Clinical Experience with Drug-Eluting Stents

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Despite dramatic improvements in catheter and stent technology, in-stent restenosis continues to hamper initial procedural success in 10% to 50% of patients undergoing coronary intervention. Recent breakthroughs in polymer science and local drug delivery have shown tremendous promise in the long-sought-after goal of delivering antirestenotic therapy directly from a stent. Clinical trials examining several novel antirestenotic agents, particularly sirolimus and paclitaxel, have shown astonishing reduction in restenosis following stenting. Through examination of the clinical experience to date, we may gain insight into the current and future utility of drug-eluting stents in our clinical practice.
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Although advances in catheter and stent design have dramatically improved procedural success and thrombosis rates following coronary intervention, the development of in-stent restenosis provokes recurrence of symptoms in 10% to 50% of patients treated with conventional stainless steel stents.[1,2] Recent breakthroughs in polymer chemistry and local drug delivery, however, have cleared the way to achieving the long-elusive goal of arming each stent with its own antirestenotic therapy.

Over the many years of development, such drug-eluting stents have often shown promise in animal models, but have not shown the same promise in humans. These differences may partly reflect the lack of homology between the therapeutic targets found in animal and human tissue culture or, perhaps, may be due to the inability to deliver the therapeutic agent to its biologic target at the appropriate time and in a concentration sufficient to achieve the desired effect without engendering toxicity. With the production of polymers that are not inflammatory or toxic themselves, and with the evolution of novel therapeutic agents, there is now a growing body of clinical evidence that demonstrates a profound reduction in restenosis with the use of drug-eluting stents. While many agents have been examined, two in particular—sirolimus and paclitaxel—have shown the greatest promise in early clinical trials.

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Sirolimus

The first-in-man experience with the sirolimus-eluting Bx Velocity™ (Cordis Corporation, Miami, FL) stent, conducted by Sousa and colleagues,[3] was designed to determine the safety and efficacy of the platform in the treatment of human coronary disease. Thirty patients were treated with the polymer-coated drug-eluting stents and were reexamined with angiography and intravascular ultrasound at 4 months after stenting. At follow-up, there was near-total abolition of neointimal hyperplasia within the stented region and no evidence of in-stent or edge restenosis: the binary restenosis rate was 0%. In addition, no major adverse cardiovascular events (death, myocardial infarction, stent thrombosis, or target lesion revascularization) were observed at 8-month follow-up. However, one patient suffered a thrombotic event 14 months after treatment, reportedly at a site within a treated vessel, but distinct from the stented segment.

The first-in-man study was followed by the RAVEL trial (RAndomized study with the sirolimus-eluting Bx VELocity™ balloon expandable stent),[4] a multicenter, larger-scale trial designed to determine the safety and efficacy of the use of sirolimus-eluting versus uncoated stainless steel stents in patients with *de novo* coronary lesions. The sirolimus-eluting stents were used in 120 patients, and control (uncoated) stents in 118 patients. Overall, lesion characteristics were notable for relatively short lesion length (~9.6 mm) and small vessel diameter (~2.6 mm); patient demographics did not differ significantly between the two treatment groups. Quantitative coronary angiography, performed 6 months following stent implantation, did not reveal significant late lumen loss in those vessels treated with sirolimus-eluting stents, but did show a decrement in mean luminal diameter in vessels receiving uncoated stents, from 2.41 mm (postprocedure) to 1.64 mm ($P < .001$). At 6 months, the mean diameter stenosis was 36.7% in vessels treated with uncoated stents versus 14.7% in those receiving sirolimus-eluting stents ($P < .01$), with corresponding binary restenosis rates of 26.6% and 0%, respectively ($P < .001$). The rate of target lesion revascularization at 6 months was 22.9% in patients treated with uncoated stents compared with 0% in those treated with sirolimus-eluting stents ($P = .001$); these rates were not significantly changed at 12-month follow-up.

Intravascular ultrasound was performed in a small subgroup of patients treated with the sirolimus-eluting stent. No significant evidence of a "candy-wrapper" effect (neointimal hyperplasia at the edges of the stented region) or of negative remodeling was observed in these patients. However, "late stent malapposition" (lack of complete approximation of stent struts against the vessel wall) was observed in 21% of patients treated with sirolimus-eluting stents compared with 4% of those treated with uncoated stents ($P = .001$).[5] While this finding may reflect "positive remodeling" (regression of the internal elastic lamina away from the stent struts), and/or delayed wound healing, the clinical significance remains unclear.

In the SIRIUS trial, the binary in-stent restenosis rate in patients receiving sirolimus-eluting stents was 3.2% compared with 35.4% in those receiving control stents (P < .001).

The SIRIUS trial (a multicenter, randomized, double-blind study of the SIRolImUS-coated Bx Velocity™ balloon-expandable stent in the treatment of patients with *de novo* coronary artery lesions), a larger-scale (1101-patient) multicenter trial, was recently presented at the Trans-

catheter Cardiovascular Therapeutics-2002 conference in Washington, D.C. SIRIUS is the pivotal U.S. trial establishing the safety and efficacy of the sirolimus-eluting stent. Of interest, the study design was directed to evaluate patients with relatively high-risk lesions: small vessels (2.5–3.5 mm in diameter) and long lesions (15–30 mm in length) were required for enrollment; 24.6% of the patients were diabetic; and a high proportion of the patients had dyslipidemia (72.6%), hypertension (67.6%), and/or multivessel disease (40.7%). Eight-month angiographic follow-up was performed in approximately 85% of patients studied, and 9-month clinical follow-up was completed in 96%.

Quantitative coronary angiography performed at 8-month follow-up revealed a profound reduction in all parameters of restenosis in the study group compared with controls. Average minimal luminal diameter at follow-up was 2.50 mm in lesions treated with sirolimus-eluting stents versus 1.68 mm in those treated with control stents ($P < .001$). This finding correlated with a percent diameter stenosis of 10.5% in sirolimus and 40.1% in control stented vessels ($P < .001$). The binary in-stent restenosis rate in patients receiving sirolimus-eluting stents was 3.2% compared with 35.4% in those receiving control stents ($P < .001$). Although still statistically significant, the results appeared somewhat less impressive when the region of analysis was extended to segments just beyond the stent margins, reflecting less effective suppression of neointimal hyperplasia at sites likely injured by balloon but not directly in contact with stent struts and drug elution. When the region of analysis was extended to include 5-mm margins on either side of the stent, the rate of so-called in-segment restenosis was 8.9% in the study group versus 36.3% in controls ($P < .001$). This "edge effect" was more prominent in smaller vessels than in larger vessels.

Two pilot clinical trials—ASPECT and ELUTES—demonstrated clear evidence of a dose response to paclitaxel delivery, with reduction in diameter stenosis, late lumen loss, and binary restenosis with increasing doses of paclitaxel.

Clinical events at 9-month follow-up were also dramatically reduced in patients treated with sirolimus-eluting stents. The primary endpoint of target vessel failure was reduced in patients in the study group (8.6%) versus those in the control group (21.0%, $P < .001$); target lesion revascularization rates were lower in the study group (4.1%) than in controls (16.6%, $P < .001$); and major adverse coronary event (MACE) rates were 7.1% (study group) and 18.9% (controls, $P < .001$). There was no significant difference in rates of death (0.9% sirolimus group, 0.6% control) or myocardial infarction (2.8% and 3.2%, respectively).[9]

The sirolimus-eluting stent was approved for use in Europe in April 2002, and the evaluation of its performance and clinical impact is eagerly awaited. A number of trials have been planned to determine the clinical impact of the sirolimus-eluting stent in the management of lesions in small vessels, bifurcation lesions, saphenous vein graft disease, multivessel disease, unprotected left main disease, in-stent restenosis, and brachytherapy failures. An additional point of interest will be a cost-benefit evaluation that will accompany further interpretation of the SIRIUS trial results.

Paclitaxel

Several pilot clinical trials have demonstrated that paclitaxel and other taxane derivatives may exhibit potent antirestenotic effects when delivered from one of several different stent-based platforms. The SCORE trial (Study to COmpare REstenosis rate between QueST and QuaDS-QP2) examined stent-based delivery of the taxane derivative 7-hexanoyltaxol (QP2).[10,11] In this trial, 127 patients were treated with the QuaDS-QP2 drug eluting stent—a Quanam™ (Quanam Medical/Boston Scientific Corporation, Natick, MA) stainless steel stent wrapped with polymer sleeves designed to elute QP2 in a controlled fashion; 139 patients were treated with the QUEST (bare) stent. A significant reduction in restenosis was observed at 5-month follow-up, with 0% restenosis in the treatment group and 52% in the control group. However, the reduction in restenosis came at the cost of late thrombotic complications, which occurred in 8% of those treated with the QP2-eluting stent versus 0% in those who received a bare stent. Thrombotic complications with the QP2-eluting stent have been ascribed to mechanical disruption and degradation of the stent platform's polymer sleeves, or to excessively high drug dosing.

The QuaDS-QP2 platform has recently been examined as a potential treatment for in-stent restenosis.[12] The drug-eluting stents were implanted within the region of in-stent restenosis in 15 patients. Intravascular ultrasound revealed minimal neointimal hyperplasia at 6-month follow-up, but the effect

was not sustained at 12 months, at which point there was angiographic evidence of significant restenosis.

Two other pilot clinical trials have examined the antirestenotic impact of a novel drug-eluting stent platform, designed by Cook Incorporated (Bloomington, IN), with paclitaxel bound directly to the metal struts. The first of these trials was ASPECT (ASian Paclitaxel-Eluting stent Clinical Trial), in which 177 patients were randomized to receive either a bare Supra-G™ (Cook, Inc.) stainless-steel stent (control group), a stent loaded with a low dose of paclitaxel, or one loaded with a high dose of paclitaxel.[13] Quantitative coronary angiography at 6-month follow-up revealed a dose response to paclitaxel delivery, with significant reduction of restenosis at the highest drug dose. The binary restenosis rates were 27% in the control group, 12% with the low dose of paclitaxel, and 4% with the high dose ($P < .001$ at high dose vs control).

In ASPECT enrollees treated with conventional antiplatelet therapy (aspirin and a thienopyridine), no thrombotic complications were noted following stent implantation. In a breech of protocol, however, 37 patients were treated with aspirin and cilostazol rather than a thienopyridine following stenting. Of this group, there were thrombotic complications in three of the 12 patients who received a high-dose stent, one of the 15 patients who received a low-dose stent, and none of the 10 patients who received a bare stent. These results indicate that locally delivered paclitaxel exhibits an important antirestenotic effect, but may also delay wound healing in a manner that may increase the risk of stent thrombosis unless conventional antiplatelet therapy is prescribed.

The second trial, ELUTES (European EvaLUation of pacliTaxel-Eluting Stents), examined the treatment of *de novo* coronary lesions with the V-Flex Plus™ (Cook Inc.) stent, loaded with directly bound paclitaxel.[14] The 192 enrolled patients were treated with stents loaded with 0 (control), 0.2, 0.7, 1.4, or 2.7 $\mu g/mm^2$ of paclitaxel and were assessed by angiography at 6-month follow-up. Again, there was clear evidence of a dose response to paclitaxel delivery, with reduction in diameter stenosis, late lumen loss, and binary restenosis with increasing doses of paclitaxel. At the highest dose, the diameter stenosis was 14.2 ± 4.1% versus 33.9 ± 4.1% in the control group ($P = .007$); late lumen loss was 0.10 ± 0.12 mm versus 0.73 ± 0.12 mm ($P = .002$), and the in-stent binary restenosis rate was 3.1% versus 20.6% ($P = .055$). One patient treated with the highest paclitaxel dose suffered a subacute thrombotic event.

The results from the 12-month clinical follow-up to the ASPECT and ELUTES trials were recently presented at the Transcatheter Cardiovascular Therapeutics-2002 conference in Washington, D.C. and indicate that the safety and efficacy endpoints of these trials were maintained at 1-year follow-up.[15,16]

The DELIVER trial, which completed enrollment of 1043 patients in March 2002, will serve as the pivotal U.S. trial for the ACHIEVE™ Drug-Eluting Stent platform (Guidant Corporation, Indianapolis, IN). In this trial, patients were randomized (in blinded fashion) to receive the ACHIEVE™ stent—with paclitaxel directly bound to a MULTI-LINK® PENTA™ stent—or a bare stent. In the DELIVER-II trial, which completed enrollment in September 2002 of 1533 patients in 76 centers outside of the United States, all patients received the ACHIEVE™ stent platform. Patients will be followed for up to 3 years, with assessment of target lesion revascularization rate (the primary endpoint), safety, device success, and cost effectiveness.

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Main Points

- The development of in-stent restenosis provokes recurrence of symptoms in 10% to 50% of patients treated with conventional stainless steel stents.
- Two novel therapeutic agents used in drug-eluting stents have shown the greatest promise in early clinical trials for reducing restenosis—sirolimus and paclitaxel.
- In trials comparing sirolimus-eluting stents to uncoated stents in the treatment of *de novo* coronary lesions, sirolimus-eluting stents showed superior results on outcomes including late lumen loss, diameter restenosis, and binary restenosis rates.
- Several pilot clinical trials have demonstrated that paclitaxel and other taxane derivatives may exhibit potent antirestenotic effects when delivered from one of several different stent-based platforms.
- Many questions remain about the impact of drug-eluting stents in different patient populations and clinical situations.

program, currently encompassed by the TAXUS trials (I-VI), has focused on the use of a non-erodible polymer-coated NIR® stent (Boston Scientific Corporation) to control local delivery of paclitaxel. The TAXUS-I trial was designed to study the safety and efficacy of the paclitaxel-eluting stent platform. Fifty-eight patients were randomized to receive either a paclitaxel-eluting or an uncoated stent. At 6-month follow-up, angiography and intravascular ultrasound revealed a binary restenosis rate of 0% in vessels treated with paclitaxel versus 11% in those treated with a bare stent. Diameter stenosis was reduced by 52% (13.2% in vessels treated with a paclitaxel-eluting stent vs 27.5% in those treated with a bare stent). Of note, there have been no subacute or late thrombotic complications to date.[17]

The TAXUS-II trial was designed to study the efficacy of a slightly different stent platform (the NIR® conformer stent) with polymer coatings that permitted either a slow or a moderate rate of paclitaxel release from the stent. Enrollment involved 536 patients in 19 countries, with 267 patients entered in the slow-release and 269 in the moderate-release cohort. In each cohort, patients were randomized to receive either the study (drug-eluting) stent or a control (bare) stent. In the slow-release cohort, 6-month intravascular ultrasound (IVUS) evaluation was performed and demonstrated a significant reduction in net volume obstruction in vessels treated with the paclitaxel-eluting stent (7.85%) compared with those treated with control stents (23.17%, $P < .0001$). At 6 months, the angiographic binary restenosis rate within the stented segments was significantly lower in patients who received the paclitaxel-eluting stent (2.3%) compared with those who received a bare stent (17.9%, $P = .0002$). Six-month rates of MACE were lower in patients in the paclitaxel group (8.5%) compared with controls (19.5%, $P = .013$), as were rates of target lesion revascularization (4.6% and 12.0%, respectively, $P = .043$).

It remains to be determined whether the impact of drug-eluting stents will be as profound and predictable when translated to "real-world" situations.

In the TAXUS-II moderate-release cohort, there were similar findings of reduction in IVUS, angiographic, and clinical evidence of restenosis in patients who received a paclitaxel-eluting stent compared with those who received a bare stent. Six-month IVUS in-stent net volume obstruction was 7.84% and 20.54%, respectively ($P < .0001$). Six-month in-stent angiographic binary restenosis rates were 4.7% and 20.2%, respectively. Clinical evidence of restenosis, including 6-month MACE rates (7.8% vs 20%, $P = .006$) and target lesion revascularization rates (3.1% vs 14.6%, $P = .002$), was also significantly reduced in the paclitaxel versus control group, respectively. Of particular interest is the fact that, in both the slow-release and the moderate-release cohorts, there appeared to be a beneficial effect of stent-based paclitaxel delivery even beyond the stent margins. When the 5-mm margins on either side of the stent were evaluated in drug-eluting versus control stented vessels, there was evidence of significant reduction of "edge restenosis" with paclitaxel, suggesting that—with this platform—the anti-restenotic effects of drug elution may extend beyond the margins of the stent.[18,19]

In the TAXUS-II trial it was found that at 6 months, the angiographic binary restenosis rate within the stented segments was significantly lower in patients who received the paclitaxel-eluting stent (2.3%) compared with those who received a bare stent (17.9%, P = .0002).

The TAXUS-III trial completed enrollment in July 2001 and was designed to examine the use of paclitaxel for the treatment of existing in-stent restenosis. The final results of the trial are pending, but preliminary findings have been presented by Dr. Gregg Stone and have indicated that the treatment strategy is safe (no thrombotic complications) and that the clinical rate of recurrent restenosis is low as long as the stents are placed accurately.[20] There is some evidence of an effect that is analogous to that of "geographic miss" seen in clinical trials involving the use of intracoronary brachytherapy. In cases of geographic miss, there may be exaggerated neointimal hyperplasia in regions that were injured during the intervention but received a sub-therapeutic dose of radiation (or, in this case, drug-eluting) therapy.

The TAXUS-IV trial will serve as the first pivotal trial in the United States for the Boston Scientific paclitaxel-eluting platform. Enrollment has just been completed (1172 patients) in 80 U.S. centers. The study was designed to determine the efficacy of a slow rate of drug delivery from single Express™ (Boston

Scientific Corporation) stents (2.5–3.5 mm in diameter and 10 mm, 24 mm, or 32 mm long) for the treatment of *de novo* lesions ranging from 10 to 28 mm long.

The plans for TAXUS-V, the second pivotal U.S. study, have not yet been finalized. The trial will likely examine the impact of slow-release, stent-based paclitaxel delivery on the treatment of coronary lesions at high risk for restenosis (long lesions, narrow-caliber vessels, diabetic patients). The enrollment criteria will include the treatment of *de novo* lesions, but may be extended to include the treatment of other lesion types as well.

TAXUS-VI has begun enrollment in Europe, and targets patients similar to those in TAXUS-V, with coronary lesions at high risk for restenosis. Whereas TAXUS-V will study slow-release paclitaxel delivery, TAXUS-VI employs the moderate-release formulation. In addition, TAXUS-VI permits the use of overlapping stents for the treatment of long lesions.

Future Directions

After more than a decade of development, recent advances in the technology of drug-eluting stents have generated tremendous excitement about the potential application of these stents in the prevention of restenosis. There is an ever-increasing body of clinical evidence that supports the efficacy and safety of drug-eluting stents, particularly those that use sirolimus and paclitaxel. Although the preliminary results of these trials are tremendously exciting, it may be prudent to proceed with some degree of caution as we incorporate this new technology into our daily practice, since several questions remain unanswered.

To date, the patient populations studied represent a highly select group, with relatively straightforward coronary lesions. It remains to be determined whether the impact of drug-eluting stents will be as profound and predictable when translated to "real-world" situations. Specifically, when stents are deployed in tortuous or complex lesions, strut expansion may occur asymmetrically. This asymmetric expansion may result in heterogeneous drug delivery, which, in turn, may produce local drug concentrations that are sub- or supra-therapeutic at the target tissues. In addition, treatment of long lesions or those involving bifurcation points may require the use of overlapping stents; sites of strut overlap may produce undesirably high local drug concentrations, with potential for toxicity.[21]

Despite the many unanswered questions surrounding the use of drug-eluting stents, there is little doubt that the findings to date mark an unprecedented advance in the percutaneous management of patients with symptomatic coronary disease.

The role of drug-eluting stents in many clinical scenarios has not yet been examined. Several trials are currently enrolling patients to determine the potential impact of drug-eluting stents in the treatment of in-stent restenosis. Will these stents be useful in treating patients who have developed recurrent in-stent restenosis following brachytherapy? Overall, will the drug effect eventually wear off, resulting in a "catch-up" phenomenon with restenosis developing months or even years after stent implantation? If local drug delivery provokes a delay in wound healing, will there be a corresponding increase in thrombogenicity and risk of late thrombotic complications? What will be the ideal antiplatelet therapy, and for how long should it be administered? Will there be a role for drug-eluting stents in noncoronary interventions?

Despite the many unanswered questions surrounding the use of drug-eluting stents, there is little doubt that the findings to date mark an unprecedented advance in the percutaneous management of patients with symptomatic coronary disease. As we gain more experience with the technology, incorporating the use of drug-eluting stents into our daily practice, we may continue to gain insights into the underpinnings of restenosis and into potential future strategies with which we may combat them. ■

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