Choosing a Drug-Eluting Stent: A Comparison Between CYPHER and TAXUS

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For patients with coronary artery disease undergoing percutaneous intervention, drug-eluting stents (DESs) have rapidly become the standard of care. This article reviews the currently available delivery-platform/drug-carrier-vehicle combinations and those expected to become available in the future. It also evaluates and compares current DES platforms in terms of the drug involved, the delivery platform, efficacy, and safety. Currently, 2 DES platforms are available: 1 eluting sirolimus and 1 eluting paclitaxel. Sirolimus is a macrolide antibiotic with a cytostatic mechanism and an anti-inflammatory effect. Paclitaxel is a chemotherapeutic (cytotoxic) agent. The delivery platform is composed of the balloon catheter, the stent, and the drug-carrier vehicle. The carrier vehicle offers controlled drug release and enhances drug distribution. It can be a polymer that serves as a diffusion barrier or a matrix (either durable or degradable) for drug loading. Alternatively, a structural modification on the surface of the stent itself, such as a groove or well in which the drug is placed, can serve as carrier. With respect to efficacy, major trials have shown that the sirolimus platform has a lower late luminal loss rate than does the paclitaxel stent. Moreover, less intimal proliferation and obstruction occurs with the sirolimus platform than with the paclitaxel platform. Also, compared to bare metal stents, the sirolimus platform reduces late luminal loss in challenging subsets of patients. Both stents offer excellent short-term safety. To improve our understanding of these stents, a head-to-head comparison is needed.

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Key words: Drug-eluting stents • Sirolimus • Paclitaxel

Drug-eluting stents (DESs) have rapidly become the standard of care in treating coronary artery disease through percutaneous intervention. Currently, there are 2 DES platforms: the CYPHER® sirolimus-eluting stent (Cordis Cardiology, Miami Lakes, FL) and the TAXUS™ paclitaxel-eluting stent (Boston Scientific, Natick, MA). In the future, many more DES platforms

will become available, featuring different drugs and new delivery platforms. This article reviews the different delivery-platform/drug-carrier-vehicle combinations that are currently being used and the ones that can be expected to become available in the future. It considers 4 broad criteria: the drug, the delivery platform, efficacy, and safety. The first 2 criteria concern the performance of the DES and the latter 2 concern the practical, clinical applications of different DESs.

Drug Options

Sirolimus and paclitaxel are very different drugs with distinct mechanisms of action. Sirolimus is a macrolide antibiotic, whereas paclitaxel is the most widely used chemotherapeutic agent in the world. Each drug affects a different stage of the cell cycle. Sirolimus arrests the cell before it enters the dividing cycle, whereas paclitaxel interrupts cell division during the mitosis phase. Therefore, given their characteristics, sirolimus is regarded as a cytostatic drug and paclitaxel as cytotoxic. Furthermore, sirolimus has a prominent anti-inflammatory effect (ie, it decreases levels of IL-6 and MCP-1 locally), which may account for a significant portion of its differential effect versus paclitaxel.

Another important consideration in evaluating these 2 drugs is their action in terms of local and systemic toxicity. Regarding local toxicity, sirolimus has a large therapeutic window. Even at increased doses (as seen with placement of multiple and overlapping stents), the drug does not exhibit local toxicity, having no untoward effects on the vascular bed. Systemically, the dosing range of sirolimus is also very safe. Even if 17 stents were simultaneously placed in a patient's coronary tree, the plasma levels of sirolimus would be within the therapeutic range for oral dosing of the drug. On the other hand, paclitaxel may exhibit significant local toxicity. Three to 4 times the dose present on a single stent may result in medial necrosis and hemorrhage.[1] Thus, paclitaxel is associated with a narrower therapeutic window, and the amount of drug that can safely be placed on the stent is limited. This may have implications for efficacy, given that both the amount of neointimal proliferation inhibition and local toxicity are directly related to the drug dose.

Delivery Platforms

The delivery platform comprises the balloon catheter, the stent, and the drug carrier vehicle. The merits of different stent designs and characteristics are explored elsewhere in this supplement. However, in briefly commenting on stent design, it is important to describe the major differences between platforms. The sirolimus-eluting Bx VELOCITY™ stent (Cordis Cardiology) has a closed cell design and is available in 2 configurations (6 cells and 7 cells). As a consequence of the closed cell design, drug distribution is theoretically more uniform, but the stent is less flexible. The advantage of having a larger stent for larger vessels is that a more constant drug-to-artery ratio is achieved. The paclitaxel-eluting Express 2™ stent (Boston Scientific), although exhibiting somewhat greater flexibility because of its open cell design, elutes a fixed dose of drug for any given length of stent (regardless of the diameter of the underlying vessel). This implies a variable drug-to-artery ratio. Compared to smaller vessels, larger ones may be relatively underdosed, so the drug may have a diminished effect in large-diameter vessels.

The other, and perhaps more important, aspect of the delivery platform is the drug carrier vehicle. There are 2 important reasons for having a drug carrier vehicle associated with a DES. The first is to offer controlled release of the drug, in regard to both rate and total duration of release. The second is to enhance drug distribution. Ideally, the drug is distributed into the wall of the blood vessel in a uniform manner. Interestingly, by using different polymers and polymer designs, the direction of distribution can also be manipulated. For ideal application with a DES, the drug carrier vehicle should have several important characteristics: it should be noninflammatory, nonthrombogenic, and sterilizable, with a durable shelf life. Also, the vehicle should neither affect the structure of the drug nor hinder delivery of the stent itself.

Even if 17 stents were simultaneously placed in a patient's coronary tree, the plasma levels of sirolimus would be within the therapeutic range for oral dosing of the drug.

The drug carrier vehicle may be present in the form of a polymer, which may serve only as a diffusion barrier or may be a matrix for drug loading (see Figure 1). This matrix may be durable or degradable (see Figure 2). The CYPHER stent has both a polymer matrix loaded with the drug and a polymer topcoat (without a drug) that serves as a diffusion barrier. The polymer, poly(ethylene-co-vinyl acetate) (PEVA)/poly(butyl methacrylate) (PBMA), elutes 100% of the sirolimus, most of which has eluted after approximately 1 month.

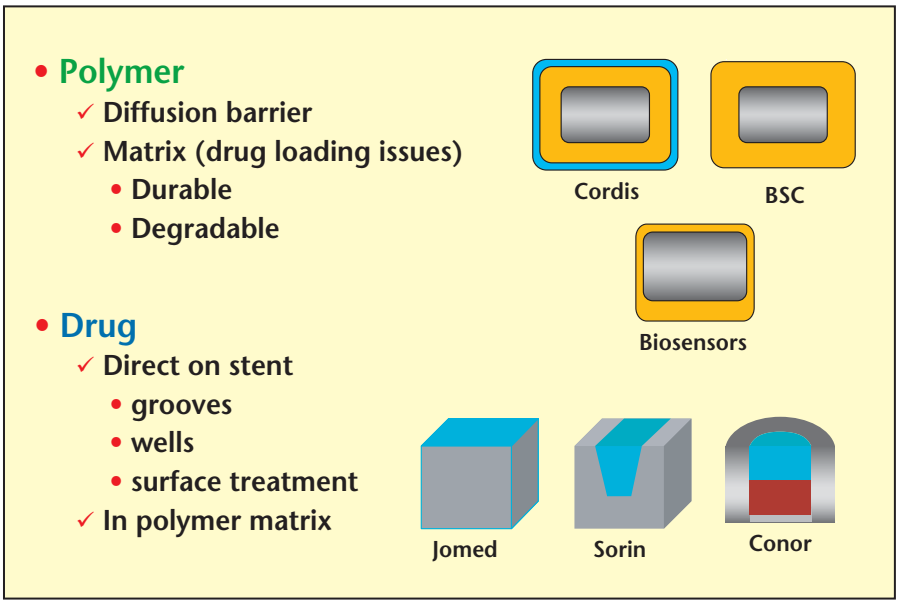


Figure 1. *Different utilizations of drug and polymer in the make-up of drug-eluting stents. BSC, Boston Scientific Corp.*

The TAXUS stent has a monolayer polymer matrix (polyisobutylene), which elutes the drug directly in a biphasic manner. There is an initial burst release of the drug on the more superficial portion of the polymer. Subsequently, up to 10% of the paclitaxel is released over the next 2 months. However, 90% of the drug remains sequestered in the polymer indefinitely. The long-term implications of the presence of the sequestered drug are unknown.

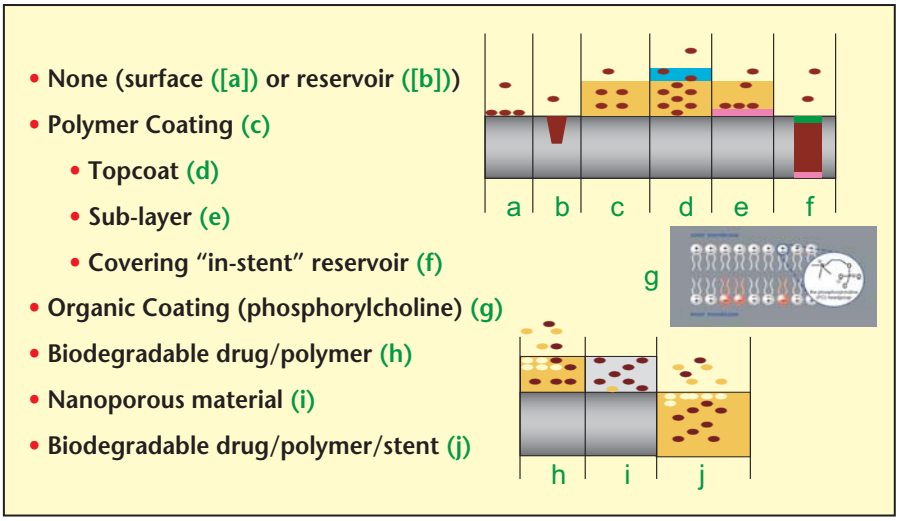
Instead of being associated with a polymer, a structural modification of the stent itself may serve as the drug delivery vehicle. The drug may be placed directly in a groove or well on the surface of the stent. In this case, a polymer may be used as mentioned above to further fine tune delivery of the drug. The Conor stent (Conor Medsystems, Inc., Menlo Park, CA) has a series of built-in wells along its struts that serve as drug reservoirs. These wells may contain 1 or more drugs in layers, and the opening of the well may be "capped" with a polymer that can serve as a partial or complete diffusion barrier. In this manner, elution of 1 or more drugs in sequence can be engineered to take place in a unidirectional fashion. The drug carrier vehicle may also be formed by a treated stent surface (i.e., in association with a nanoporous material). Clearly, use of a drug carrier vehicle adds to the precision and performance of a DES.

Efficacy

In comparing the CYPHER and TAXUS stents, efficacy may be the most important consideration. In evaluating stents, research protocols can obtain widely different restenosis rates, depending on the clinical variables involved (vessel size, stent design, clotting status, the presence of unstable angina, and the overall clinical situation). Therefore, any valid comparison should rely on the variable that changes the least, which in this case is late loss.

Stent placement causes an arterial injury, which commonly includes vessel medial dissections. The smooth muscle cells within the artery become active, proliferate, migrate, and produce extracellular matrix. The end result is neointima formation, and the thickness of the neointima is directly proportional to late loss (Figure 3). The lower the level of this variable, the better the clinical outcome. As late loss increases, there is more neointimal volume, or intimal hyperplasia obstructing the vessel, and patients are more likely to need target-lesion revascularization (TLR). Because late loss is minimally influenced by other clinical variables, it

Figure 2. *Options in combining drug carrier vehicles and stents.*



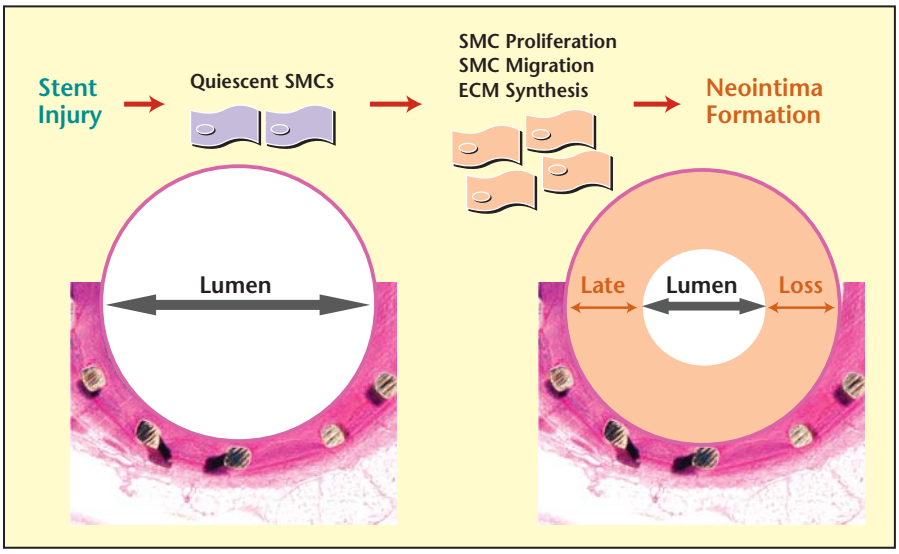


Figure 3. *The pathophysiology of late luminal loss. Late loss after stenting reflects the biological response to injury inside the vessel: neointimal formation.*

can be used to determine which stent is more effective at suppressing neointimal proliferation.

In 7 different trials (Figure 4),[2-8] late loss with a bare metal stent stayed relatively constant, ranging from 0.8 to 1.0 or 1.1 mm. A variety of bare metal stents were assessed: the MULTI-LINK stent (Guidant Corporation, Indianapolis, IN);[2] the NIR stent (Scimed, Boston Scientific, Maple Grove, MN);[3] the MULTI-LINK PENTA™ stent (Guidant);[5] the MULTI-LINK VISION™ stent (Guidant),[6] which is made of cobalt chromium; the Bx VELOCITY stent (Cordis);[7] and the BiodivYsio™ stent (Abbott Laboratories and Biocompatibles International PLC, Abbott Park, IL).[8]

The Randomized Study With the Sirolimus-Eluting Bx VELOCITY Balloon-Expandable Stent (RAVEL)[9-11] and the TAXUS II trial (Figure 5), which involved benign lesions, had a late luminal loss of 0 and 0.31 mm, respectively. The relative reduction in TLR was 100% in RAVEL[7] and 61% in TAXUS II. More clinical trial results are now available, including those from the SIRIUS and New SIRIUS studies, the latter representing pooled data from the C-SIRIUS (Canadian) and E-SIRIUS (European) trials, which set a new benchmark for evaluating sirolimus-eluting stents in real-world conditions. Respective late losses of 0.17 and 0.18 mm, which are typical with these stents, can be compared to a late loss of 0.39 mm in the TAXUS IV trial,[11] which represented real-world clinical results with the TAXUS stent. The relative reduction in TLR was lower with the TAXUS (58%)[11] than with the CYPHER stent (83%).

With respect to volume obstruction (the ability of the drug to inhibit neointimal proliferation), the TAXUS II trial[12] showed less reduction in TLR than did the RAVEL trial.[7] This

Figure 4. *Late luminal loss at 6-month follow-up for bare metal stents in various trials.*

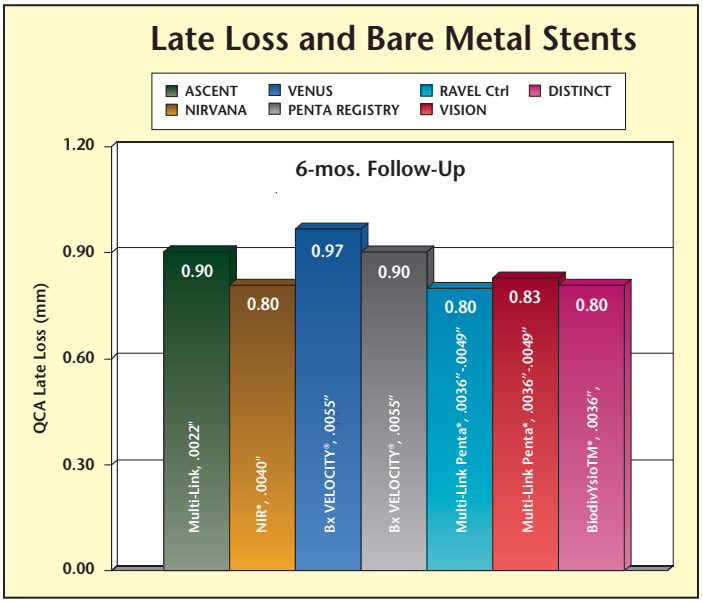
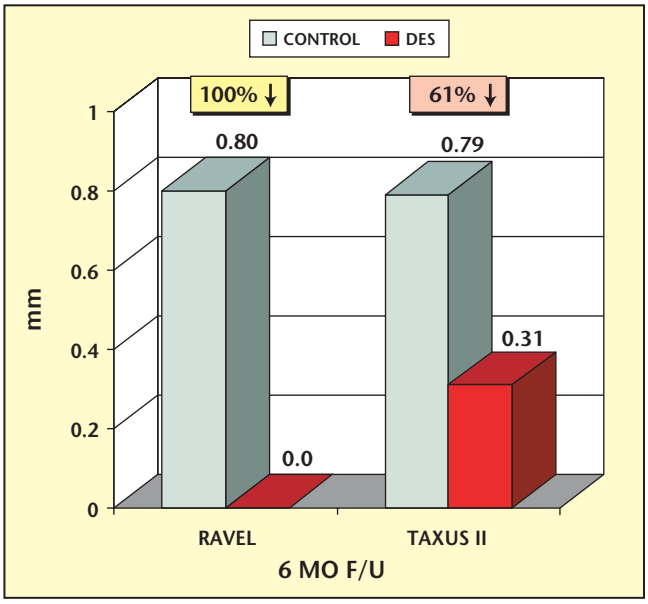


Figure 5. *In-stent late luminal loss for the CYPHER and TAXUS devices.*



finding held true in more complex patient subsets that, again, had a smaller decrease in volume obstruction in TAXUS IV[11] than in SIRIUS and New SIRIUS.[9]

The occurrence of clinical events seems to parallel the reduction in late luminal loss. The relative reduction in TLR was 100% in RAVEL, 75% in SIRIUS, 80% in New SIRIUS, 63% in TAXUS II, and 73% in TAXUS IV.

In the odds ratio plot for the SIRIUS trial, based on results obtained at 9 months (Figure 6), the overall TLR rate was 4.1%. The most striking result was the overwhelming effect that sirolimus had in the different subsets of patients in the trial, including those with diabetes mellitus, left anterior descending coronary artery disease, small vessels, larger vessels, overlapping stents, and nonoverlapping stents.

At 9 months, the difference between the TAXUS IV and SIRIUS data was less dramatic, and 2 subgroups showed no significant improvement (Figure 7). One of these subgroups consisted of insulin-treated diabetic patients, but this group was so small that firm conclusions were hard to reach. The other subgroup consisted of patients with larger vessels (≥ 3.0 mm), who did not fare significantly better with a TAXUS stent than with a bare metal one.

With respect to the 12-month TLR rate in the TAXUS IV and New SIRIUS trials, a significant improvement was seen with both devices. However, the New SIRIUS patients had a much more dramatic reduction in TLR rate than did the TAXUS IV patients (1.3% versus 3.0%, respectively) (Figure 8).

There is a question regarding the best DES for treating diabetic patients. In the different randomized clinical trials, the results have

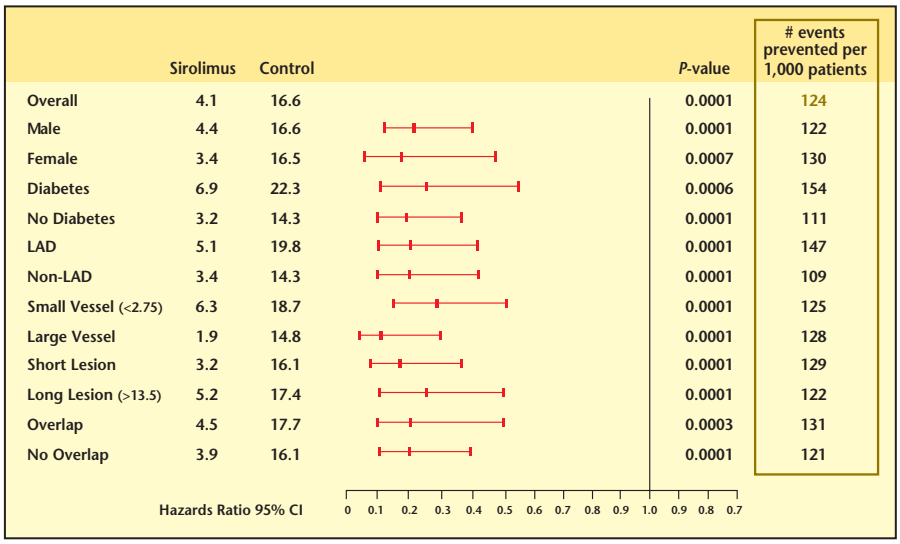
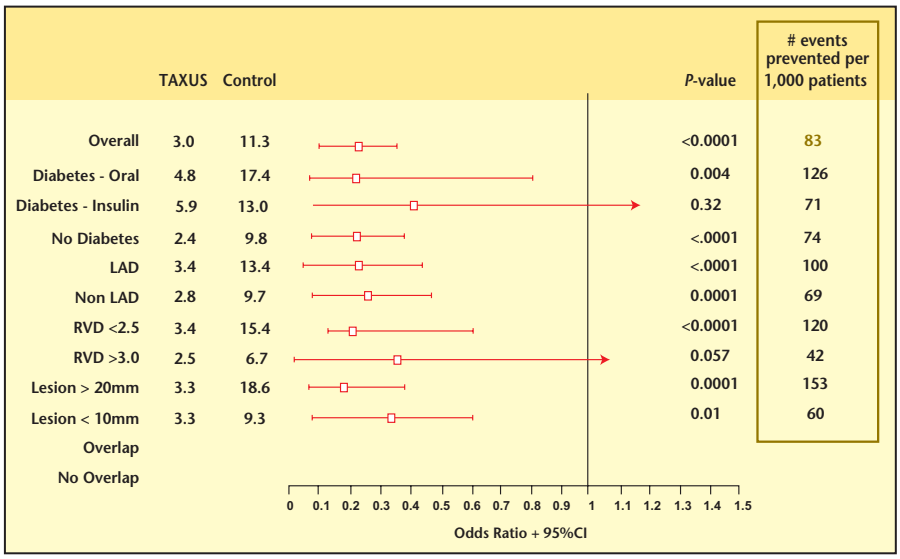


Figure 6. *Odds ratios for target-lesion revascularization, by subgroup, in the SIRIUS trial at 9-months follow-up. LAD, left anterior descending.*

generally been similar with both sirolimus- and paclitaxel-eluting stents (Figure 9).[7,9-15] The e-CYPHER results (with adjudicated registry data) were recently presented at EuroPCR (the Paris Course on Revascularization)[16] with a favorable TLR rate of 1.4% in 2716 patients. These results are significant, given the sheer number of patients involved. For insulin-treated diabetic patients, the data are, again, fairly similar with both stents. It is reassuring that the e-CYPHER group included 884 of these patients, which is one of the largest groups of diabetic patients analyzed in this regard.

For patients with small vessels, late luminal loss ranges from 0.01 mm to 0.22 mm in the sirolimus trials[7,9-11,17,18] versus 0.35 mm in the TAXUS IV[11] trial (Figure 10). In assessing the effects of these stents in challenging subsets of patients (Table 1),[19-21] it

Figure 7. *Odds ratios for target-lesion revascularization, by subgroup, in the TAXUS IV trial at 9-months follow-up. LAD, left anterior descending; RVD, reference vessel diameter.*



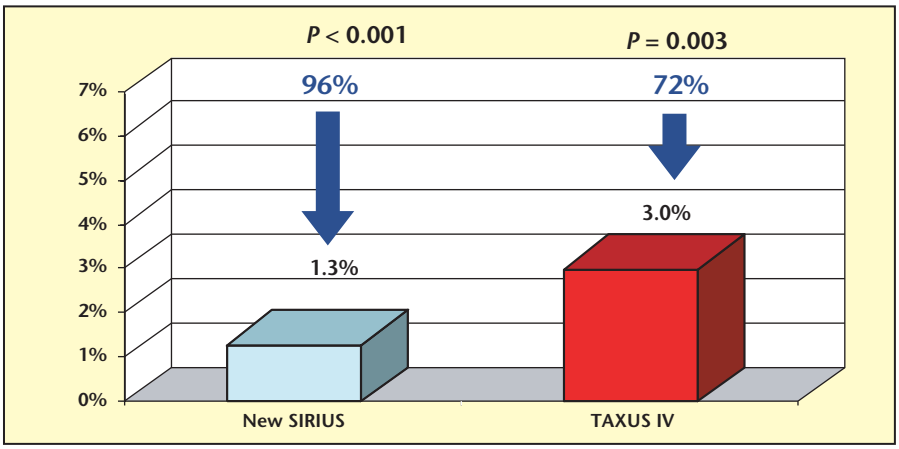


Figure 8. *Target-lesion revascularization associated with the CYPHER and TAXUS stents at 12 months in the New SIRIUS and TAXUS IV trials.*

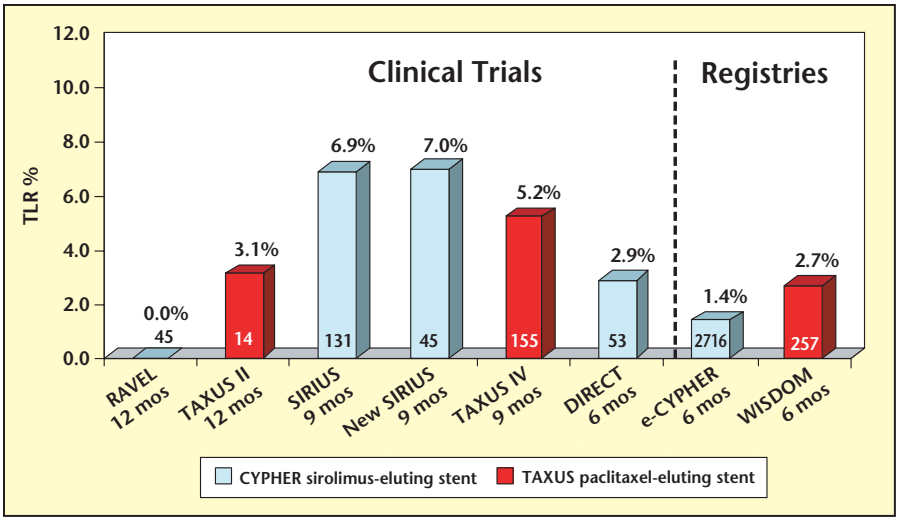


Figure 9. *Target-lesion revascularization (TLR) associated with the CYPHER and TAXUS stents in diabetic subpopulations of randomized controlled clinical trials and registries.*

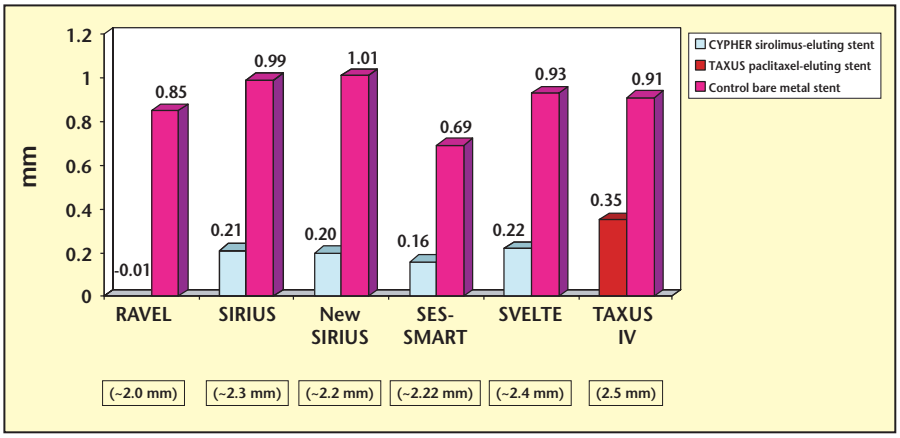


Figure 10. *Late luminal loss associated with the CYPHER and TAXUS stents in small vessel subgroups of 6 trials.*

is important to note that whereas specific data are available for the CYPHER stent regarding the different clinical correlates of TLR, from the European and Canadian SIRIUS[22,23] trials, the Sirolimus-eluting stent in Chronic Total Occlusion (SICTO) Trial,[24] the Rotterdam trial,[25] and the TROPICAL Study[26] recently presented at EuroPCR, similar data are not available for the TAXUS stent at this time.

With regard to in-stent restenosis (Table 2), a different profile of restenosis patterns[27] has emerged between sirolimus- and paclitaxel-eluting stents as shown in the TAXUS IV, TAXUS VI, and SIRIUS trials. When in-stent restenosis patterns were analyzed in the SIRIUS trial, with the CYPHER stent, most of the restenosis (87%) was focal as opposed to nonfocal (13%). In TAXUS IV and TAXUS VI, however, focal lesions accounted for 63% and 62% of the restenoses, respectively, the remainder being nonfocal. Total occlusion as a result of restenosis occurred twice as often with TAXUS stents as with CYPHER stents. These findings are significant in terms of clinical outcomes because the TLR associated with the treatment of nonfocal restenosis is higher than that associated with focal restenosis.

With respect to long-term follow-up, the insight gained from follow-up of the GAMMA I Trial[28] may raise important concerns. At 1 year, brachytherapy treatment was considered to have worked exceptionally well. After 3 to 4 years, however, there was no significant difference between the study group and the control group. This experience highlights the importance of long-term follow-up data for any new therapy in interventional cardiology. Follow-up results from the First-in-Man trial, performed in Brazil,[29] are very reassuring: 4 years after placement of the CYPHER stent, the

results are similar to those obtained immediately after the procedure.

Safety

The fourth broad category for comparison of the CYPHER and TAXUS stents is safety. In this regard, the most important consideration is the rate of major adverse cardiac events (MACE). The 3-year follow-up data from the RAVEL study show favorable MACE curves for the CYPHER stent (Figure 11). The 12-month MACE rate was 10.6% in the TAXUS IV study and 8.0% in the New SIRIUS study. Moreover, stent thrombosis, which was initially believed to be a cause for concern, has not been a problem with either stent system. The recent presentation of the US e-CYPHER registry demonstrates a real-world pattern of usage of CYPHER stents in the United States.[30] It showed an overall MACE rate of 3.9% and a total stent thrombosis rate of 0.7% at 6-months follow-up.

The TAXUS VI trial,[31] recently completed in Europe, involved patients with long lesions. When the TAXUS VI cohort is compared to 2 SIRIUS and New SIRIUS subgroups that had comparable lesion lengths, the TLR rate is very similar; rather surprisingly, however, the MACE rate was significantly elevated (16.4%) in the TAXUS VI group, which was not different from the control group in this respect.

Few data are available for the TAXUS stent concerning overlapping of stents, but data have recently become available from the TAXUS VI trial. The comparison might not be clinically relevant, as the TAXUS moderate-release stent (not available in Europe or the United States) was used in TAXUS VI. Nonetheless, some lessons can be gained from this trial. In the TAXUS VI cohort, 27.8% of the patients received overlapping stents. They were followed up for

Table 1
Stent Efficacy in Challenging Subsets

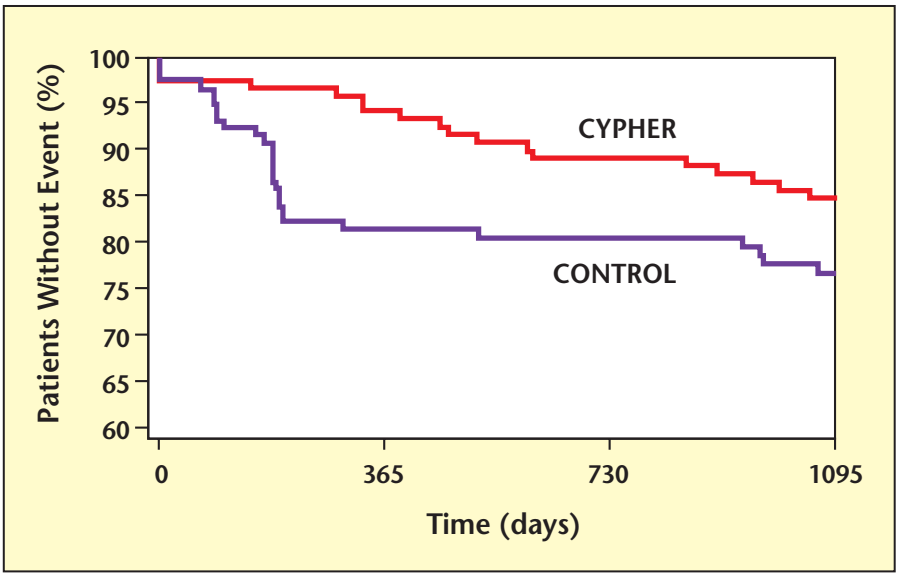
	CYPHER Stent	TAXUS Stent
Direct stenting[10]	1.8% TLR (12 months) 0% restenosis at margins	—
Chronic total occlusion[24]	0.0% TLR-PTCA (6 months) - 0.03 late loss	—
Acute myocardial infarctions[25]	1.1% TVR (300 days) 0 Thrombosis	—
Multivessel stenting[25]	4.0% TLR (9 months)	—
Bifurcations[25]	8.2% TLR (2 year)	—
In-stent restenosis[26]	2.5% TLR (6 months)	—

TLR, total lesion revascularization; PTCA, percutaneous transluminal coronary angioplasty.

Table 2
CYPHER and TAXUS Stent Patterns of Restenosis

	Focal	Non-Focal
SIRIUS Trial	87 %	13 %
TAXUS IV Trial	63 %	37 %
TAXUS VI Trial	62 %	38 %

Figure 11. *Event-free survival in the RAVEL trial at 3-year follow-up. Major adverse coronary events include death, myocardial infarction, coronary artery bypass graft, and subsequent percutaneous transluminal coronary angioplasty.*



9 months, and their rate of subacute stent thrombosis was comparable to that of the control group. Thus, with respect to TLR, overlapping with the moderate-release TAXUS stent was not associated with increased hazardous events.

Data regarding overlapping CYPHER stents are significantly more robust, including 2-year follow-up results from SIRIUS and 1-year results from New SIRIUS. In these 2 trials, the fraction of patients who received overlapping stents was 28% and 35%, respectively. The stents significantly reduced the need for TLR and did not significantly increase the rate of subacute thrombosis.

Speaking at the EuroPCR, Virmani[32] directly compared overlapping of the TAXUS slow-release stent (which is available in the United States and Europe) to overlapping of the CYPHER stent in a rabbit model. The latter device resulted in a significantly higher percentage of surface endothelialization, which is an important indicator of stent safety.

Conclusion

In conclusion, with respect to efficacy, the CYPHER stent has a lower late luminal loss rate than the TAXUS stent. The significance of this finding and its impact in clinical practice remains unclear and is still subject to the individual physician's judgment. However, all of the above-mentioned trials have shown that less intimal proliferation and obstruction occurs with the sirolimus platform than with the paclitaxel platform. Both stents offer excellent short-term safety. In addition, compared to bare metal stents, the CYPHER device reduces late loss in challenging subsets of patients. No parallel data are available for the TAXUS stent. Further knowledge, from a head-to-head comparison (reality trial) of these 2 stents, should improve our understanding of their varying applications. ■

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Main Points

- Currently, there are 2 drug-eluting stent (DES) platforms: the CYPHER sirolimus-eluting stent and the TAXUS paclitaxel-eluting stent.
- Sirolimus is a macrolide antibiotic, whereas paclitaxel is the most widely used chemotherapeutic agent in the world. Furthermore, sirolimus has a prominent anti-inflammatory effect (ie, it decreases levels of IL-6 and MCP-1 locally), which may account for a significant portion of its differential effect versus paclitaxel.
- Systemically, the dosing range of sirolimus is very safe, whereas paclitaxel may exhibit significant local toxicity and is associated with a narrower therapeutic window, which may have implications in terms of efficacy.
- In evaluating stents, research protocols can obtain widely different restenosis rates, depending on the clinical variables involved (vessel size, stent design, clotting status, the presence of unstable angina, and the overall clinical situation). Therefore, any valid comparison should rely on the variable that changes the least, which in this case is late loss.
- In 7 different trials, late loss with a bare metal stent stayed relatively constant, ranging from 0.8 mm to 1.0 mm or 1.1 mm.
- The SIRIUS and New SIRIUS studies set a new benchmark for evaluating sirolimus-eluting stents in real-world conditions. Respective late losses of 0.17 and 0.18 mm, which are typical with these stents, can be compared to a late loss of 0.39 mm in the TAXUS IV trial, which represented real-world clinical results with the TAXUS stent.

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