

## EDITORIAL COMMENT

# A Generation 2.5 Drug-Eluting Stent?\*

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One might easily ask: “Do we really need another second-generation limus-eluting stent?”

To answer this question, one has to look at the limitations of first-generation drug-eluting stents (DES) and the improvements demonstrated with second-generation DES. The initial Cypher and Taxus products are remarkably effective in reducing the previous “Achilles’ heel” of stents—restenosis—although they are not perfect. For example, the 6-year freedom from target lesion revascularization recently reported for Cypher from the SIRIUS (Sirolimus-Eluting Stent in De Novo Native Coronary Lesions) trial was just over 10%, a 50% relative reduction compared with the bare-metal stent. Similar data at 5 years are available with the Taxus stent from the Taxus IV study. Admittedly, differences in revascularization are exaggerated somewhat

See page 977

due to early mandatory angiographic follow-up, and results for both stents are from a relatively low-risk population, reflecting 30% to 40% of stent usage today. Restenosis rates rise as lesion complexity increases. The principal limitation of these stents is the associated risk of stent thrombosis—the new “Achilles’ heel” of stents. In the low-risk patient populations noted earlier, the risk of Academic Research Consortium–defined definite plus probable stent thrombosis is approximately 1% in the first year, with a continued approximate 0.3%/year risk through at least year 4 to 5, but in certain patient populations it might be considerably higher (e.g., 3% in the first year for ST-segment myocardial infarction [1], or 0.4% to 0.6%/year continuing at least through 5 years the Bern/Rotterdam experience [2] in complex patients). Such stent thrombosis is fatal in 20% to 30% of patients and, when nonfatal, usually results in a substantial myocardial infarction. Stent thrombosis has been

linked to a variety of factors, some that relate to procedural technique (stent under expansion) or patient characteristics and others that are linked to delayed endothelial healing and inflammation resulting from the anti-restenosis agent and its accompanying polymer.

Current (U.S.) second-generation stents are the Medtronic Endeavor, Abbott/Boston Scientific Xience V/Promus, and Taxus Liberte stents. The Medtronic Endeavor stent is unique in that it uses the nondurable rapid release phosphorylcholine/2-methacryloyloxyethylpolymer phosphorylcholine polymer combination in conjunction with the antiproliferative agent zotarolimus. Likely due to the relatively brisk release of the active agent, this stent is intermediate between bare metal stents and other limus-eluting stents in terms of its capacity to reduce restenosis but at the same time seems likely to have less risk of stent thrombosis after the first 9 to 12 months. The Xience/Promus stent uses the durable polymer poly-vinylidene fluoride-hexafluoropropylene in conjunction with its limus agent, everolimus. Restenosis rates with this stent seem quite similar to that of the “gold standard” Cypher product, as does risk of stent thrombosis, although data from the truly large number of patients required to reduce the uncertainty about the point estimate of risk of stent thrombosis for this product do not yet exist. The Taxus Liberte stent is a relatively minor modification of the original Taxus Express stent, with a more closely knit stent structure leading to a more homogenous distribution of drug. This stent uses the durable polymer SIBS, polystyrene-*b*-isobutylene-*b*-styrene, in conjunction with the unique antiproliferative drug paclitaxel. This seems to improve target lesion revascularization in small vessels compared with the original Taxus stent. Long-term estimates of risk of stent thrombosis are not available, but it would seem unlikely that they differ substantially from the original Taxus stent. Some investigators have pointed to an apparent difference in rates of target lesion revascularization after 1 year in pivotal trials with somewhat similar patient populations (Endeavor 1.3%, Cypher 3.0%, Taxus 3.4% through 4 years), postulating chronic “irritation” from residual polymer and/or drug, but comparisons such as this are somewhat challenging because of changing concomitant drug use and lack of head-to-head randomized comparison. In addition to their anti-restenosis effects noted in the preceding text, all of these second-generation stents provide somewhat greater deliverability than either of the first-generation stents, and Xience V/Promus and TAXUS Liberte probably have similar safety to first-generation DES. True demonstration that Endeavor has a lesser risk of stent thrombosis must await the results of the large PROTECT study comparing the Endeavor and Cypher products (2-year data will not be available until early 2011).

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From a biologic standpoint, the Endeavor Resolute stent differs from the original Endeavor stent due only to its polymer and from other second-generation stents by virtue of its antiproliferative agent and its polymer. It is simplistic to think that all limus agents are the same—certainly they differ with regard to relative impact on the mammalian target of rapamycin (mTOR) antiproliferative and calcineurin pathways and lipophilicity, amongst other attributes. Compared with sirolimus, zotarolimus has comparable binding to FKBP12 (a prelude to binding mTOR) and, on a nanomolar basis, has somewhat less inhibition of smooth muscle proliferation and greater inhibition of concanavalin A-induced T cell proliferation and mixed lymphocyte response inhibition (3). At the doses used in the Cypher and Endeavor Resolute stents, both drugs are probably on the flat portion of their dose response curves with regard to smooth muscle cell/neointimal proliferation inhibition during the first few weeks after stent implantation. These agents also delay endothelial healing after DES placement, probably to a similar degree. It has been postulated that the carrier polymer on DES is at least partially responsible for the chronic inflammatory response that is sometimes seen (4). This has been attributed, with some conjecture, to the presence of irritants (solvents, residual monomers), hydrophobic/hydrophilic properties, and degradation products. The Endeavor Resolute polymer is a blend of 3 polymers, C19 (a mixture of hexyl methacrylate, vinyl pyrrolidone and vinyl acetate), C10 (primarily butylmethacrylate), and polyvinyl pyrrolidone, which release one-half of their zotarolimus load over the 10 to 14 days and the remainder more gradually over 8 to 10 weeks (5). Bench testing in comparison with the poly-(butyl methacrylate) (Cypher cap coat polymer), SIBS (Taxus), and VFH-Fluoropolymer (Xience V/Promus) polymers finds this polymer to be associated with less monocyte adhesion and less tissue factor and protease-activated receptor-2 expression (6). This has been attributed, at least in part, to the contribution of the outer surface hydrophilic C19 polymer (the other polymers are hydrophobic) (7).

In this first reported experience, 139 patients with relatively simple lesions (de novo, diameter 2.5 to 3.5 mm, length 14 to 27 mm) were treated with the Endeavor Resolute stent and evaluated with the primary study end point of 9-month in-stent late loss (8). Recent myocardial infarction was an exclusion criterion, and diabetic subjects were infrequent. The 12-month clinical outcomes were also tracked. Mean late loss was 0.22 mm, and the important right side of the Gaussian distribution of late loss that drives target vessel revascularization was not described. One possible late stent thrombosis (9 months) occurred.

What, ideally, is needed now? Although it might be understandable that the Food and Drug Administration

required initial DES trials to test safety and efficacy in low-risk patients, to continue to limit DES studies to a group of patients making up the minority of those undergoing percutaneous coronary intervention today does a tremendous disservice to the interventional community. They should give up the idea that a new DES must be tested within the confines of approved indications, when such patients make up only one-third or so of all patients treated and others have been well-studied in registries. A head-to-head study with Endeavor Resolute and any of a number of comparators (Cypher, Xience V/Promus, or even the original Endeavor Stent) in an all-comer's population in a study of sufficient size to ascertain relative benefit with follow-up long enough to judge efficacy and get an initial read on safety would be tremendously helpful. A registry study compared results with previous trial data might be sufficient when there are only minor changes in the configuration of a stent (e.g., Taxus Express and Taxus Liberte), but suffers from the weakness of not being able to adjust for changes in technique or concomitant medications (e.g., more intravascular ultrasound or new thienopyridine usage). Ascertaining differences in low-frequency events such as stent thrombosis is much more difficult. Approximately 8,000 patients total are required for an 80% power, assuming stent A has a thrombosis risk of 2% and stent B has a risk of 3%. Adequate post-provisional approval surveillance would likely be a more reasonable approach, providing that basics such as consecutive patient enrollment, complete follow-up, adequate auditing (the same or nearly the same as that done for pivotal randomized trials), and follow-up (at least 3 years, preferably 5 years) were followed. Only then will we know whether or not this stent is really generation 2.5.

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- Key Words:** drug-eluting stents ■ stent thrombosis ■ restenosis.