Late Follow-Up From RAVEL
Transition From Intention to Observation

Warren K. Laskey, MD

The astonishing, sometimes dismaying, pace with which drug-eluting stents (DES) have made the transition from their bench origins\(^1,2\) to proof of principle,\(^3\) hypothesis testing,\(^4\)–\(^6\) and now routine clinical practice\(^7\) leaves even the least skeptical among us breathless. With each new advance, however, we should not lose sight of the fundamental elements of evidence-based clinical practice: “Does it work?” and “Is it safe?” It is equally astonishing and dismaying to realize the enormous investments in time, money, and sheer hard work that are required to adequately answer these deceptively simple questions. Using the RAVEL trial (Randomized Study with the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with de Novo Native Coronary Artery Lesions) as a model, I attempt here to outline the essentials for understanding how answers to these questions are provided, or not provided.

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As for the first element—“Does it work?”—the following questions must be addressed: What is being measured? With what is it being compared? What is the magnitude of the treatment effect? What is the relationship between time and treatment effect?

In the RAVEL trial,\(^4\) the primary measure of efficacy was the angiographically assessed late lumen loss at 6 months, and a convincing case was made for the superiority of the sirolimus-eluting stent as compared with the bare metal stent (BMS). A secondary measure of efficacy (the RAVEL study was designed and powered to address the angiographic end point), target lesion revascularization (TLR) rate at 1 year, confirmed the superiority of the DES (sirolimus-eluting stent TLR rate, 0%; BMS TLR rate, 23%) with a treatment effect (ie, difference in the end points) of 23%. Intuition tells us that these 2 measures of efficacy (angiographic and clinical) should be closely correlated, but the degree of association is less than precise and confounded by bias, a bias that stems from the requirement for mandatory angiography.\(^8\)

The true treatment effect in a population is always unknown and is only approximated by the observed treatment effect in the samples studied. That uncertainty, coupled with the between-study variation in recently published DES studies (Table),\(^4\)–\(^6,9,10\) leads to a disquieting imprecision in this critical measure.

That a similar phenomenon occurs over the long term, in which variation in clinical practice is uncontrollable, can be seen in the long-term follow-up report from the RAVEL trial in this issue of Circulation.\(^11\) By 3 years, the TLR treatment effect was either 18.7% (for all TLRs) or 9.2% (for clinically driven TLRs). Clearly, if the former rate is cited, then one would have to conclude that only modest loss of treatment effect has occurred over time. If, however, the latter rate is cited, then the treatment effect is attenuated over time.

The treatment effect—the absolute difference in event rates—varies with the underlying risk (in this instance, for repeat revascularization) in the study population. A low-risk population will be manifest by low overall event rates and a small absolute difference between treatment arms. Conversely, a high-risk population will be manifest by considerably higher overall event rates and a larger absolute difference, assuming that the increase in risk in each arm is proportionate. If, however, the increase in risk is disproportionate despite the best efforts of randomization to maintain equality, then the true measure of the treatment effect is again unclear. In the SIRIUS trial (Sirolimus-Eluting Balloon Expandable Stent in the Treatment of Patients With De Novo Native Coronary Artery Lesions), in which a higher-risk patient population underwent either DES or BMS implantation,\(^9\) the difference in the clinically driven TLR rates was 15% at both 1 year\(^9\) and 2 years\(^12\). The SIRIUS patients were at “higher risk,” although the TLR rate in the BMS group was lower than the TLR rate in the BMS group of the “low-risk” RAVEL population. Thus, it is essential to understand the vagaries of control arm rates before assigning meaning to the difference in rates.

Finally, it is essential to remind readers that whatever consistency may or may not exist between pivotal randomized trials, these measures of efficacy likely will differ from real-world data, in which the uncontrolled interplay of patient, operator, and device rule the day. Carefully designed, long-term observational studies derived from the pivotal trials, as well as from unselected, consecutive patients undergoing stent implantation, may provide more meaningful estimates of effectiveness, not only by virtue of their size but also as a result of more clinically relevant event rates. The obvious limitation of the latter, however, is the absence of a comparator; hence, the fundamental importance of reliable long-term data from the BMS era.\(^13,14\) Notably, the repeat revascularization rate in the National Heart, Lung, and Blood Institute’s (NHLBI) Dynamic Registry (from the pre-DES era) is available at http://www.circulationaha.org

DOI: 10.1161/01.CIR.0000157895.19538.0B
Comparative Target Lesion Revascularization Rates at ≤1 Year

<table>
<thead>
<tr>
<th>Study</th>
<th>DES Arm, %</th>
<th>BMS Arm, %</th>
<th>Treatment Effect, %</th>
</tr>
</thead>
<tbody>
<tr>
<td>RAVEL (1 y)</td>
<td>0</td>
<td>22.9</td>
<td>23</td>
</tr>
<tr>
<td>SIRIUS (9 mo/1 y)</td>
<td>4.1/4.9</td>
<td>16.6/20.0</td>
<td>12.5/15.1</td>
</tr>
<tr>
<td>TAXUS (9 mo)</td>
<td>3.0</td>
<td>11.3</td>
<td>8.3</td>
</tr>
<tr>
<td>RESEARCH registry (1 y)</td>
<td>5.1</td>
<td>10.9</td>
<td>5.8</td>
</tr>
</tbody>
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era) is 24.2% at 3 years (F. Selzer, PhD, unpublished data, 2004) and is in remarkable agreement with the 3-year all-TLR rate in the BMS arm of RAVEL.4

Concordant with our understanding of the mechanism and timing of in-stent restenosis, the treatment effect with DES should be most apparent by 6 months. In this regard, the data from RAVEL are exactly what we would expect and are in qualitative agreement with other DES trial data.5,6 The report from the RAVEL investigators in this issue of *Circulation* extends the period of observation to 3 years and provides important insight into the timing of the treatment effect, as well as our understanding of the determinants of the duration of effect. The characteristic separation in DES and BMS survival curves by 180 days supports the former, whereas the (almost) parallel trajectories from 1 through 3 years speak to the preserved duration of treatment effect, notwithstanding the caveats discussed earlier with regard to the true magnitude of the treatment effect. Notably, little evidence can be found of “creep” or “time shift”—early concerns about this technology—in which restenosis is delayed rather than abrogated. A statistically significant difference between these time-dependent outcomes refers to the overall difference between curves. Not commented on by Fajadet et al11 is the virtually flat character of the BMS TLR curve, which speaks to the inherently low-risk (for restenosis) population in the RAVEL trial.

To address the second element—“Is it safe?”—the following questions must be answered: What is the most clinically meaningful measure of safety? What are the determinants of this measure of safety? How precisely can we assess safety given the first 2 questions? Does short-term safety ensure long-term safety?

Traditional measures of safety in interventional cardiology include freedom from in-hospital major adverse clinical events (MACE) and MACE rates varying from 6 to 9 months. The inclusion of all-cause mortality, procedure-related myocardial infarction, and nonelective coronary bypass surgery have served us well during the past 20 years; however, the arrival of pharmacological—or biological—stent ensembles requires a more focused metric that includes low-frequency, albeit serious, adverse events and longer observation times. The latter is necessary given the number of permutations of drug or biological stent combinations without sufficient phase II clinical data and the unreliability of extrapolating from preclinical studies to humans. Furthermore, the competing risk from the underlying disease is a critical confounding variable in any analysis of long-term outcomes, particularly safety. Therefore, detailed characterization of the study population is of fundamental importance in interpreting event rates over the long term.

The long-term data from RAVEL published in this issue of *Circulation* provide some reassurance about the safety of the sirolimus DES and, as in the case of efficacy, some insight into the interpretation of long-term safety data in the DES era.11 The separation of the DES and BMS MACE-free survival curves mirrors the efficacy analysis—an increase in MACE that is evident by 6 months (reflecting repeat revascularization) and then remains relatively flat to the 3-year point. What is encouraging is the apparent lack of any signal in the DES group of late MACE. The benign nature of underlying disease progression in this population is nowhere more evident than in the decidedly flat character of the MACE-free survival curve in the BMS patients. This aspect directly relates to the generalizability of the findings from RAVEL to the real world, where recurrent adverse events >1 year after percutaneous coronary intervention reflect the inexorable progression of coronary heart disease.14,15 Whether the latter observations hold in the current era of unrestricted DES use in clinical practice is unknown. The absolute difference in these rates over the long term likely will reflect the severity of the underlying disease (ideally, but not assuredly, balanced by the randomization process). Differences in disease management strategies between clinical trials and usual practice will limit extrapolation from small-scale, randomized, controlled studies to the real world. It is, however, reassuring that at 3-year follow-up, the MACE rate in the NHLBI Dynamic Registry (34.9%; F. Selzer, PhD, unpublished data, 2004) is in agreement with the MACE rate in the BMS arm of RAVEL (33.1%).

Are these long-term data from RAVEL a best-case scenario? Indeed they are, for all of the reasons mentioned above. Does this limit their generalizability? Curiously, only somewhat. The agreement between the RAVEL BMS data and the NHLBI Dynamic Registry data is both striking in the level of agreement and puzzling given the vastly different patient populations investigated. Despite its small sample size, delimitied angiographic end point, and short-term primary end point assessment, RAVEL and its long-term outcomes serve as a reliable bridge between the world of clinical trials and the real world. Perhaps this bridge supplies additional support for the powerful treatment effect of sirolimus. As suggested in a recent *Circulation* editorial,16 however, the improved and expanded surveillance of real-world DES use (and nonuse) along with the collection of critical patient-level data will enable us to answer the deceptively simple questions posed above.

References


**KEY WORDS:** Editorials ■ stents ■ trials ■ revascularization ■ restenosis
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_Circulation_. 2005;111:958-960
doi: 10.1161/01.CIR.0000157895.19538.0B
_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/111/8/958

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