Studies of Drug-Eluting Stents
To Each His Own?

Laura Mauri, MD, MSc; Sharon-Lise T. Normand, PhD

All technology has limitations, some of which are not recognized at the time of introduction. Once adopted, technology may be challenged as to whether the initial promise of patient benefit demonstrated in clinical trials has been achieved in the setting of routine practice. This challenge is the objective of observational studies. Among interventional cardiologists, the jury on drug-eluting stents is still out.

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Progress has not been linear for coronary stenting technology. The introduction of 2 new stents that largely prevented the problem of restenosis was met by an explosive adoption of these techniques by physicians and requests by patients. Within the first 8 months of introduction in Massachusetts, the rate of drug-eluting stents (DES) as a proportion of total stent procedures reached 90%. However, reports of late adverse events and stent thrombosis, a rare but morbid event, raised alarm in patients and prompted caution from regulators and physicians. The net outcome has been a return to increased use of bare-metal stents, with DES use decreasing to 64% in the United States (Millenium Research Group, Waltham, Mass, written communication, 2007).

The benefits of restenosis prevention observed in randomized trials comparing DES to bare-metal stents were far greater in magnitude than many other incremental changes in medicine. Relative reductions in the need for repeat procedures to treat restenosis reached 75% to 80%, a larger jump forward than that achieved with the introduction of bare-metal stents to replace balloon angioplasty. Although the composite end points in the pivotal trials of drug-eluting stents included myocardial infarction and death and patients were followed for 5 years after stenting, the trials were not powered to detect harm in these important end points.

What Randomized Trials Tell Us

Some have voiced concern that the trials leading to DES approval did not anticipate the broad adoption of these stents. Like most randomized trials, the approval studies that supported the safety and efficacy of DES enrolled a narrow population of patients undergoing single-vessel stenting in stable or unstable angina. However, numerous reports have since demonstrated the use of drug-eluting stents outside of the parameters tested in these trials (off-label use); these off-label uses represent about half of current practice.

Randomized trials are carefully designed experiments that vary only one condition between groups: the assigned treatment. It is appropriate that human studies begin within populations that are well-understood; in this case, it was a patient population that had been well-characterized in the era of bare-metal stents: those undergoing single-vessel treatment of de novo coronary stenoses. An attempt to include all patients in initial studies could have the unintended consequence of masking either benefit or harm by combining heterogeneous effects of treatment.

The deficits of this initial strategy are generalizability and power. Additional randomized trials may seek to address benefits and risks in some of the excluded subgroups or to define adjunctive therapy, but observational studies are necessary to understand the ultimate questions of risk and benefit across the full range of practice.

What Observational Studies Tell Us

A well-conducted observational study can provide valuable information regarding adoption rates and risks and benefits of new technologies. Because randomized trials are (appropriately) confined to both narrow patient populations and narrow physician populations, the expectation of similar rates of treatment benefits and safety profiles in the usual care setting is unrealistic. The strong external validity of observational studies, however, is pitted against their weaker internal validity: Patients are not randomized to stent types. This is an old and familiar problem. Researchers can utilize a variety of techniques to bolster the internal validity of observational studies. These include the use of different design adjustments: cross-sectional designs; use of multiple comparison groups; propensity-score adjustment (such as matching, stratifying, or weighting end points by the estimated propensity score); and landmark analyses. These strategies work only to the extent that additional adjustment methods balance the groups on the basis of observable confounders. For example, the more the treatment selection depends on physician and patient factors, the more susceptible the analysis is to bias.

Analytical adjustments can be used to make the treatment groups more comparable. These include regression adjustment (such as the use of a Cox or logistic regression model); propensity-score adjustment (such as matching, stratifying, or weighting end points by the estimated propensity score); and instrumental variables adjustment. Standardized data collection tools and complete follow-up are required to minimize bias. Because of the inability to rule out unmea-

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sured confounders, a sensitivity analysis that measures how much unmeasured confounding must exist to refute the findings must be performed.

Another Piece of the Puzzle
In the present issue of Circulation, Hannan and colleagues attempt to answer a fundamental question for current DES technology: Have outcomes improved since their introduction? The authors compare 2 time periods: one before the introduction of DES and one after. Controlling for measured confounders (patient, anatomic, and hospital characteristics) with a Cox proportional hazards model, they report that patients in the DES era had lower rates of death and myocardial infarction and of repeat revascularization than patients in the prior era.

The empirical strategy adopted by the authors avoids directly estimating the association between DES and coronary artery stenting outcomes. Rather, the authors suggest that the improved outcomes in the post-DES period compared with the pre-DES period are due to DES in addition to other factors. Their statistical approach is somewhere between an “ecological approach” and an “instrumental variables (IV) approach.” An instrument is a variable that is predictive of treatment assignment but not predictive of the outcome once treatment is taken into account. Intuitively, an instrumental variables estimate of the treatment effect is the difference in mean outcomes between treatment groups divided by the difference in the fraction of patients predicted by the instrument to receive DES in both treatment groups.

On the one hand, Hannan and colleagues are almost using time as an instrument that predicts DES use. They assume the second component in the denominator, the probability of receiving a DES in the pre-DES era, is 0 (which is sensible). However, they never report the proportion of patients receiving DES in the post-DES era, nor do they divide the mean outcome differences by the differences in predicted DES use. The reason to re-scale the numerator is to appropriately allocate the DES effect to patients for whom there is some variation in their propensity to receive a DES. Such patients are referred to as marginal patients. These are patients whose medical, demographic, and anatomic characteristics are such that they would receive a DES in the post-DES era but would have received a BMS in the pre-DES era, even if a DES had been available; that is, in these cases, the treatment assignment depends entirely on the instrumental variable (time in this case). In some sense, the marginal patients correspond to those who could be randomized to either treatment strategy.

On the other hand, the authors are basically using blocks of time, that is, DES eras, to characterize 2 different populations by DES penetration rates. This approach is similar to ecological analyses where outcomes are compared between 2 geographic areas with different treatment penetration rates. The usual problems with ecological analyses apply here; the relative benefit attributable to DES as compared with other concomitant changes in medical practice (eg, duration of dual-antiplatelet therapy or treatment of hyperlipidemia) was not assessed. Hannan and colleagues are appropriately cautious in interpreting their findings. Regardless, the study by Hannan and colleagues gives the holistic conclusion that outcomes have improved since the introduction of DES.

Are there alternative explanations for this conclusion? Yes. First, changes in medical therapy over the time period were not taken into account. Both the requirement of extended clopidogrel use for patients with DES and the concomitant realization of benefit in acute coronary syndromes was likely a cause for longer durations of clopidogrel therapy in the later period, although not measured in the study. Second, there may have been differences in patients treated with percutaneous coronary interventions over the 2 time periods that cannot be accounted for by regression modeling that assumes linearity of measured confounders. A nonlinear difference in the types of patients referred for percutaneous coronary intervention between the time periods, whether more complex or less, would further confound the relationship between time and outcomes. To better understand the improvement in outcomes after percutaneous coronary interventions in New York reported by Hannan et al, it would be helpful to understand whether certain groups of patients were more or less likely to receive percutaneous coronary intervention over time.

Are Drug-Eluting Stents Getting a New Look?
Overall, although performed in different locations and with different methods, recent observational studies have shown reassuring results; in general, the prevention of restenosis promised by the randomized trials is evident in clinical practice and does not come at the expense of an increase in death or myocardial infarction compared with bare-metal stenting (Table). Although an early report from Sweden was a cause for alarm, the findings of increased late death associated with DES have been more recently reversed after more follow-up in the same study. The results from several other independent population-based studies across North America and Europe comparing the effect of DES on outcomes at 2 years have shown both no increase in death and preserved restenosis benefit.

Conclusion
Dramatic shifts in DES usage relative to bare-metal stents have occurred since their introduction in 2003. This suggests that the vast proportion of cardiologists and interventional cardiologists are responding to reports that have punctuated the past 5 years, some of which have been borne out in longer-term follow-up and some of which have been reversed. Although no single method to design or analyze data is correct, some methods may be weaker than others. Rather than having each individual choose the study that suits what he or she expects to be the truth regarding DES, well-designed randomized and observational studies must respond to the demand for greater knowledge regarding the safety of drug-eluting stenting and coronary intervention. To be sure, we need to continue to ask questions about this technology and the newer iterations to the concept. As technology improves, the questions become more refined, moving beyond restenosis to understanding of late events and to appreciation of the implications of adopting new technology in the general population.
Table. Observational Studies of DES, 2006 to 2007

<table>
<thead>
<tr>
<th>Study</th>
<th>Location</th>
<th>Total N</th>
<th>DES n (%)</th>
<th>Exclusion Criteria</th>
<th>Main End Points</th>
<th>Completeness of Follow-Up</th>
<th>Groups Compared</th>
<th>Adjustment Method</th>
<th>Treatment Difference Between DES and BMS</th>
</tr>
</thead>
<tbody>
<tr>
<td>Mauri et al, 200727</td>
<td>All Massachusetts non-federal acute care hospitals</td>
<td>17 726</td>
<td>11 516 (65)</td>
<td>Treatment with both DES and BMS</td>
<td>Death, MI, or any revascularization at 2 years</td>
<td>100% at 2 years for mortality</td>
<td>DES vs BMS, concurrent, April 2003 through December 2004</td>
<td>Propensity score–matched analysis</td>
<td>Rate differences: death, –2.5% [−3.6%, −1.3%]; MI, −1.8% [−2.8%, −0.7%]; revascularization: −5.4% [−6.9%, −3.9%]</td>
</tr>
<tr>
<td>Williams et al, 200619</td>
<td>Selected US hospitals</td>
<td>6906</td>
<td>6509 (94)</td>
<td>Inability to provide informed consent</td>
<td>Composite death + MI; TVR at 1 year</td>
<td>89.6% at 1 year</td>
<td>DES vs BMS, concurrent, January through June 2005</td>
<td>Cox proportional hazards adjustment</td>
<td>Adjusted hazard ratio: death + MI, 0.74 [0.52, 1.07]; TVR, 0.58 [0.40, 0.83]</td>
</tr>
<tr>
<td>Lagerqvist et al, 200721</td>
<td>Sweden</td>
<td>19 771</td>
<td>6033 (31)</td>
<td>None reported</td>
<td>Composite death + MI to 3 years*</td>
<td>18% DES; 33% BMS at 3 years*</td>
<td>Any DES vs BMS (patients with both were classified as DES), concurrent, January 1, 2003 through December 31, 2004</td>
<td>Propensity score regression adjustment</td>
<td>Adjusted relative risk: death: 1.18 [1.04, 1.35]; death and MI after 6-mo landmark, 1.2 [1.05, 1.37]</td>
</tr>
<tr>
<td>Tu et al, 200722</td>
<td>Ontario</td>
<td>13 353</td>
<td>5106 (38)</td>
<td>PCI in the past 1 year; left main disease; treatment with both DES and BMS</td>
<td>Death, MI, and TVR at 2 years</td>
<td>100% at 1 year, 74% and 72% for DES and BMS at 2 years, respectively, for mortality</td>
<td>DES vs BMS, concurrent, December 1, 2003 through March 31, 2005</td>
<td>Propensity score matching</td>
<td>Rate differences: death: −2.2% (P&lt;0.001); MI, 0.5% (P&lt;0.95); TVR, –3.3% (P&lt;0.001)</td>
</tr>
<tr>
<td>Jensen et al, 200723</td>
<td>Western Denmark</td>
<td>12 395</td>
<td>3548 (29)</td>
<td>Treatment with both DES and BMS</td>
<td>Death, MI, and ST at 15 months</td>
<td>100%</td>
<td>DES vs BMS, concurrent, January 1, 2002 through June 30, 2005</td>
<td>Cox proportional hazards adjustment</td>
<td>Hazard ratio: death, 0.90 [0.75, 1.29]; MI, 1.14 [0.89, 1.45]; ST, 0.91 [0.67, 1.24]</td>
</tr>
<tr>
<td>Marzocchi et al, 200724</td>
<td>Emilia, Romagna, Italy</td>
<td>10 629</td>
<td>3064 (29)</td>
<td>Treatment with both DES and BMS, STEMI</td>
<td>Death, MI, TVR, and ST at 2 years</td>
<td>100% for included patients for mortality</td>
<td>DES vs BMS, concurrent, July 2002 through June 2005</td>
<td>Propensity score matching</td>
<td>Risk differences: death, −0.6% (P&lt;0.35); MI, −0.5% (P&lt;0.46); TVR, –3.8% (P&lt;0.0001); ST, 0.4% (P&lt;0.09)</td>
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<tr>
<td>Abbott et al, 200725</td>
<td>Selected US centers</td>
<td>3223</td>
<td>1460</td>
<td>Death, MI, or any revascularization at 1 year</td>
<td>96% for DES, 83% for BMS at 1 year</td>
<td>DES vs BMS, nonconcurrent; DES: February through May 2004, BMS: October 2001 through March 2002</td>
<td>Cox proportional hazards adjustment</td>
<td>Hazard ratio: death, 0.97 [0.66, 1.43]; MI, 1.02 [0.73, 1.43]; revascularization, 0.38 [0.25, 0.60]</td>
<td></td>
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BMS indicates bare-metal stent; MI, myocardial infarction; TVR, target vessel revascularization; ST, stent thrombosis; and STEMI, ST-segment myocardial infarction. Values in brackets are 95% confidence intervals.

*Estimated from reported numbers at risk and numbers of deaths.

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