Survival Benefit With Drug-Eluting Stents in Observational Studies

Fact or Artifact?

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Background—Recently, there has been increased interest in leveraging observational studies for comparative effectiveness research. Without robust and valid risk adjustment, however, findings from these nonrandomized studies may remain biased. Previous studies examining long-term mortality with drug-eluting stents (DESs) have demonstrated discordant results between randomized trials and observational studies. To examine the impact of treatment selection bias on these findings, we used data from a prospective percutaneous coronary intervention (PCI) registry (EVENT [Evaluation of Drug Eluting Stents and Ischemic Events]) to compare clinical outcomes between DESs and bare metal stents (BMSs) using conventional (multivariable regression and propensity matching) and novel (instrumental variable analysis) risk-adjustment techniques.

Methods and Results—The study population consisted of 9266 patients who underwent nonemergent PCI with stent placement at 55 US centers between 2004 and 2007. All-cause mortality and target lesion revascularization (TLR) were assessed prospectively over 1 year of follow-up. Overall, 8171 patients (88%) received DES, but this proportion substantially differed by treatment year (93% in 2004–2006 and 73% in 2007; P<0.001). One-year rates of death and TLR were significantly lower with DES versus BMS (death, 2.5% versus 5.6%; TLR, 4.2% versus 6.9%; P<0.001 for both), findings that persisted in both multivariable-adjusted and propensity-matched analyses. In contrast, instrumental variable analysis, using enrollment period (2004–2006 versus 2007) as the instrument, demonstrated no significant difference in 1-year mortality (predicted absolute difference, 2.0%; 95% CI, -1.8% to 5.7%; P=0.30) and a strong trend toward reduced TLR with DES use (predicted absolute difference, -4.2%; 95% CI, -8.8% to 0.4%; P=0.07).

Conclusions—Among unselected PCI patients in contemporary practice, DES use tended to be associated with a consistent reduction in TLR regardless of risk-adjustment method but showed discordant effects on mortality with conventional risk adjustment compared with instrumentable variable analysis. These findings underscore the limitations of standard risk-adjustment methods to adequately address treatment selection bias in nonrandomized studies and have important implications for comparative effectiveness research using observational data. (Circ Cardiovasc Qual Outcomes. 2011;4:587-594.)

Key Words: drug-eluting stent | mortality | observational studies | risk adjustment | instrumental variable analysis

In the United States, variability in healthcare resource use and increasing costs have prompted interest in comparative effectiveness research, to inform and guide both clinical and policy decisions. Although randomized trials remain the gold standard for comparative effectiveness studies, the many potential research questions, coupled with the substantial time and expense required, makes clinical trials impractical for addressing most unanswered questions. Accordingly, efforts are underway to leverage existing observational databases (including both clinical registries and administrative data sets) for comparing treatment strategies. However, unless robust and valid risk adjustment can be performed to adequately correct for the many sources of confounding and selection biases inherent to the nonrandomized framework, findings from these studies may remain biased.

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One contemporary treatment strategy that has been under intense scrutiny, for both clinical and economic reasons, is the use of drug-eluting stents (DESs) in percutaneous coronary intervention (PCI). Although DESs demonstrated dramatic reductions in both clinical and angiographic restenosis in their original registration trials, current use patterns have extended...
well beyond the original trial populations. Indeed, more than half of all DES implants are performed for “off-label” or “unproven” indications. These use patterns, coupled with emerging safety concerns, have led to substantial interest in comparative effectiveness studies of DESs versus bare metal stents (BMSs) in routine clinical practice. These studies, based on observational data, have generally confirmed the benefits of DESs on clinical restenosis and the need for repeat revascularization that were seen in the original clinical trials. However, virtually all of the studies have demonstrated substantial reductions in mortality with DESs as well; these results contrast with those of randomized clinical trials. Whether these findings relate to a unique benefit of DESs in more complex high-risk individuals who were excluded from the original randomized trials or to a failure of the available risk-adjustment methods is unknown.

To further examine this issue, we used data from the multicenter EVENT (Evaluation of Drug Eluting Stents and Ischemic Events) registry to compare the effect of DESs versus BMSs on both all-cause mortality and restenosis-related repeat events (ie, target lesion revascularization [TLR]) according to 3 alternative risk-adjustment strategies: (1) multivariable regression analysis, (2) propensity matching, and (3) instrumental variable (IV) analysis. We hypothesized that the results of IV analysis that accounts for the presence of unmeasured confounding due to selection bias would differ from the other 2 techniques that only adjust for measured confounding.

### WHAT IS KNOWN
- Both randomized trials and observational studies comparing drug-eluting stents (DESs) with bare metal stents (BMSs) have demonstrated substantial reductions in target lesion revascularization (TLR) with DES use. Data on mortality, however, are strikingly disparate, with only observational studies supporting a benefit with DESs.
- Standard risk-adjustment techniques, such as multivariate regression and propensity matching, account for measured confounders in observational data.
- Instrumental variable (IV) analysis is a quasi-experimental approach for observational studies that has the theoretical advantage of adjusting for both observed and unobserved confounders.

### WHAT THE STUDY ADDS
- Among unselected PCI patients in contemporary practice, DES use is associated with a consistent reduction in TLR regardless of risk-adjustment method.
- The degree of concordance in treatment effects for 1-year mortality, however, varied across alternative analytic techniques, with no significant association seen with IV analysis. Differences in risk estimates may be predominantly related to residual selection biases in nonrandomized studies.

## Methods
### Study Population and Data Collection
The methods and population of the EVENT registry have been previously described. Briefly, EVENT is a collaborative effort to assess the contemporary practice of coronary stenting by prospective evaluation of patients undergoing attempted implantation of an approved coronary stent at 55 centers in the United States. Patients undergoing PCI were sequentially enrolled in “waves” from 2004 to 2007 (wave 1, August 2004–March 2005; wave 2, June 2005–September 2005; wave 3, February 2006–June 2006; and wave 4, July 2007–December 2007). Specific efforts were made to consecutively enroll patients during each enrollment period (eg, on predetermined days of the week) to minimize selection bias. For the present analysis, we excluded patients who did not receive DESs or BMSs, those who underwent index PCI primarily for ST-elevation myocardial infarction, and those who died in the hospital. Patients who received both DESs and BMSs were considered as DES patients.

Data on patient characteristics, clinical presentation, and treatment were prospectively collected on standardized case report forms and submitted to the data coordinating center. Patients were contacted by telephone at 6 and 12 months after the index PCI, and information on subsequent hospitalizations and medication use, including antiplatelet therapy, was obtained. In the case of suspected clinical events identified by telephone contact, additional source data, including hospital discharge summaries and catheterization laboratory reports, were obtained to allow detailed review of each event by the Clinical Events Committee.

### End Points
The 2 end points of interest for our study were all-cause mortality within 1 year after discharge after the index procedure and the occurrence of TLR during the same time frame. For our study, TLR was defined as repeat PCI or bypass graft placement for a stenosis in or occurring within 5 mm of the stent(s) placed during the index PCI.

### Statistical Analyses
Baseline sociodemographic, clinical, angiographic, and treatment-related characteristics were compared between the DES and BMS groups using the Student t test for continuous variables and the χ² test for categorical variables. Event rates between hospital discharge and 1-year follow-up were estimated using the Kaplan-Meier method and compared using the log-rank statistic.

To obtain adjusted risk estimates for 1-year events, we used 3 analytic approaches (multivariable risk adjustment, propensity-matched analysis, and IV analysis) and included the following covariates: age, sex, insurance status (any versus none), hyperlipidemia, hypertension, diabetes, smoking status, prior myocardial infarction, prior stroke, history of heart failure, peripheral arterial disease, prior PCI or bypass surgery, estimated glomerular filtration rate, indication for PCI (mortality models only), left ventricular ejection fraction, multivessel disease, lesion location (left main, left anterior descending artery, or saphenous vein graft), number of lesions treated, total stent length (as a surrogate for lesion length), maximum stent diameter (as a surrogate for reference vessel diameter), and number of stents implanted.

### Multivariable Regression and Propensity-Matched Analysis
For standard multivariable analysis, we used Cox proportional hazards regression to calculate adjusted hazard ratios (HRs) and associated CIs for all-cause mortality and TLR with DES versus BMS use while controlling for each of the covariates previously listed. For the propensity-matched analysis, we first used logistic regression to develop a propensity score that reflects the probability of receiving a DES, conditional on the same covariates. We then matched each patient in the BMS group with those in the DES group who had an estimated logit within 0.2 SDs of the selected BMS patient (one-to-many nearest neighbor matching). The success of matching was examined using weighted standardized differences in the distribution of the potential confounders between the 2 stent types, and a difference of 10% between the 2 groups was considered acceptable. Finally, we used Cox proportional hazards regression, conditional on matching, to compare the risk of outcomes with DES versus BMS use. Because IV analysis produces estimates of risk differences on an absolute rather than a relative scale, we also...
calculated adjusted risk differences from the multivariable risk-adjusted and propensity-matched models using standard linear regression (PROC GENMOD in SAS) with robust SEs.

**IV Analysis**

The IV analysis is a “quasi-experimental” approach for observational studies that has the theoretical advantage of adjusting for both observed and unobserved confounders. The IV analytic technique compares patient groups that differ in the likelihood of receiving a treatment, determined by a randomly distributed “IV,” rather than comparing patients with respect to the actual treatment received (which may be biased). An IV is an observable factor that is associated with a specific treatment pattern but is otherwise unrelated to underlying patient characteristics and does not directly affect the outcome of interest. Based on our previous work in the EVENT registry, we identified enrollment year (2004–2006 versus 2007) as a potential instrument, given that it was significantly associated with DES use (ie, consistently high rates of use in 2004–2006 versus lower rates in 2007), whereas most other patient and treatment characteristics were similar over time. In this study, we used Cox proportional hazards models to validate the assumption that the enrollment year was not associated with differences in either mortality or TLR, independent of DES use.

After confirming that the enrollment year was a suitable instrument, we performed a fully adjusted IV analysis using a simultaneous 2-stage least-squares approach. Unlike the use of logistic regression analysis for estimating the probability of DES use (propensity scores) as a function of measured covariates, the first stage in the 2-stage least-squares approach predicted the receipt of DES (treatment) as a linear function of enrollment year (the instrument) and other observed covariates previously listed. In the second stage, 1-year clinical outcomes were regressed on the predicted probability of DES use, derived from the first stage, along with the same measured confounders. In this manner, the 2-stage least-squares approach to IV analysis generates consistent estimates of treatment effects with appropriate SEs that are unrelated to variations in treatment selection. The effect of DES versus BMS use on each outcome was estimated by subtracting the mean predicted probability of DES use and represents an estimate of the impact of DES use on 1-year outcomes in the marginal population (ie, those patients who would have received a DES in 2004–2006 but not in 2007).

Finally, to assess the potential bias from treatment effect heterogeneity on these results, we adapted the theoretical framework proposed by Brookhart and Schneeweiss to examine the strength of the instrument across various patient subgroups when using preference-based instruments. In this framework, the strength of the instrument is examined across observed patient covariates that are used as proxies for an unmeasured factor across which average treatment effects may be expected to vary. If the variation in treatment selection induced by the instrument is stronger or weaker across these measured factors when compared with that in the overall cohort, it is possible that variation across unmeasured factors may render the IV estimator biased for the average effect of treatment in the population under study.

Statistical analyses were performed using SAS, version 9.2 (SAS Institute; Cary, NC). All P values are 2 sided, and P<0.05 was considered statistically significant unless otherwise specified.

**Results**

Between August 2004 and July 2007, 10,144 patients underwent PCI at 55 study centers and were included in the EVENT registry. After excluding patients in whom no stents were deployed (n=150) and those who underwent PCI as primary treatment for ST-elevation myocardial infarction (n=728), the remaining 9266 patients constituted the study population. Of these patients, 8171 (88%) received at least 1 DES and 1095 (12%) received only BMSs.

**Multivariable Regression Analysis**

Table 1 shows the baseline clinical characteristics of patients in the overall cohort according to stent type. On average, patients receiving DESs were slightly younger and were more likely to have had insurance coverage than those receiving BMSs. Patients treated with DESs were also less likely to have undergone PCI in the setting of an acute coronary syndrome and more often had a history of a prior PCI. In addition, there were several differences in angiographic and procedural characteristics according to stent type. Although the extent of coronary artery disease was similar in both groups, patients receiving DESs had more lesions and vessels treated during the index procedure. On average, patients treated with DESs received slightly more stents, with greater total lengths and smaller maximum diameters, than those treated with BMSs.

Of the entire study cohort, 14 patients (<1%) died during the index hospitalization and 251 patients (2.7%) were missing follow-up information. The proportion of patients with missing follow-up data ranged from 2.5% to 3.0% and did not differ by stent type or enrollment period. Figure 1 shows the cumulative rates of postdischarge events over 1 year, according to the type of stent received during the index PCI. Compared with patients receiving only BMSs, patients treated with DESs had lower unadjusted mortality rates (2.5% versus 5.6%; P<0.001) and were less likely to require TLR during follow-up (4.2% versus 6.9%; P<0.001). Multivariable Cox regression models that accounted for patient and procedural characteristics demonstrated a significantly lower adjusted risk of death (HR, 0.50; 95% CI, 0.37–0.69) and TLR (HR, 0.49; 95% CI, 0.37–0.63) with DES versus BMS use (Table 2). Absolute risk differences based on multivariable linear regression were similar (mortality difference with DES, -2.4%; 95% CI, -3.8% to -1.0%; TLR difference, -3.3%; 95% CI, -4.9% to -1.8%).

**Propensity-Matched Analysis**

Matching patients based on their propensity to receive DES versus BMS yielded a cohort of 8082 DES patients and 997 BMS patients with a high degree of similarity (standardized difference, <10%) in baseline characteristics (Figure 2; mortality model). Similar results were seen for factors included in the TLR model (which included 8083 DES and 999 BMS patients), with the exception of total stent length, which was slightly longer in the DES group (standardized difference, 10.5%). Similar to results from multivariable regression analysis, both Cox and linear regression models, conditional on matching, demonstrated a significantly lower risk of mortality (HR, 0.51 [95% CI], 0.36–0.71; absolute risk difference, -1.8% [95% CI], -3.3% to -0.3%) and TLR (HR, 0.50 [95% CI], 0.38–0.67; absolute risk difference, -3.0% [95% CI], -4.5% to -1.4%) with DES use.

**IV Analysis**

The DES use decreased from 93% in 2004 to 2006 (liberal DES era) to 73% in 2007 (selective DES era), P<0.001.
Figure 3). Table 3 summarizes baseline clinical and procedural characteristics according to the enrollment period. Most characteristics were similar between the liberal and selective DES periods, although patients treated in 2007 were somewhat more likely to have undergone PCI in the setting of an acute coronary syndrome. Angiographic characteristics were also stable over time, with the exception of total stent length, which was slightly shorter in 2007 compared with 2004 to 2006. Mortality rates were similar in the liberal versus selective DES periods (3.0% versus 2.6%; \( P = 0.46 \)), whereas TLR rates tended to be lower for patients enrolled in the liberal DES era (4.3% versus 5.2%; \( P = 0.06 \)).

In contrast to the results of our multivariable regression models and propensity-matched analyses, IV analyses using the study enrollment period as the instrument (2004–2006 versus 2007) demonstrated no significant difference in 1-year mortality according to stent type (predicted absolute difference for DES versus BMS: unadjusted, 1.4% [95% CI, -2.5% to 5.2%; \( P = 0.49 \)]; adjusted, 2.0% [95% CI, -1.8% to 5.7%; \( P = 0.30 \)]). For the end point of TLR, however, IV analysis demonstrated a strong trend toward reduced TLR with DES use (predicted absolute difference: unadjusted, -4.6% [95% CI, -9.4% to 0.1%; \( P = 0.06 \)]; adjusted, -4.2% [95% CI, -8.9% to 0.4%; \( P = 0.07 \)]).

Results of subgroup analyses examining the difference in percentage DES use between the liberal and selective DES eras among various patient subsets are provided in Table 4. The strength of the instrument was similar to that in the overall cohort across most observed patient characteristics, with the exception of 4 factors for which the difference...
reached statistical significance. The difference in percentage DES use across enrollment period was slightly smaller than average in patients with prior coronary artery bypass grafting, multivessel disease, and long lesions, factors that may be expected to confer an increased risk of TLR but not mortality with BMS. Assuming these variables are reasonable proxies for unmeasured factors for restenosis risk, the TLR benefit with DES use observed in our IV analysis may slightly underestimate the treatment effect in the overall population. On the other hand, the difference in percentage DES use across enrollment period was somewhat larger than average in patients with a history of congestive heart failure, a risk factor for increased long-term mortality. Because patients with congestive heart failure are less likely to receive DES, it is likely that the IV analysis overestimates the survival benefit of DES to a slight degree as well.

Discussion
The association of DES use with long-term mortality after PCI differs substantially across study designs, with only data from observational studies demonstrating a survival benefit. To better understand the influence of treatment selection (bias) on outcomes in such nonexperimental settings, we used 3 alternative approaches to risk adjustment of observational data to examine the benefits of DES over BMS among patients undergoing PCI. We found that, for the comparison of 1-year clinical outcomes between DES and BMS, the degree of concordance in treatment effects derived using alternative analytic techniques varied according to the end point of interest.

For TLR, a surrogate for clinically significant restenosis, DES use was associated with a lower event rate across all 3 approaches. On the other hand, for mortality, there were important differences in the estimated treatment effect according to the analytic method. In both multivariable models and propensity-matched analysis (techniques that only account for measured confounders), the use of DES was associated with a significant reduction in long-term mortality compared with BMS. In contrast, IV analysis showed no significant association between stent type and 1-year mortality, and the point estimate actually favored BMS use. Such variability in the estimated impact of DES versus BMS on mortality from different analytic approaches highlights methodological issues that are increasingly relevant in the emerging field of comparative effectiveness research.

Table 2. Comparison of Risk-Adjusted Clinical Outcomes by Stent Type

<table>
<thead>
<tr>
<th>Variable</th>
<th>Death (95% CI)</th>
<th>P Value</th>
<th>TLR (95% CI)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Multivariable regression*</td>
<td>HR 0.50 (0.37 to 0.69)</td>
<td>&lt;0.001</td>
<td>0.49 (0.37 to 0.63)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Risk difference, %</td>
<td>-2.4 (-3.8 to -1.0)</td>
<td>0.001</td>
<td>-3.3 (-4.9 to -1.8)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Propensity-matched regression*</td>
<td>HR 0.51 (0.36 to 0.71)</td>
<td>&lt;0.001</td>
<td>0.50 (0.38 to 0.67)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Risk difference, %</td>
<td>-1.8 (-3.3 to -0.3)</td>
<td>0.02</td>
<td>-3.0 (-4.5 to -1.4)</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Instrumental variable analysis*</td>
<td>Risk difference, %</td>
<td>2.0 (-1.8 to 5.7)</td>
<td>0.30</td>
<td>-4.2 (-8.9 to 0.4)</td>
</tr>
</tbody>
</table>

TLR indicates target lesion revascularization.
*Negative values indicate lower rates of the outcome with DES vs BMS use. Variables included in the models are described in the Methods section.
Comparison With Previous Studies

Our findings regarding the impact of DES versus BMS on clinical restenosis (TLR) are similar to many previous randomized trials and observational studies. In a network meta-analysis of 38 randomized trials with up to 4 years of follow-up, Stettler and colleagues reported an overall 60% to 70% reduction in the need for TLR with both paclitaxel- and sirolimus-eluting stents compared with BMSs. In a more contemporary meta-analysis that included clinical trials and observational studies, Kirtane and colleagues reported similar significant reductions in target vessel revascularization with DES use across both study designs.

Table 3. Select Baseline Characteristics and Clinical Outcomes by Study Enrollment Period

<table>
<thead>
<tr>
<th></th>
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<th></th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>65±12†</td>
<td>65±11†</td>
<td>0.06</td>
</tr>
<tr>
<td>Male sex</td>
<td>69</td>
<td>69</td>
<td>0.79</td>
</tr>
<tr>
<td>Uninsured</td>
<td>3</td>
<td>3</td>
<td>0.30</td>
</tr>
<tr>
<td>Diabetes</td>
<td>35</td>
<td>36</td>
<td>0.29</td>
</tr>
<tr>
<td>Hypertension</td>
<td>79</td>
<td>81</td>
<td>0.03</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>75</td>
<td>77</td>
<td>0.08</td>
</tr>
<tr>
<td>PAD</td>
<td>10</td>
<td>14</td>
<td>&lt;0.001</td>
</tr>
<tr>
<td>Smoking in the past year</td>
<td>23</td>
<td>22</td>
<td>0.47</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>9</td>
<td>10</td>
<td>0.46</td>
</tr>
<tr>
<td>Prior MI</td>
<td>35</td>
<td>36</td>
<td>0.37</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>10</td>
<td>11</td>
<td>0.63</td>
</tr>
<tr>
<td>Prior PCI</td>
<td>38</td>
<td>40</td>
<td>0.06</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>23</td>
<td>24</td>
<td>0.30</td>
</tr>
</tbody>
</table>

Table 4. DES Use Across Study Enrollment Period Among Subgroups Defined by Observed Risk Factors

<table>
<thead>
<tr>
<th>Group</th>
<th>Liberal DES Era, 2004–2006 (n=7038)</th>
<th>Selective DES Era, 2007 (n=2228)</th>
<th>Difference in % DES Use</th>
<th>95% CI</th>
</tr>
</thead>
<tbody>
<tr>
<td>Full cohort</td>
<td>93</td>
<td>73</td>
<td>20</td>
<td>19–21</td>
</tr>
<tr>
<td>Aged &gt;65 y</td>
<td>92</td>
<td>71</td>
<td>21</td>
<td>20–22</td>
</tr>
<tr>
<td>Men</td>
<td>93</td>
<td>73</td>
<td>20</td>
<td>19–21</td>
</tr>
<tr>
<td>Uninsured</td>
<td>87</td>
<td>61</td>
<td>26</td>
<td>19–33</td>
</tr>
<tr>
<td>Diabetes</td>
<td>94</td>
<td>75</td>
<td>19</td>
<td>17–21</td>
</tr>
<tr>
<td>Hypertension</td>
<td>93</td>
<td>73</td>
<td>20</td>
<td>19–21</td>
</tr>
<tr>
<td>Hyperlipidemia</td>
<td>93</td>
<td>74</td>
<td>19</td>
<td>18–20</td>
</tr>
<tr>
<td>PAD</td>
<td>93</td>
<td>70</td>
<td>23</td>
<td>20–26</td>
</tr>
<tr>
<td>Smoking in the past year</td>
<td>92</td>
<td>71</td>
<td>21</td>
<td>19–23</td>
</tr>
<tr>
<td>Prior stroke</td>
<td>91</td>
<td>71</td>
<td>20</td>
<td>17–23</td>
</tr>
<tr>
<td>Prior MI</td>
<td>92</td>
<td>70</td>
<td>22</td>
<td>20–24</td>
</tr>
<tr>
<td>Congestive heart failure</td>
<td>93</td>
<td>63</td>
<td>30</td>
<td>27–33</td>
</tr>
<tr>
<td>Prior PCI</td>
<td>94</td>
<td>76</td>
<td>18</td>
<td>16–20</td>
</tr>
<tr>
<td>Prior CABG</td>
<td>90</td>
<td>74</td>
<td>16</td>
<td>14–18</td>
</tr>
<tr>
<td>PCI for non-ST elevation ACS</td>
<td>93</td>
<td>71</td>
<td>22</td>
<td>20–24</td>
</tr>
<tr>
<td>eGFR =60 mL/min per 1.73 m²*</td>
<td>92</td>
<td>70</td>
<td>22</td>
<td>20–24</td>
</tr>
<tr>
<td>LVEF &lt;25</td>
<td>3</td>
<td>3</td>
<td>0.28</td>
<td></td>
</tr>
<tr>
<td>25–35</td>
<td>8</td>
<td>8</td>
<td></td>
<td></td>
</tr>
<tr>
<td>&gt;50</td>
<td>24</td>
<td>27</td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of diseased vessels</td>
<td>65</td>
<td>63</td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

In our study, the association of DES with TLR is consistent with these previous studies and underscores the true clinical benefit of DES. Although the association of DES with TLR in our IV analysis was not statistically significant by conventional standards, it is reassuring that both the direction and magnitude of the treatment effect was similar to that seen in our conventional analyses and in previous reports from randomized clinical trials and observational studies. The lack of statistical significance in the IV analysis most likely reflects the reduced power of the IV approach because of the relatively modest contrast in the exposure of interest (DES use) defined by the instrument.

Regarding DES and long-term mortality, data from randomized clinical trials have consistently demonstrated no significant difference in survival between DES and BMS. On the other hand, reports from large nonrandomized studies have suggested substantial reductions in mortality with DES.
use, regardless of whether they were based on administrative data or detailed clinical data sets. Mauri and colleagues examined 2-year clinical outcomes by stent type among 5549 patient pairs, matched on 63 baseline characteristics, and found a significant 2% absolute difference in 2-year mortality in favor of DES. These mortality differences were not explained by the need for clinically driven revascularization and were observed as early as 2 days after the index procedure. Similar findings were reported from the Cardiac Care Network Registry across 12 hospitals in Ontario, Canada, and in a larger cohort of Medicare beneficiaries from 650 hospitals in the National Cardiovascular Data Registry. Indeed, despite rigorous risk adjustment using widely accepted methods, all of the nonrandomized studies to date have suggested a survival benefit with DES use. In light of these previous studies, our results strongly suggest that the estimated mortality reductions with DES in previous observational studies are likely because of inadequate adjustment for unmeasured confounding.

**Practical Implications**

Recently, there has been a greater emphasis on increasing the quantity and quality of comparative effectiveness research to help inform and guide clinical practice and policy in typical care settings in the United States. Given limitations in both resources and time, coupled with the need for generalizability to routine practice, much of this investigation will inevitably be based on observational data from electronic medical records, administrative data sets, and clinical registries, with reliance on conventional analytic techniques to account for differences between treatment groups. Our study demonstrates that, even with rigorous risk adjustment and the availability of detailed clinical descriptors, these sophisticated analytic techniques may have limitations for providing unbiased estimates of treatment effects. Furthermore, our results caution that, even though several independent observational studies might produce consistent findings with respect to estimates of relative effectiveness, results from such studies cannot provide the same strength of evidence as results from randomized trials and should, therefore, be viewed with appropriate caution when determining individual treatment decisions or guidelines.

**Study Limitations**

Our findings should be interpreted in the context of the following limitations. First, the validity of results from IV analysis depends on the validity of the instrument. Our choice of “enrollment period” as the instrument was based on the recent shifts in patterns of DES use in response to the safety concerns of stent thrombosis. Based on these reports and our prior work, we assumed that the year of treatment would not be correlated with underlying patient characteristics (measured or unmeasured) and would not directly affect long-term clinical outcomes in this patient cohort. Although our own analyses support the validity of these assumptions, they cannot be proved with certainty. It is, therefore, possible that other unobserved factors, including hospital or operator characteristics, may explain some of our results. However, the fact that patients who underwent PCI in 2004 to 2006 and 2007 in the EVENT registry were similar in most baseline characteristics and that no significant differences in 1-year clinical outcomes were observed across these 2 cohorts, independent of stent type, strongly supports the use of PCI era as an effective instrument. Moreover, our results are consistent with those reported in randomized trials.

Second, standard risk adjustment, with multivariable models and propensity matching, is inherently different from IV approaches, which may account for the different results. From an analytic perspective, Cox regression models, used for generating relative risk estimates after multivariate risk adjustment and propensity matching, account for time to event and censoring of data. The IV analysis, on the other hand, uses a 2-stage least-squares regression approach and provides absolute risk differences. Moreover, the former 2 approaches are attempts to address a clinical question: what is the expected benefit of DES over BMS for a population of patients? The IV approach, on the other hand, provides inference only on the “marginal” cases (ie, patients who would have received a DES in 2004–2006 but not in 2007), which may not necessarily reflect the mean benefit for a given individual (or population). Consequently, the results of our IV analysis relate only indirectly to individual clinical decision making because the specific characteristics of patients in the marginal group are not easily discernible. Nonetheless, the finding that an incremental increase in DES use was associated with minimal benefit at the population level is particularly useful for informing policy decisions that generally do not lend themselves to randomized trials. Moreover, our sensitivity analyses demonstrate only minimal heterogeneity in the strength of the instrument across observed patient characteristics, further supporting the generalizability of our findings.

**Conclusions**

Among unselected PCI patients in contemporary practice, DES use tended to be associated with reduced TLR, independent of the analytic approach, but showed discordant effects on mortality with conventional risk adjustment compared with IV analysis. These findings underscore the limitations of standard risk-adjustment methods to adequately address treatment selection bias in nonrandomized studies and have important implications for comparative effectiveness research using observational data.

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