Safety and Efficacy of Drug-Eluting and Bare Metal Stents
Comprehensive Meta-Analysis of Randomized Trials and Observational Studies

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Background—The safety and efficacy of drug-eluting stents (DES) among more generalized “real-world” patients than those enrolled in pivotal randomized controlled trials (RCTs) are controversial. We sought to perform a meta-analysis of DES studies to estimate the relative impact of DES versus bare metal stents (BMS) on safety and efficacy end points, particularly for non–Food and Drug Administration–labeled indications.

Methods and Results—Comparative DES versus BMS studies published or presented through February 2008 with ≥100 total patients and reporting mortality data with cumulative follow-up of ≥1 year were identified. Data were abstracted from studies comparing DES with BMS; original source data were used when available. Data from 9470 patients in 22 RCTs and from 182,901 patients in 34 observational studies were included. RCT and observational data were analyzed separately. In RCTs, DES (compared with BMS) were associated with no detectable differences in overall mortality (hazard ratio [HR], 0.97; 95% confidence interval [CI], 0.81 to 1.15; \( P = 0.72 \)) or myocardial infarction (HR, 0.95; 95% CI, 0.79 to 1.13; \( P = 0.54 \)), with a significant 55% reduction in target vessel revascularization (HR, 0.45; 95% CI, 0.37 to 0.54; \( P < 0.0001 \)); point estimates were slightly lower in off-label compared with on-label analyses. In observational studies, DES were associated with significant reductions in mortality (HR, 0.78; 95% CI, 0.71 to 0.86), myocardial infarction (HR, 0.87; 95% CI, 0.78 to 0.97), and target vessel revascularization (HR, 0.54; 95% CI, 0.48 to 0.61) compared with BMS.

Conclusions—In RCTs, no significant differences were observed in the long-term rates of death or myocardial infarction after DES or BMS use for either off-label or on-label indications. In real-world nonrandomized observational studies with greater numbers of patients but the admitted potential for selection bias and residual confounding, DES use was associated with reduced death and myocardial infarction. Both RCTs and observational studies demonstrated marked and comparable reductions in target vessel revascularization with DES compared with BMS. These data in aggregate suggest that DES are safe and efficacious in both on-label and off-label use but highlight differences between RCT and observational data comparing DES and BMS. (Circulation. 2009;119:3198-3206.)

Key Words: angioplasty ⊗ coronary disease ⊗ meta-analysis ⊗ registries ⊗ stents

Drug-eluting stents (DES) are currently implanted in the majority of the >2 million patients undergoing percutaneous coronary intervention each year. The evidence base for initial DES approvals by the US Food and Drug Administration (FDA) has consisted largely of randomized controlled trials (RCTs) enrolling patients with mostly stable coronary artery disease and relatively noncomplex, de novo coronary artery lesions. Data from these RCTs have suggested that overall rates of death and myocardial infarction (MI) are similar among DES- and bare metal stent (BMS)–treated patients,1–3 perhaps because of the offsetting risks/benefits of DES.4,5 Yet, DES are currently being used...
“off label” in higher-risk patients and in more complex lesions in 60% to 70% of cases, and concerns have arisen about the appropriateness of the routine use of DES in the “real world.”

Clinical Perspective on p 3206

These concerns have been based primarily on 2 factors: the observation of higher stent thrombosis rates when DES are used in more unrestricted patient populations than in the carefully controlled approval RCTs and the hypothesis that DES efficacy may be mitigated outside the carefully selected clinical trial population of approval RCTs. Although adequately powered RCTs designed to address these issues comprehensively in off-label patient and lesion subsets have not been completed, modest-sized RCTs and numerous large-scale observational analyses examining real-world use of DES have been conducted. To date, there has been no systematic attempt to synthesize the current data on DES off-label and real-world DES use. We therefore performed a systematic review and meta-analysis to examine the relative safety and effectiveness of DES compared with BMS across a broad spectrum of patients.

Methods

Study Objectives and Criteria for Inclusion/Exclusion

Studies eligible for inclusion included those published or presented at a major cardiovascular meeting through February 2008 in which ≥100 patients were enrolled comparing either the commercially available versions of the CYPHER (Cordis, Miami Lakes, Fla) or TAXUS (Boston Scientific, Natick, Mass) DES with BMS and in which mortality data with follow-up ≥1 year from stent implantation were available. Landmark data, or analyses that censored patients at a specified time point after stent implantation, were not included unless presented cumulatively. For example, the Basel Kosten Effektivitats Trial (BASKET) study was included that used all cumulative data rather than landmarked data presented as BASKET–Late Thrombotic Events (BASKET–LATE); the Global Registry of Acute Coronary Events (GRACE) registry data presented at the European Society of Cardiology World Congress 2007 were excluded because in-hospital events were censored. Also excluded were studies that did not report outcomes data at a fixed time point (and with the same follow-up duration for both stent types), studies using a control group from another study already in the meta-analysis, and studies that were themselves meta-analyses.

Data Search and Acquisition

We searched several sources for published/presented studies, including MEDLINE, the Cochrane database, www.clinicaltrials.gov, www.clinicaltrialresults.org, www.ctctrnd.com, www.cardiosource.com, EuroIntervention journal, and abstracts/presentations from major cardiovascular meetings. The search string broadly included “stent and (-eluting or sirolimus or paclitaxel)” with slight modifications based on the source. Studies were identified in 2 independent searches (performed by A.G. and S.I.) with conflicts adjudicated by a third reviewer (A.J.K.).

Because of the varying lengths of follow-up and varying baseline risk among included studies, the measure of association derived was a relative risk rather than absolute risk or event rate. As a result, studies with zero events in either the BMS or DES arm for a given end point were abstracted but were not used in the analyses (total of 2 studies). Hazard ratios (HRs) or relative risks with confidence intervals (CIs) were either directly abstracted or derived on the basis of the ratio of reported event rates. The most updated or most inclusive data for a given study were chosen for abstraction.

Analyses of RCTs and Observational Studies

We prespecified separate analyses of RCTs and observational studies given the inherent differences between these types of study designs. For RCTs, all studies meeting inclusion/exclusion criteria were included in the primary analysis. Additional prespecified stratified analyses of trials according to US FDA labeling (instructions for use) were conducted. Trials confined to MI patients or involving nonapproved indications (eg, chronic total occlusions, bifurcation lesions, or other complex lesions) were classified as off-label uses. Additional sensitivity analyses confined to RCTs with follow-up extending to ≥2, ≥3, and ≥4 years were prespecified.

For observational studies (defined as nonrandomized comparisons of DES versus BMS, including nonrandomized comparisons within an RCT investigating other therapies), all studies meeting inclusion/exclusion criteria were included in the primary meta-analysis. However, given the a priori heterogeneous nature of observational analyses, separate subanalyses were prespecified. An analysis confined to large observational studies (≥1000 total patients) was conducted. Separate analyses using unadjusted estimates and adjusted estimates were assessed. Additionally, estimates derived from studies using propensity score matching were considered within a separate substratum. An individual included study could be used in several categories (eg, if unadjusted, adjusted, and propensity-matched data were reported); however, the highest-quality estimate was picked for the overall meta-analysis (using the following rank order: propensity matched→adjusted→unadjusted). Additional sensitivity analyses confined to observational studies with follow-up extending to ≥2 and ≥3 years were prespecified. Finally, analyses were performed stratified by the type of enrollment: sequential (consecutive time periods of BMS followed by DES use) or concurrent (simultaneous BMS and DES use).

Meta-Analyses

Meta-analyses were based on cumulative data from the time of stent implantation. A single time point estimate for each study end point was chosen for the analysis, assuming a constant hazard of DES versus BMS throughout the follow-up period. Both fixed-effects (inverse-variance weighted) and random-effects (DerSimonian and Laird) models are reported. Statistical heterogeneity was assessed with Cochran Q via χ² test and was quantified with the I² test.
The influence of individual studies was examined by excluding studies 1 at a time, and testing for systematic bias was performed using funnel plots and the Begg test. Exploratory bivariate meta-regressions were performed to assess heterogeneous study effects and included regressions of the log-HR on the total number of patients within a study, total number of DES patients, percentage of diabetic patients, and percentage of patients undergoing protocol-mandated angiographic follow-up. All analyses were performed with Stata 10.0 (Stata Corp, College Station, Tex).

Results

A total of 22 RCTs that enrolled 9470 patients and 34 observational studies reporting data from 182,901 patients met the study criteria and were included in the comprehensive meta-analysis. A flow diagram depicting the overall search strategy is demonstrated in Figure 1, and characteristics of the included studies are shown in the Appendix of the online-

Figure 2. Meta-analysis of all-cause mortality with DES vs BMS. A, RCTs; B, observational studies. Dots represent the individual study estimates; boxes, study weights; and lines, 95% CIs.
Mortality

In 21 RCTs, the mortality HR for DES versus BMS was 0.97 (95% CI, 0.81 to 1.15; P = 0.72) in both fixed-effects and random-effects models with no observed heterogeneity (Figure 2A). Mortality also was not significantly different between DES- and BMS-treated patients in analyses restricted to trials with concurrent enrollment (13 116 612 patients) enrolled off-label patients (including 7 trials of DES versus BMS in acute MI). Among the observational studies, 19 studies (136 558 patients) used statistical designs (matching, covariate adjustment, or propensity-based adjustment) to adjust for differences between the DES and BMS patients.

Table 1. All-Cause Mortality in RCTs and Observational Studies

<table>
<thead>
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<th>RCTs</th>
<th>Observational studies</th>
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<tr>
<td></td>
<td>Studies, n</td>
<td>Patients, n</td>
</tr>
<tr>
<td>Overall</td>
<td>21</td>
<td>8867</td>
</tr>
<tr>
<td>Trials with ≥2 y of follow-up</td>
<td>11</td>
<td>5273</td>
</tr>
<tr>
<td>Trials with ≥3 y of follow-up</td>
<td>8</td>
<td>4684</td>
</tr>
<tr>
<td>Trials with ≥4 y of follow-up</td>
<td>6</td>
<td>3328</td>
</tr>
<tr>
<td>On-label trials</td>
<td>10</td>
<td>4818</td>
</tr>
<tr>
<td>Off-label trials</td>
<td>12</td>
<td>4049</td>
</tr>
<tr>
<td>Overall</td>
<td>31</td>
<td>169 595</td>
</tr>
<tr>
<td>Studies with ≥1000 patients</td>
<td>22</td>
<td>166 386</td>
</tr>
<tr>
<td>Studies with ≥2 y of follow-up</td>
<td>18</td>
<td>143 217</td>
</tr>
<tr>
<td>Studies with ≥3 y of follow-up</td>
<td>8</td>
<td>76 398</td>
</tr>
<tr>
<td>Studies with ≥4 y of follow-up</td>
<td>2</td>
<td>39 799</td>
</tr>
<tr>
<td>Unadjusted analyses</td>
<td>24</td>
<td>129 328</td>
</tr>
<tr>
<td>Adjusted analyses</td>
<td>19</td>
<td>136 558</td>
</tr>
<tr>
<td>Propensity-matched analyses</td>
<td>6</td>
<td>34 350</td>
</tr>
<tr>
<td>Sequential enrolment</td>
<td>14</td>
<td>41 237</td>
</tr>
<tr>
<td>Concurrent enrolment</td>
<td>13</td>
<td>116 612</td>
</tr>
</tbody>
</table>

Mortality In 21 RCTs, the mortality HR for DES versus BMS was 0.97 (95% CI, 0.81 to 1.15; P = 0.72) in both fixed-effects and random-effects models with no observed heterogeneity (Figure 2A). Mortality also was not significantly different between DES- and BMS-treated patients in analyses restricted to studies including follow-up extending to ≥2, ≥3, and ≥4 years (Table 1). Among trials examining off-label use of DES, the HR was 0.84 (95% CI, 0.62 to 1.13; P = 0.24).

In 31 observational studies, DES versus BMS use was associated with a 22% reduction in mortality (HR, 0.78; 95% CI, 0.71 to 0.86; P < 0.001) in a random-effects model and an 18% reduction in mortality (0.82; 95% CI, 0.78 to 0.85) in a fixed-effects model (Figure 2B). There was a high level of heterogeneity (I² = 71%; P < 0.001). However, the relative benefit of DES versus BMS was consistent among large observational analyses (those enrolling ≥1000 patients), among studies reporting follow-up extending to ≥2 and ≥3 years, and among studies reporting adjusted data (Table 1).

There was no apparent systematic bias as assessed by funnel plots among either the RCTs or observational studies (Begg test, P = 0.79 and 0.71, respectively). No individual study unduly influenced the primary effects estimate, and meta-regressions conducted to investigate the heterogeneity in studies demonstrated no variability in the HR based on number of enrolled patients, number of DES patients, or percentage of diabetic patients.

Myocardial Infarction In 20 RCTs, the HR for DES versus BMS was 0.95 (95% CI, 0.79 to 1.13; P = 0.54) in the fixed-effects model with minimal heterogeneity (I² = 3.0%; P = 0.42; Figure 3A). The hazard of MI was similar in analyses restricted to studies including follow-up extending to ≥2, ≥3, and ≥4 years (Table 2). Among trials of off-label use, the HR was 0.77 (95% CI, 0.54 to 1.10; P = 0.19).

In 25 observational studies, DES versus BMS use was associated with a 13% reduction in MI (HR, 0.87; 95% CI, 0.78 to 0.97; P = 0.014 in a random-effects model; Figure 3B). There was again a high level of heterogeneity (I² = 60.3%; P < 0.001). However, the relative benefit of DES versus BMS was consistent among large observational analyses (those enrolling ≥1000 patients), as well as among studies reporting follow-up extending to ≥2 and ≥3 years, but was somewhat attenuated when restricted to observational studies reporting adjusted data (HR, 0.91; 95% CI, 0.81 to 1.01; P = 0.08; Table 2).

A trend was present that was suggestive of systematic bias as assessed by funnel plots favoring DES in the RCTs but not in the observational studies with respect to the MI end point (Begg test, P = 0.052 and P = 0.12, respectively). No individual randomized or observational study unduly influenced the primary effects estimate, and meta-regressions demonstrated no variability in the HR based on number of enrolled patients, number of DES patients, or percentage of diabetic patients.

Target Vessel Revascularization In 16 RCTs, DES versus BMS resulted in a 55% reduction in TVR (HR, 0.45; 95% CI, 0.37 to 0.54; P < 0.001) in the
random-effects model with a high level of heterogeneity ($I^2=53.2\%; P=0.006; \text{Figure 4A}$). The benefit of DES versus BMS with respect to TVR was similar in analyses restricted to studies including follow-up extending to $\geq 2$, $\leq 3$, and $\leq 4$ years with less heterogeneity, particularly among the last group (Table 3). Randomization to DES versus BMS reduced TVR by 62% in trials examining off-label DES use (HR, 0.38; 95% CI, 0.27 to 0.52; $P<0.001$).

In 18 observational studies, use of DES compared with BMS reduced TVR by 62% in trials examining off-label DES use (HR, 0.38; 95% CI, 0.27 to 0.52; $P<0.001$). However, the relative benefit of DES versus BMS was consistent with the aggregate analysis among large observational studies (those enrolling $\geq 1000$ patients), studies reporting follow-up extending to $\geq 2$ and $\leq 3$ years, unadjusted studies, and studies reporting adjusted data, including propensity-matched registries and multivariable-adjusted registries (Table 3).

There was no evident systematic bias assessed by funnel plots evident in either the RCTs or observational studies with respect to the TVR end point (Begg test, $P=0.56$ and $P=0.11$, respectively). Meta-regressions performed in the RCTs demonstrated a consistent HR of TVR reduction with
end points such as death or MI, and large-scale observational studies, in which the results of the nonrandomized selection of DES versus BMS have been compared in routine clinical practice. These 2 different types of study designs have strengths and limitations that affect the clinical context and interpretation of their results. Although RCT data, by minimizing the influence of both measured and unmeasured confounders, represent the purest comparison between 2 treatment strategies and can minimize treatment selection bias, observational studies may be more generalizable and less subject to enrollment bias. Thus, both types of data are useful in assessing the relative safety and efficacy of DES compared with BMS.

There may be several possible explanations why the rates of death and MI were found to be significantly reduced with the use of DES compared with BMS in the observational studies with an attenuated effect in the RCTs. Proponents of observational data cite their added generalizability and the fact that nearly 20 times more patients have been studied in the observational registries as in the RCTs, providing much more power to detect differences in low-frequency safety events. Conversely, observational analyses are subject to confounding with respect to the nonrandomized choice of either DES or BMS. Multivariable adjustment and/or propensity matching can be used to mitigate the effect of measured confounders on the DES versus BMS effect estimate within individual studies. As such, the observed attenuation of the overall summary estimate of mortality and MI favoring DES compared with BMS in the adjusted compared with the unadjusted analyses is notable.

Nonetheless, conventional statistical approaches used in observational analyses have limited ability to address the influence of unmeasured confounders on the overall effect estimate. For example, the decision to use DES may be based on unmeasured patient characteristics and may importantly

Table 2. MI in RCTs and Observational Studies

<table>
<thead>
<tr>
<th>Study Type</th>
<th>Overall</th>
<th>Patients, n</th>
<th>Median Follow-Up, y</th>
<th>Random Effects HR</th>
<th>Random Effects CI</th>
<th>Fixed Effects HR</th>
<th>Fixed Effects CI</th>
<th>I², % Heterogeneity</th>
<th>P, %</th>
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<tbody>
<tr>
<td>RCTs</td>
<td>Overall</td>
<td>20</td>
<td>8850</td>
<td>2.9</td>
<td>0.94 (0.78–1.13)</td>
<td>0.95 (0.79–1.13)</td>
<td>0.54</td>
<td>3</td>
<td>0.42</td>
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<tr>
<td>Trials with ≥2 y of follow-up</td>
<td>11</td>
<td>5273</td>
<td>4.1</td>
<td>0.96 (0.74–1.25)</td>
<td>0.99 (0.81–1.23)</td>
<td>0.76</td>
<td>25</td>
<td>0.20</td>
<td></td>
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<tr>
<td>Trials with ≥3 y of follow-up</td>
<td>8</td>
<td>4684</td>
<td>4.4</td>
<td>1.08 (0.86–1.34)</td>
<td>1.08 (0.86–1.34)</td>
<td>0.52</td>
<td>0</td>
<td>0.61</td>
<td></td>
</tr>
<tr>
<td>Trials with ≥4 y of follow-up</td>
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<td>3328</td>
<td>5.0</td>
<td>1.04 (0.80–1.34)</td>
<td>1.04 (0.80–1.34)</td>
<td>0.79</td>
<td>0</td>
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<td>On-label trials</td>
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<td>4318</td>
<td>4.4</td>
<td>1.03 (0.81–1.30)</td>
<td>1.03 (0.81–1.30)</td>
<td>0.82</td>
<td>0</td>
<td>0.76</td>
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<tr>
<td>Off-label trials</td>
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<td>4532</td>
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<td>0.77 (0.54–1.10)</td>
<td>0.83 (0.62–1.10)</td>
<td>0.19</td>
<td>26</td>
<td>0.19</td>
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<tr>
<td>Observational studies</td>
<td>Overall</td>
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<td>130 191</td>
<td>2.5</td>
<td>0.87 (0.78–0.97)</td>
<td>0.95 (0.91–1.00)</td>
<td>0.01</td>
<td>60</td>
<td>&lt;0.01</td>
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<tr>
<td>Analyses with ≥1000 patients</td>
<td>16</td>
<td>126 931</td>
<td>2.6</td>
<td>0.90 (0.81–0.99)</td>
<td>0.96 (0.91–1.01)</td>
<td>0.03</td>
<td>63</td>
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<tr>
<td>Analyses with ≥2 y of follow-up</td>
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<td>103 663</td>
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<td>0.23</td>
<td>64</td>
<td>&lt;0.01</td>
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<tr>
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<td>5</td>
<td>58 255</td>
<td>3.6</td>
<td>0.88 (0.70–1.11)</td>
<td>0.97 (0.89–1.05)</td>
<td>0.28</td>
<td>68</td>
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<td>35 262</td>
<td>4.0</td>
<td>1.01 (0.91–1.11)</td>
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<td>Unadjusted analyses</td>
<td>19</td>
<td>88 457</td>
<td>2.0</td>
<td>0.81 (0.69–0.96)</td>
<td>0.88 (0.83–0.93)</td>
<td>0.01</td>
<td>78</td>
<td>&lt;0.01</td>
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<tr>
<td>Adjusted analyses</td>
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<td>107 294</td>
<td>2.8</td>
<td>0.91 (0.81–1.01)</td>
<td>0.96 (0.91–1.01)</td>
<td>0.08</td>
<td>61</td>
<td>&lt;0.01</td>
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<td>22 830</td>
<td>2.0</td>
<td>0.94 (0.79–1.12)</td>
<td>0.95 (0.87–1.03)</td>
<td>0.48</td>
<td>61</td>
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<td>10</td>
<td>20 108</td>
<td>2.0</td>
<td>0.69 (0.55–0.87)</td>
<td>0.70 (0.60–0.82)</td>
<td>&lt;0.01</td>
<td>43</td>
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<td>Concurrent enrolment</td>
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<td>98 337</td>
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<td>1.01 (0.95–1.08)</td>
<td>0.73</td>
<td>60</td>
<td>&lt;0.01</td>
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</table>
affect subsequent treatment decisions, including medication use. The longer duration of dual antiplatelet therapy required with DES\(^2\)\(^,\)\(^3\) may reduce long-term adverse event rates independently of stent selection.\(^1\)\(^4\) Thus, it is likely that at least some of the differences observed in the relative safety of DES versus BMS between the observational studies and the RCTs represent the effect of residual (or unmeasured) confounding.

These limitations notwithstanding, the observed point estimates for both death and MI with DES compared with BMS were less than unity in both the RCTs and the observational studies, suggesting that DES are safe across a broad cross
section of patients and lesions with coronary artery disease. Prior analyses of on-label DES use have demonstrated an “offsetting risk” of restenosis and stent thrombosis over longer-term follow-up, with an increased rate of restenosis-related events among BMS-treated patients balanced against an increased rate of primary thrombosis-related events among DES-treated patients.\(^4\),\(^5\),\(^15\) The absolute benefits of DES compared with BMS in more unselected (and higher restenosis risk) patients may be greater. Whether the relative and absolute risks of stent thrombosis are also concomitantly increased rate of primary thrombosis-related events among BMS-treated patients balanced against an increased rate of restenosis-related events among DES-treated patients.\(^4\),\(^5\),\(^15\) The absolute benefits of DES compared with BMS in more unselected (and higher restenosis risk) patients may be greater. Whether the relative and absolute risks of stent thrombosis are also concomitantly higher with DES versus BMS in such patients is unknown, but it is clear that late thrombotic events also occur with unselected use of BMS.\(^16\)

With respect to the efficacy of DES, the results of both RCT studies and observational analyses were concordant in demonstrating a marked reduction in recurrent ischemia necessitating repeat TVR. This effect was similar in magnitude between the RCT studies and observational analyses and in the RCTs was independent of the percentage of routine angiographic follow-up performed. The consistency and magnitude of the reduction in TVR with DES are notable, particularly given concerns that high levels of routine angiographic follow-up and a lack of lesion complexity may have overestimated the efficacy of DES in pivotal randomized trials. Among RCTs, the reduction in TVR, death, and MI with DES compared with BMS tended to be greater in off-label compared with on-label studies, supporting the data from the observational studies that DES are likely safe and effective in an unrestricted real-world population.

As with any systematic review and meta-analysis, the conclusions drawn from such data are subject to the limitations of the original included studies themselves. Although strict criteria were used, the included studies represent a comprehensive attempt to cull together published and unpublished literature in this area, and as such, summary-level estimates of individual study effects were used. Finally, heterogeneity was present among the observational studies included in this meta-analysis. Attempts to investigate sources of heterogeneity through various sensitivity analyses and meta-regression did not reveal a simple explanation or way to account for this variability, and the overall magnitude and directionality of the summary DES versus BMS estimates appeared consistent in these subanalyses. Even if one were to consider the degree of heterogeneity to be so significant so as to preclude quantitative assessment of a summary estimate, from this systematic review, it appears that the preponderance of the evidence does not suggest an adverse safety signal with DES compared with BMS.

**Conclusions**

The use of DES compared with BMS does not appear to be associated with adverse safety outcomes such as death or MI when used either off label in RCTs or in an unrestricted fashion as selected in the nonrandomized observational studies and was associated with a significant and comparable
reduction in TVR in both types of studies. Large-scale RCTs are required to ascertain the true effects of DES compared with BMS with respect to rates of death and MI. However, in the absence of definitive large-scale randomized data directly comparing DES to BMS in unselected patients, these findings, derived from >190,000 total patients treated in 56 studies, suggest that DES are safe for both on-label and off-label use and have comparable efficacy in both RCTs and in the real world.

Disclosures
Dr Kirtane has received honoraria/lecture fees from Medtronic, Boston Scientific, Abbott Vascular, and St Jude Medical and served as a consultant to Medtronic and Abbott Vascular. Dr Moses has received research support from and served as a consultant to Cordis. Dr Leon has been a consultant to Cordis, Abbott Vascular, Medtronic, and Boston Scientific. Dr Applegate has received research support from Cordis, Abbott Vascular, and Medtronic. Dr Stone has received research support from Abbott Vascular, Cordis, and Boston Scientific and honoraria from Medtronic. The other authors report no conflicts.

References

CLINICAL PERSPECTIVE
Drug-eluting stents (DES) are currently implanted in the majority of the >2 million patients undergoing percutaneous coronary intervention each year. The evidence base for initial DES approvals by the US Food and Drug Administration has consisted largely of randomized controlled trials enrolling patients with relatively noncomplex lesions. Data from these trials have suggested that rates of death and myocardial infarction are similar among DES- and bare metal stent–treated patients. Yet, DES are currently being used “off label” in the majority of cases, and concerns have arisen about the appropriateness of the use of DES in the “real world.” Here, we sought to address DES safety and efficacy by synthesizing studies of the commercially available formulations of the 2 originally approved DES. A statistical methodology known as meta-analysis was used to quantitatively combine these studies. Given the inherent differences between randomized controlled trials and observational studies, each type of study was analyzed separately. In randomized controlled trials, no significant differences were observed in the long-term rates of either death or myocardial infarction after DES or bare metal stent use for both off-label and on-label indications. In nonrandomized observational studies, DES use was associated with reduced death and myocardial infarction. Both randomized controlled trials and observational studies demonstrated marked and comparable reductions in repeat revascularization with DES compared with bare metal stents. In aggregate, the unrestricted use of DES compared with bare metal stents did not appear to be associated with adverse safety outcomes and was associated with a significant reduction in repeat revascularization of the treated vessel.
Safety and Efficacy of Drug-Eluting and Bare Metal Stents: Comprehensive Meta-Analysis of Randomized Trials and Observational Studies


_Circulation_. 2009;119:3198-3206; originally published online June 15, 2009; doi: 10.1161/CIRCULATIONAHA.108.826479

_Circulation_ is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/119/25/3198

Data Supplement (unedited) at:
http://circ.ahajournals.org/content/suppl/2009/06/15/CIRCULATIONAHA.108.826479.DC1

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SUPPLEMENTAL MATERIAL

Safety and Efficacy of Drug-Eluting and Bare Metal Stents: Comprehensive Meta-Analysis of Randomized Trials and Observational Studies

Ajay J. Kirtane, MD, SM; Anuj Gupta, MD; Srinivas Iyengar, MD; Jeffrey W. Moses, MD; Martin B. Leon, MD; Robert Applegate, MD; Bruce Brodie, MD; Edward Hannan, PhD; Kishore Harjai, MD; Lisette Okkels Jensen, MD; Seung-Jung Park, MD, PhD; Raphael Perry, MD; Michael Racz, PhD; Francesco Saia, MD, PhD; Jack V. Tu, MD, PhD; Ron Waksman, MD; Alexandra J. Lansky, MD; Roxana Mehran, MD; and Gregg W. Stone, MD
# Supplemental Table 1: Randomized Controlled Trials

<table>
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<tr>
<th>Name of Study</th>
<th>First Author</th>
<th>BMS pts</th>
<th>DES pts</th>
<th>Assessed Outcomes</th>
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*Original study data obtained from study sponsors. BMS = bare metal stents. DES = drug-eluting stents
Supplemental Table 2: Observational Studies

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*Data updated directly from study principal investigators
BMS = bare metal stents. DES = drug-eluting stents. UA=unadjusted; MV=multivariable analysis; PS=propensity score adjusted; PM=propensity-matched
Supplemental Study References


29. Shah AM SD, Swenson K, Jaquez S, Martinez M, Choi J, French WJ. Paclitaxel Eluting Stents are associated with a high rate of Stent Thrombosis compared to Bare Metal Stents in an


35. Park SJ. Risk of Stent Thrombosis After Placement of Drug-Eluting Stent Compared With Bare-Metal Stent: Real World Experience in Asan Medical Center. [http://www.sbhci.org.br/pdf/Late_breaking_st.pdf#search=%22asan%22](http://www.sbhci.org.br/pdf/Late_breaking_st.pdf#search=%22asan%22).


