Bringing Reality to Drug-Eluting Stents

David P. Faxon, MD

"Nothing ever becomes real till it is experienced"
—John Keats (1795–1821), letter to George and Georgiana Keats, March 19, 1819

The introduction of drug-eluting stents has unquestionably been one of the most important advances in interventional cardiology during the past decade. The impact has already been profound, despite the release of the first drug-eluting stent, the Cypher stent (Cordis Corp), in the United States earlier this year. Practitioners are now using these devices for a wide variety of clinical and anatomic situations, many of which have not been specifically studied. Many have expressed concerns about the widespread use of these devices in real practice situations because clinical experience might be significantly different from that reported in the randomized clinical trials that led to the devices' approval.

See p 190

The principal advantage of drug-eluting stents has been the substantial reduction in the incidence of in-stent restenosis. Until recently, the clinical experience has been largely confined to the sirolimus-coated Bx Velocity stent (Cypher stent). Sirolimus (rapamycin) is a macrolide antibiotic discovered on Easter Island.1 The agent is now recognized to activate the kinase target of rapamycin (TOR), which subsequently inhibits cyclin-induced transition from G0 to G1 cell cycle, thus preventing cell division. It also has potent antiinflammatory effects. The initial randomized clinical trial, RAVEL (Randomized study with the sirolimus-eluting Bx VElocity balloon-expandable stent), evaluated 238 patients with de novo single lesions.2 The restenosis rate at 6 months (>50% stenosis) was an astounding 0% in the sirolimus-eluting stent (SES) group, compared with 26% in the bare metal stent group. Subsequently, the larger SIRIUS trial (multicenter randomized double-blind study of the SIRollImUS-coated Bx Velocity stent in the treatment of patients with de novo coronary artery lesions) studied 1058 patients, including patients with more complex disease.3 This pivotal trial demonstrated that SES reduced target vessel failure from 21% to 8.9%. Benefit was shown for higher-risk subgroups, such as those with long lesions, small vessels, or diabetes. The subsequent E-SIRIUS (the European randomized trial) (n = 352)4 and C-SIRIUS (the Canadian randomized trial) (n = 100)5 used a similar protocol and also demonstrated benefit in patients with even longer lesions and smaller vessels. The combined study (NEW-SIRIUS) reported a 5.1% in-lesion restenosis rate. These reports led to the approval of SES in the United States and Europe, and to date, >250 000 stents have been implanted.

Clinicians have embraced the concept of drug-eluting stents, particularly with the recently reported results from the Treatment of de novo coronary disease using a single paclitAXel-elUtng Stent IV (TAXUS IV) study, in which the drug paclitaxel was used. In this multicenter randomized trial, 1314 patients were randomized to a paclitaxel-eluting stent or a bare metal stent, with a reduction in restenosis from 26.6% with bare metal stents to 7.9% for the TAXUS stent.6 The US Food and Drug Administration (FDA) panel has recently recommended approval, and the device should be available in the United States shortly. A growing number of randomized trials are currently ongoing, evaluating a variety of pharmacological agents directed toward inhibition of cell cycle and/or inflammation.7–8 It is extremely likely that we will have a number of drug-eluting stents available in the near future. At present, the results of randomized clinical trials are sufficiently convincing for us to be certain that drug-eluting stents have found a place in the armamentarium of the interventional cardiologist. The consistent results of sirolimus and paclitaxel drug-eluting stents are remarkable and have led many to suggest that all patients who require stenting should receive these devices. The only major constraint to doing so at the present time is cost.9–11 With the approval of additional devices in the future, cost is likely to go down. Although there is no doubt that the results of these trials are impressive, it is critical to realize that randomized clinical trials rarely mimic clinical practice. The pivotal SIRIUS trial included only patients with single-lesion intervention on lesions in vessels between 2.5 and 3.5 mm in diameter and from 5 to 30 mm in length. No patients with acute myocardial infarction, severe unstable angina (Braunwald class III or IV), or chronic renal failure were included. Lesions in saphenous vein grafts, bifurcation lesions, total occlusions, and in-stent restenotic lesions were also excluded from the study. Thus, many of the clinical and anatomic features that commonly occur in most interventional practices were not reflected in this clinical trial because of these and other exclusions. The National Heart, Lung, and Blood Institute (NHLBI) has sponsored a comprehensive registry that has been monitoring the progress of angioplasty since 1977. The most current registry, the Dynamic Registry, involves 26 clinical centers. All patients undergoing percutaneous coronary intervention (PCI) at each center are included in this registry, and 3 separate waves of
Comparison of SIRIUS and the Research and Dynamic Registries

<table>
<thead>
<tr>
<th></th>
<th>SIRIUS¹</th>
<th>Research³</th>
<th>Dynamic Registry²</th>
</tr>
</thead>
<tbody>
<tr>
<td>No. of patients</td>
<td>556</td>
<td>508</td>
<td>2109 (Wave 2)</td>
</tr>
<tr>
<td>Any stent</td>
<td>100%</td>
<td>100%</td>
<td>70%</td>
</tr>
<tr>
<td>% SES</td>
<td>100%</td>
<td>100%</td>
<td>0%</td>
</tr>
<tr>
<td>Clinical, %</td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>UA</td>
<td>NA</td>
<td>37</td>
<td>42</td>
</tr>
<tr>
<td>AMI</td>
<td>0</td>
<td>18</td>
<td>25</td>
</tr>
<tr>
<td>DM</td>
<td>24</td>
<td>16</td>
<td>28</td>
</tr>
<tr>
<td>Anatomic, %</td>
<td></td>
<td></td>
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</tr>
<tr>
<td>MVD</td>
<td>40</td>
<td>48</td>
<td>58</td>
</tr>
<tr>
<td>SVG lesion</td>
<td>0</td>
<td>2.5</td>
<td>8</td>
</tr>
<tr>
<td>Bifurcation lesion</td>
<td>0</td>
<td>16</td>
<td>14</td>
</tr>
<tr>
<td>Thrombus laden lesion</td>
<td>0</td>
<td>NA</td>
<td>19</td>
</tr>
<tr>
<td>Ostial lesion</td>
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<td>NA</td>
<td>8</td>
</tr>
<tr>
<td>Calcified lesion</td>
<td>0</td>
<td>NA</td>
<td>24</td>
</tr>
<tr>
<td>Total occlusion</td>
<td></td>
<td></td>
<td>12</td>
</tr>
<tr>
<td>In-stent restenosis</td>
<td>0</td>
<td>0</td>
<td>11</td>
</tr>
<tr>
<td>No. lesions treated/patient</td>
<td>1</td>
<td>NA</td>
<td>1.4</td>
</tr>
</tbody>
</table>

Excluded in SIRIUS: in-stent restenosis, SVG lesion, nonstenented lesions, multivessel PCI, ostial lesions, thrombus-containing lesion, calcified lesions, and ejection fraction <25%. Excluded in Research: In-stent restenosis and nonstenented lesions. Excluded in the Dynamic Registry: None. UA indicates unstable angina; AMI, acute myocardial infarction; DM, diabetes mellitus; MVD, multivessel disease; and SVG, saphenous vein graft.

≈2000 patients have been studied over the past 6 years. In a recent report of waves 1 and 2, these and other exclusionary features were present in at least 50% of the patients undergoing contemporary PCI¹² (Table). This is also true for the most current wave of 2141 patients collected between October 2001 and March 2002 (K. Detre, MD, PhD, unpublished data, 2003). Although exclusion from randomized trials leads to a more homogenous study group, it also frequently excludes those at the highest risk for complications and those who are least likely to show benefit. This is an extremely common and potentially serious problem with many randomized trials.

The report from the Research Registry in the present issue of Circulation goes a long way in reassuring the practitioner that drug-eluting stents are in fact safe and effective in a wide variety of patients undergoing “real-world” angioplasty.¹³ In this registry, 508 consecutive patients with de novo lesions treated with SES were compared with 450 patients treated with bare metal stents before the routine introduction to SES at a single center. The short- and long-term outcomes parallel those reported in the randomized trials, with a 1-year major adverse cardiac event rate of 9.7% in the SES group versus 14.8% in the bare metal stent group and a target vessel revascularization rate of 3.7% versus 10.9%, respectively. The patient characteristics are remarkably similar to those seen in the Dynamic Registry. Notably, patients with an acute myocardial infarction were included in the Research Registry. In the Dynamic Registry, these patients composed 25% of patients undergoing a PCI. The use of SES in acute myocardial infarction in the Research Registry has been a subject of a previous report in Circulation that showed SES to be safe and effective in this setting.¹⁴ Some differences between the two Registries are apparent. First, only patients receiving a stent were included in the Research Registry. In the Dynamic Registry, 30% did not have a stent, largely because of a very small vessel diameter. Also, only de novo lesions were selected for the Research Registry. In the NHLBI Dynamic Registry, 10% of cases involved the treatment of in-stent restenotic lesions and 7% the treatment of saphenous vein graft lesions. A higher percentage of patients with acute coronary syndromes, diabetes, and multivessel/multilesion angioplasty was seen in the Dynamic Registry. Unfortunately, we still need considerably more information on groups of patients who are at high risk for complications or restenosis, such as patients with insulin-dependent diabetes, lesions in saphenous vein grafts, thrombus-laden lesions, bifurcation lesions, ostial lesions, unprotected left main lesions, and total occlusions. Small preliminary reports do suggest benefit in most of these subgroups, but much larger numbers of patients need to be studied, and longer follow-up is necessary for practitioners to be confident about the safety and efficacy of these devices in all situations.¹⁵–¹⁸

Although randomized trials are essential to establish efficacy, great value can be obtained from a properly conducted registry. The current postmarketing survey process used by the FDA is inadequate in this regard. Even monitoring serious complications is difficult, because it relies heavily on voluntary reporting from physicians. Recently, two FDA public notifications have warned physicians of subacute thrombosis and hypersensitivity reactions with the use of the Cordis Cypher Coronary Stent.¹⁹ As of October 20, 2003, ≥290 occurrences of subacute stent thrombosis (SAT) have been reported, and >60 patients have died. Although this is cause for concern, it is important to note that there have been ≥250 000 stents placed, leading to an overall rate of subacute stent thrombosis of ≈1%. This incidence is within the expected range of SAT for bare metal stents. The randomized trials also did not see any excess rate of SAT, and the Research Registry has not reported an increased incidence. However, it is not certain that all events have been reported to the FDA, and the details of the individual patients have not been fully analyzed to determine if procedural, patient, or device factors were responsible. Clearly, a better reporting system, or preferably, a national database for new devices with careful prospective collection of data should be established. This would allow rapid identification of problems and offer the ability to clearly understand the nature of the problems and factors responsible for them. In addition, it would allow careful monitoring of practitioners’ use of these devices in real-world patients. Although the Research Registry, the ongoing Wisdom Registry, and the E-SIRIUS Registry are helpful, they are not designed to collect information on all patients whether they had a drug-eluting stent or not.²⁰–²¹ Inclusion of all consecutive patients allows a better understanding of who does and who does not get the device. In addition, the quality of the data in this type of voluntary registry is unknown. Isn’t it time to seriously consider instituting such a system to collect real-world experiences?
National organizations such as the American College of Cardiology have set up a national database, and the NHLBI is funding the continuation of the Dynamic Registry. This will help, but a mandatory FDA requirement for such a registry, run by the NHLBI, for all new devices would greatly improve our understanding and use of these new treatments. Technology is advancing at such a rapid pace, particularly in the field of interventional cardiology, that the need for such a system is greater than at any time in the past. The time to make this happen is now.

References

Key Words: Focused Perspectives • drugs • stents • restenosis
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