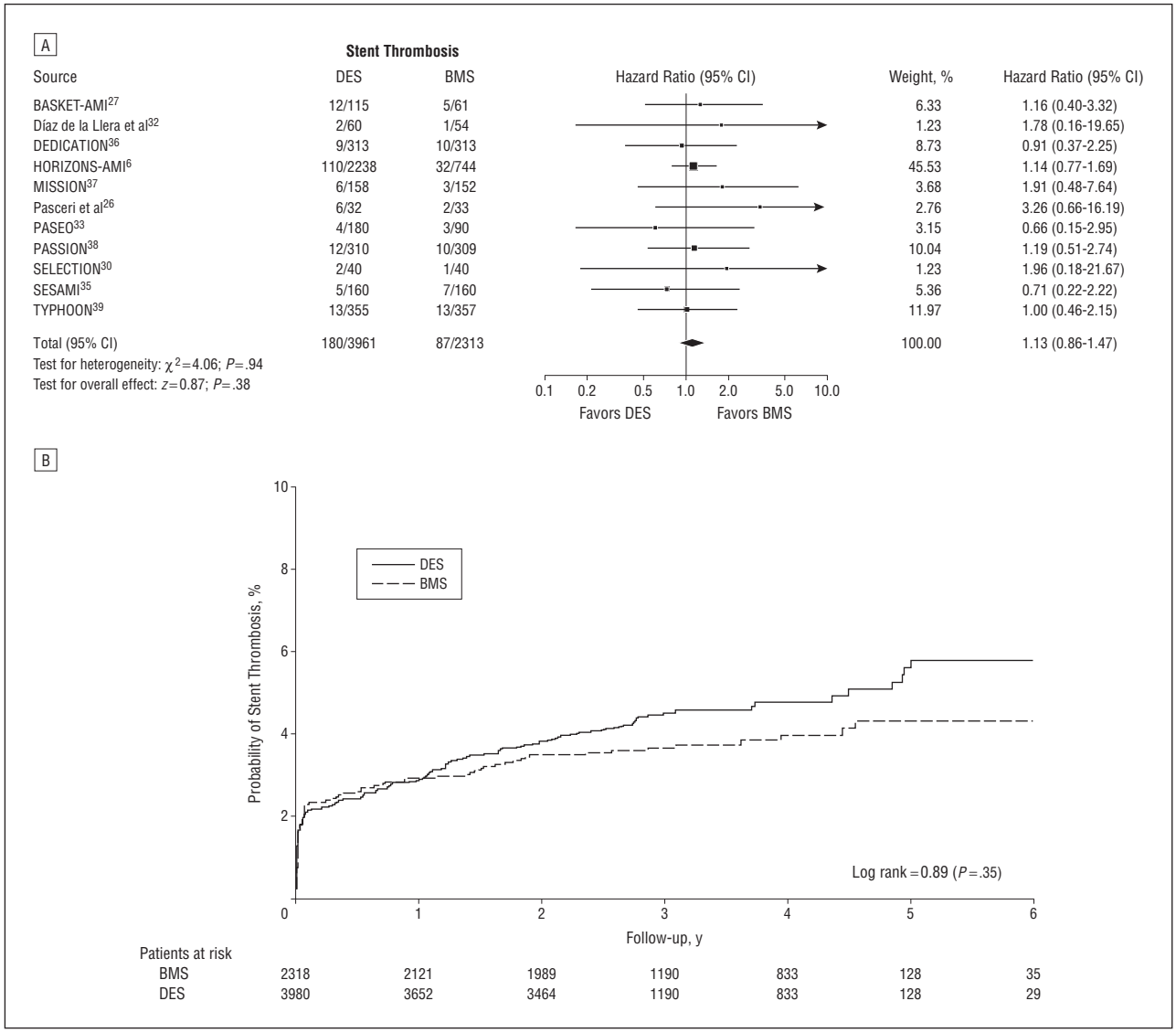

Figure 3. Drug-eluting stent (DES) and stent thrombosis (definite and probable according to the Academic Research Consortium definitions) at long-term follow-up. A, Absolute numbers of stent thrombosis and hazard ratios for this end point with DES vs bare-metal stent (BMS) for individual trials and the pooled population (fixed-effect model). Hazard ratios are shown on a logarithmic scale. The size of the square is proportional to the weight of the individual studies, measured as the inverse of the estimated variance of the log hazard ratio. B, Kaplan-Meier curves of probability of in-stent thrombosis in each of the stent groups for the pooled population. Trial name acronyms are spelled out in Table 1 footnote.

discontinuation of dual antiplatelet therapy.[20,21] In this regard it may be difficult to forecast future long-term patient medication compliance at the time of intervention for STEMI.[18]

Several meta-analyses have been conducted in many settings on long-term follow-up data, showing contrasting results in terms of higher ST with DES,[49-54] in particular in STEMI. However, in this specific setting, no concern has emerged so far in almost all the randomized trials, potentially because of underpowering.

The results of the present study, based on individual patients' data, provide strong evidence of the beneficial effects of SES and PES during primary PCI in STEMI. With follow-up as late as 6 years, a robust and sustained decrease in TVR was noted with use of these DES. Although the rates of late reinfarction and ST progressively increased, with the difference becoming statistically significant after 2 years in patients receiving SES and PES, the HR for mortality, while not significantly different between DES and BMS, favored DES.

The increase in very late reinfarction and ST in the DES group bears discussion. Similarly to our data, in a large report of patients with stable coronary artery disease undergoing elective stent implantation, PES has been associated with an increased rate of very late myocardial infarction (>1 year) compared with BMS.[55] However, both experiences have also found no significant differences in survival between the BMS and DES groups, potentially because of the beneficial effects from preventing restenosis.[56] The lower mortality with DES use, despite the higher rates of late reinfarction and ST, may also be explained by the time-related prognostic impact of in-stent thrombosis. In fact, both early and late ST carry a worst prognostic on survival compared with very late in-stent thrombosis.[57]

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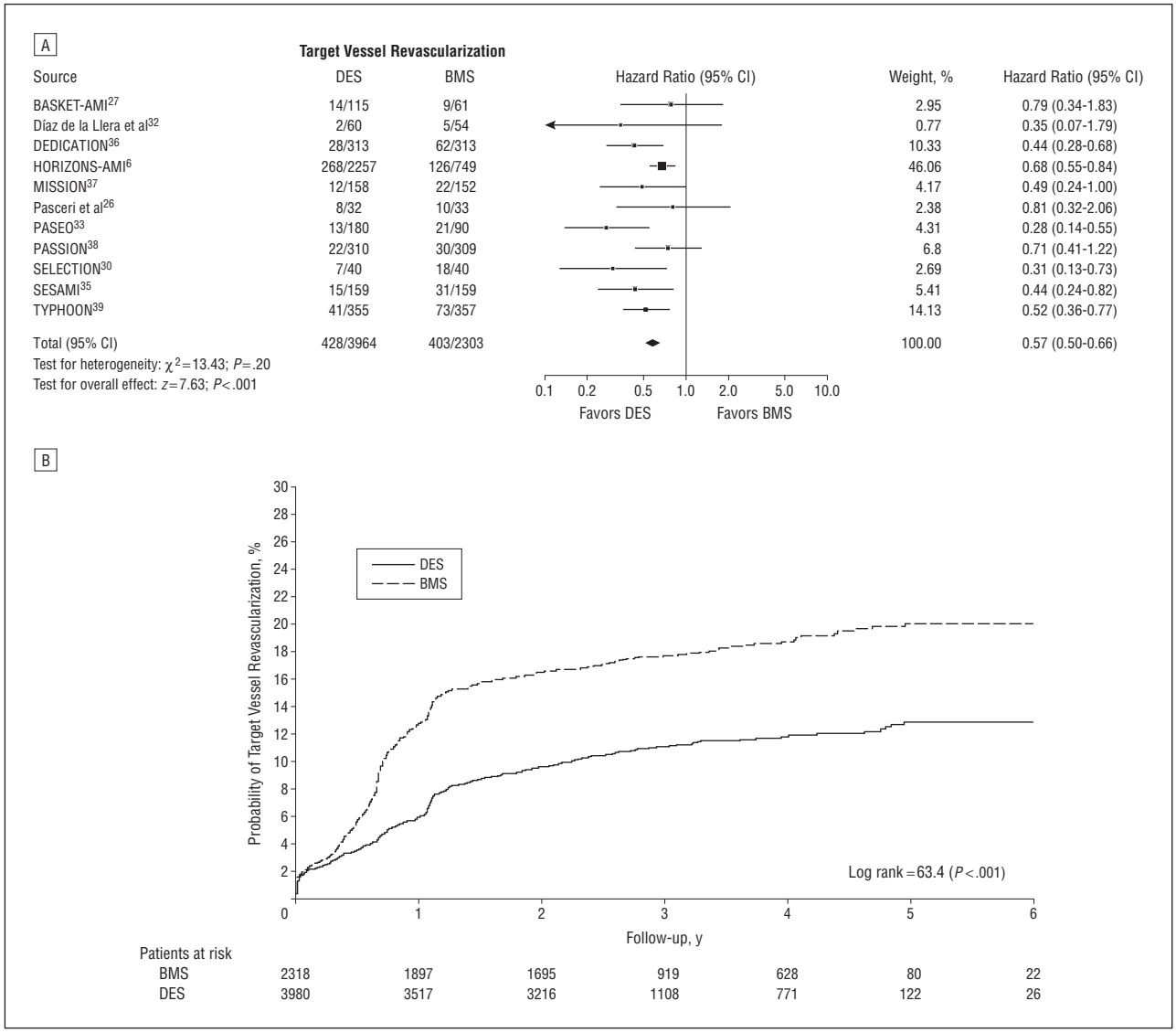

Figure 4. Drug-eluting stent (DES) and target-vessel revascularization at long-term follow-up. A, Absolute numbers of target-vessel revascularization and hazard ratios for this end point with DES vs bare-metal stent (BMS) for individual trials and the pooled population (fixed-effect model). Hazard ratios are shown on a logarithmic scale. The size of the square is proportional to the weight of the individual studies, measured as the inverse of the estimated variance of the log hazard ratio. B, Kaplan-Meier curves of probability of target-vessel revascularization in each of the stent groups for the pooled population. Trial name acronyms are spelled out in Table 1 footnote.

Recent studies have shown that newer-generation DES (with thinner, fracture-resistant stent struts, and novel biocompatible polymers) are associated with significantly improved clinical outcomes and reduced ST rates.[58-60] Future randomized trials are needed to evaluate the safety and efficacy of these DES in the setting of primary PCI in STEMI, especially coupled with the benefits from more potent and/or prolonged dual antiplatelet therapy.[61,62]

There are some limitations to this study. The patients enrolled in the current randomized trials were highly selected, with few patients having cardiogenic shock. Thus the conclusion of this meta-analysis cannot be extended to all patients undergoing primary PCI for STEMI. We were not able to obtain individual data from 2 randomized trials, including 920 patients.[34,40] However, the inclusion of these 2 studies would have certainly not changed our conclusions, especially in terms of mortality. Availability of costs at discharge and at follow-up would have further improved our results. However, these data were not routinely collected in almost all trials. Approximately 5.5% of patients (n = 346) were lost to follow-up within the first 2 years (most of them [61%] from the TYPHOON study). In fact, long-term follow-up was not an end point in some of the included studies. However, the results did not change after the exclusion of these patients (data not shown). Even though clinically relevant, exact information on adherence/compliance to the prescription of dual antiplatelet therapy was not routinely collected.

Our study was certainly underpowered to show a statistically significant difference in mortality between the groups. In fact, based on the 3-year results (0.8% absolute mortality reduction), with a significance level (α) of .05 and a statistical power of 0.8, we would have

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needed a population of 30 130 (19 084 with DES and 11 226 with BMS) to reach this end point.

Finally, the results of the current analysis apply only to Cypher (SES) and Taxus (PES), as substantial randomized studies in STEMI have not yet been performed with newer DES. However, the huge number of patients treated worldwide with first-generation DES in the setting of STEMI in the last few years certainly support the high clinical relevance of our findings at long-term follow-up, especially concerning the potential prolongation of dual antiplatelet therapy.

In conclusion, the present meta-analysis, based on pooled patient-level data from 11 trials with 6270 randomized patients, shows that among selected patients with STEMI undergoing primary PCI, compared with BMS, SES and PES, are associated with a significant reduction in TVR and target-lesion revascularization at long-term follow-up. Despite a slightly higher rate of very late reinfarction and ST with SES and PES compared with BMS, there were no significant differences in overall or very late mortality, with the point estimate favoring DES in all periods.

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INVITED COMMENTARY

Drug-Eluting Stents in ST-Segment Elevation Myocardial Infarction

Looking for Just Deserts

In this issue of the *Archives*, De Luca et al[1] and the Drug-Eluting Stent in Primary Angioplasty (DESERT) Cooperation have performed a meta-analysis of the long-term (3- to 6-year) results from 11 randomized clinical trials (RCTs) comparing drug-eluting stents (DES) with bare-metal stents (BMS) in ST-segment elevation myocardial infarction (STEMI). They observed that DES implantation reduced the occurrence of target-vessel revascularization (TVR) by 43% (12.7% [DES] vs 20.1% [BMS]; hazard ratio [HR], 0.57 [95% CI, 0.50-0.66]), without any significant overall difference in terms of mortality, reinfarction, and stent thrombosis. However, the landmark analysis revealed a statistically significant increase with DES in the risk of very late (>1 year) reinfarction (6.6% [DES] vs 3.0% [BMS]; HR, 1.57 [95% CI, 1.08-2.27]) and stent thrombosis (3.1% [DES] vs 1.4%, [BMS]; HR, 1.89 [95% CI, 1.13-3.15]). Despite these worrisome findings, the authors conclude that this study provides reassurance that the DES benefits in STEMI warrant the potential risks.

How clinicians interpret this study will depend on an assessment of its overall quality, precision, and integration with other evidence. Specific study strengths include its collaborative nature, patient-level data allowing the landmark analysis, and the inclusion of the "gray" literature (abstracts). A notable limitation is incomplete reporting of lost-to-follow-up patients (differential lost to follow-up may introduce significant bias, particularly in unblinded trials) in these extended reports where primary outcomes were often observed at 12 months or less. There is also the questionable generalizability of results to real-world populations.

Meta-analysis often forms the backbone for comparative effectiveness research (CER), but CER is predicated on real-world applications in real-world settings. In the current study, the effectiveness of DES over BMS implantation in reducing target vessel revascularizations may be artificially inflated by protocol-mandated, rather than clinically driven, repeated angiograms. While the best estimate of the relative reduction in TVR with DES implantation (43%) comes from these controlled RCTs, the absolute reduction requires an unbiased BMS rate arising from routine clinical practice. For example, a real-world registry has reported repeat revascularization rates with BMS of 12%,[2] as opposed to the 20% average in these clinical trials. Real-world drug compliance is also likely less than that observed in the structured RCT environment of motivated patients and practitioners. As DES effectiveness in preventing restenosis is paradoxically its Achilles' heel with delayed vessel healing leading to late stent thrombosis and reinfarctions, ensuring patient compliance with long-term dual antiplatelet therapy to counteract this risk is an absolute necessity.[3]

Clinicians should be concerned about the lack of precision with the

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