EDITORIAL

Second-Generation Drug-Eluting Coronary Stents

Richard A. Lange, M.D., and L. David Hillis, M.D.

Percutaneous coronary intervention (PCI) is usually performed with drug-eluting stents; since the introduction of these stents in 2002, more than 2 million have been implanted worldwide. Drug-eluting stents are metal stents that are coated with a polymer containing an antiproliferative agent, which is released gradually over the course of weeks to months after the stent is inserted, thereby providing sustained inhibition of the neointimal proliferation (the process that is responsible for restenosis) that occurs as a result of vascular injury. First-generation drug-eluting stents, which released sirolimus or paclitaxel, were shown to be superior to bare-metal stents and to balloon angioplasty in reducing the magnitude of neointimal proliferation, the incidence of clinical restenosis, and the need for reintervention.[1,2]

Unfortunately, late stent thrombosis (i.e., thrombosis that occurs 30 days or more after implantation of the stent) is more likely to occur with drug-eluting stents than with bare-metal stents.[1] The gradual release of the antiproliferative agent effectively inhibits endothelialization of the stent struts, thereby allowing them to continue to serve as a nidus for platelet aggregation and thrombus formation. Angioscopic assessment in humans 3 to 6 months after stent deployment showed that bare-metal stents were completely endothelialized, whereas 87% of drug-eluting stents were not, and in 50% of the drug-eluting stents, thrombi were visible.[3] Postmortem studies conducted 40 months after the placement of a drug-eluting stent showed that there was poor endothelialization in 45% of the cases.[4] Although the risk of stent thrombosis with drug-eluting stents is relatively small (0.5 to 3.1%), its occurrence is unpredictable, does not diminish with the passage of time, and is often catastrophic, with fatal myocardial infarction occurring in up to 65% of patients in whom it occurs.[5]

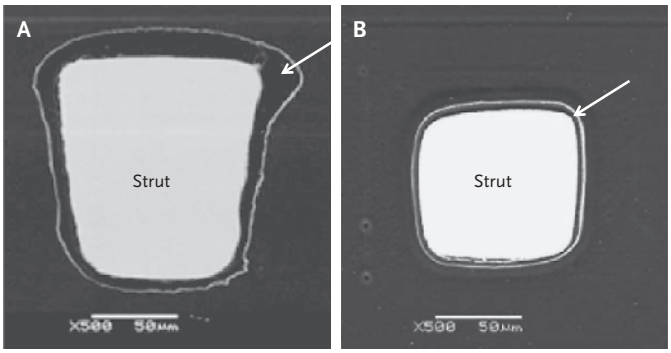
Second-generation drug-eluting stents are designed to provide better stent deployment, safety, and efficacy. In this issue of the *Journal*, Stone et al. show that a second-generation everolimus-eluting stent is superior to a first-generation paclitaxel-eluting stent in preventing the clinical manifestations of stent thrombosis and restenosis (i.e., a composite end point of cardiac death, target-vessel myocardial infarction, or ischemia-driven target-lesion revascularization) — so-called target-lesion failure.[6] Specifically, the use of an everolimus-eluting stent as compared with a paclitaxel-eluting stent resulted in a significantly lower incidence of stent thrombosis (0.3% vs. 1.1%), myocardial infarction (1.9% vs. 3.1%), and target-lesion revascularization (2.5% vs. 4.6%).

Why are second-generation drug-eluting stents more effective than their older counterparts? They differ from the first-generation stents with respect to the antiproliferative agent, the polymer layer (which acts as a reservoir for controlled drug delivery), and the stent frame.[7] With the newer drug-eluting stents, everolimus, a semisynthetic sirolimus analogue, is released from a thin coating of a biocompatible fluoropolymer on a flexible cobalt–chromium stent frame with thin struts. In contrast, in the older drug-eluting stents, paclitaxel is released from a proprietary polymer coating affixed to a less flexible stainless steel stent with thicker struts (Fig. 1). It is not known which of these differences is responsible for the improved outcomes with the second-generation stent. Improved efficacy or delivery of the antiproliferative drug (everolimus) may result in less neointimal proliferation and restenosis than those

that occur with older drug-eluting stents. Improvements in stent structure may result in better stent apposition to the vessel wall, improved endothelialization (i.e., a thin stent strut elicits less neointimal proliferation and requires less endothelialization to cover the struts completely), and reduced platelet aggregation and thrombus formation, thereby reducing the incidence of stent thrombosis. Studies involving experimental animals have shown that everolimus-eluting stents are more rapidly and extensively endothelialized than are drug-eluting stents with thicker struts.[8] Since the individual contributions of stent platform, polymer, and drug to the superiority of the second-generation stents are unknown, the results of this study are not necessarily applicable to other drug-eluting stents, which may have different specific characteristics from those of the everolimus-eluting stents that were used in this study.

The results of the study by Stone et al. are remarkably similar to those reported in the recently published COMPARE study (ClinicalTrials.gov number, NCT01016041),[9] a single-center trial involving 1800 patients, in which the safety and efficacy of everolimus-eluting and paclitaxel-eluting stents were compared. Both studies showed that the everolimus-eluting stent as compared with the paclitaxel-eluting stent was associated with a significant reduction in the rates of early stent thrombosis, myocardial infarction, and target-vessel revascularization.

In the study by Stone et al., the everolimus-eluting stent, as compared with the paclitaxel-eluting stent, was associated with a reduction in the incidence of target-lesion failure in patients without diabetes mellitus (a 3.6-percentage-point reduction in absolute risk and a 53% relative risk reduction with everolimus-eluting stents), but did not have a significant effect in subjects with diabetes. Similar results were noted in a post hoc analysis of the data from the COMPARE study. Taken together, these data suggest that the mechanisms of restenosis or the response to antiproliferative agents, or both, may differ between patients with diabetes and those without diabetes. The fact that the everolimus-eluting stent was more effective than the paclitaxel-eluting stent in other patient groups in which target-lesion failure is more likely to occur (i.e., those with acute coronary syndromes, complex lesions, restenosis lesions, proximal coronary stenoses, smaller vessel lumen sizes, and longer lesions) suggests that patients with diabetes, for some reason, do not derive a demonstrable benefit from second-generation stents.



Strut thickness: 132 μm
Coating thickness: 19.6 μm

Strut thickness: 81 μm
Coating thickness: 7.8 μm

Figure 1. Scanning Electron Micrographs of a Paclitaxel-Eluting Stent and an Everolimus-Eluting Stent.

Shown are scanning electron micrographs of a cross-section of a paclitaxel-eluting stent strut (TAXUS Express, Boston Scientific) (Panel A) and an everolimus-eluting stent strut (XIENCE V, Abbott) (Panel B). As compared with the everolimus-eluting stent, the paclitaxel-eluting stent has a thicker strut and a thicker polymer coating (arrow). Reprinted from Doostzadeh et al.[7] with the permission of the publisher.

Should we abandon paclitaxel-eluting stents in favor of second-generation everolimus-eluting stents on the basis of the results of the study by Stone et al.? For patients without diabetes, an analysis of cost-effectiveness would help to determine whether the absolute reduction of 1 to 2 percentage points in myocardial infarction (mostly non–ST-segment elevation) and the absolute reduction of 2 to 3 percentage points in target-lesion revascularization associated with the more costly everolimus-eluting stent (which is approximately $300 more expensive than the paclitaxel-eluting stent) warrant its routine use. For patients with diabetes (who comprise 20 to 30% of patients undergoing PCI), the less expensive paclitaxel-eluting stent may be appropriate. Further studies are needed to determine whether second-generation stents are superior in reducing the incidence of stent thrombosis and myocardial infarction when antiplatelet therapy that is more effective than clopidogrel — that is, prasugrel — is administered.

Disclosure forms provided by the authors are available with the full text of this article at NEJM.org.

From the Department of Medicine, University of Texas Health Science Center, San Antonio.

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