The Drug-Eluting Stent: Is It the Holy Grail?

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Although the restenosis rate of coronary stenting is generally 10% to 20%, it can go as high as 60% in patients with diabetes or complex lesions. Currently, the only effective treatment for restenosis is brachytherapy. Drug-eluting stents may be the way to prevent restenosis that cardiologists have been seeking: the drug-coated stents are simple to use and help prevent negative remodeling and the intimal hyperplasia caused by stenting. In studies comparing sirolimus-coated and bare-metal stents, the sirolimus-coated stents resulted in less smooth muscle cell colonization, minimal intimal hyperplasia, and no edge effect; moreover, no adverse clinical events were reported. Currently ongoing, multicenter clinical trials of drug-eluting stents may soon come up with the answers that cardiologists have been hoping for. [Rev Cardiovasc Med. *2001;2(4):190–196*]

Key words: Restenosis • Intimal hyperplasia • Drug-eluting stent • Sirolimus-coated stent • Bare-metal stent

Coronary stenting is the most frequently performed percutaneous coronary intervention in this country and in the world, representing over 80% of the interventions done worldwide. Compared to balloon angioplasty, coronary stenting has a more favorable outcome, and its angiographic restenosis rate is only 10% to 20% in short lesions and large vessels.[1] In-stent restenosis occurs, however, in over 30% to 60% of patients with diabetes, diffuse lesions, or lesions that occur in small vessels or are located at a bifurcation.[2] Regardless of treatment strategy—repeat balloon angioplasty, rotational atherectomy, laser angioplasty, cutting balloon angioplasty, or repeat stenting—the re-restenosis rate is extremely high and ranges from 20% to 80% with long, diffuse lesions at the highest risk.[3] Currently, the only effective treatment for in-stent restenosis is brachytherapy, which still has a target lesion

revascularization rate (TLR) of 11% and a target vessel revascularization rate (TVR) of 20%.[4] A recently completed study of brachytherapy treatment of de novo lesions demonstrated marginal benefit with the use of radiation combined with stent implantation to prevent restenosis.[5]

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Further reduction of the in-stent restenosis rate in high-risk patients remains elusive. It is well known that stenting prevents restenosis by eliminating negative remodeling and elastic recoil. Stenting actually results, however, in increased intimal hyperplasia, but it creates less angiographic restenosis because of a larger initial lumen size.[6] This late loss ranges from 0.8 mm to 1.0 mm, leading to a 56% to 75% loss in area. The etiology of in-stent restenosis is mechanical arterial injury and foreign-body response to the prosthesis that incites acute and chronic inflammation in the vessel wall.[7] The subsequent elaboration of cytokines and growth factors induces multiple signaling pathways to activate smooth muscle cell migration and proliferation.

Systemic strategies designed to prevent in-stent restenosis have been disappointing. Recently, the use of drug-eluting stents has been proposed as a means of preventing restenosis. This is an attractive method that addresses both components of in-stent restenosis, the negative remodeling and the intimal hyperplasia. The device is simple to use and, hopefully, will be cost effective. The issues, however, of polymer biocompatibility, sterilizability, suitability of pharmacological agents, suboptimal in vivo pharmacokinetic properties, and local drug toxicity must be addressed.

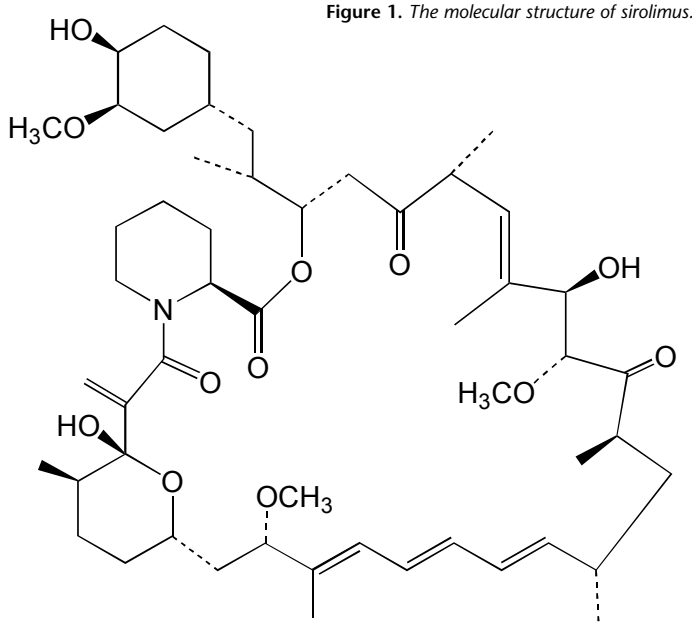

Figure 1. *The molecular structure of sirolimus.*

Development of a Drug-Coated Stent

Candidate drug. The development of a drug-coated stent begins with the identification of suitable pharmacological agents. The current investigational agents include sirolimus (Rapamycin), Taxol and its derivative paclitaxel, and actinomycin. Sirolimus is a naturally occurring macrolide antibiotic produced by the fungus *Streptomyces,* found on Easter Island (Figure 1). It was discovered in 1974 while screening for fermentation products, and it has FDA approval as an immunosuppressive agent. It is a potent inhibitor of cytokine and growth-factor–mediated cell proliferation. Sirolimus binds to a cellular receptor FKBP-12 and reduces cdc2 and cdk2 activities as well as pRb phosphorylation. It also induces late G1 cell-cycle arrest.[8,9]

Taxol and its derivatives are microtubule inhibitors that prevent cell migration and proliferation by inducing the microtubules to form long, stable chains. It is derived from the Pacific yew tree, and it has been approved by the FDA for the treatment of ovarian cancer.[10] Actinomycin D is derived from *Streptomyces parvullus,* inhibits DNA and RNA synthesis, and was approved in 1964 for treatment of certain types of cancer.

Coating Technology

Much of the stent-coating technology is proprietary. One method is to create a polymer sheath in which the drug is embedded.[11] The sheath is then wrapped around the unexpanded stent. With stent deployment, the polymer sheath is trapped between the stent and the vessel wall (Figure 2). Another method of

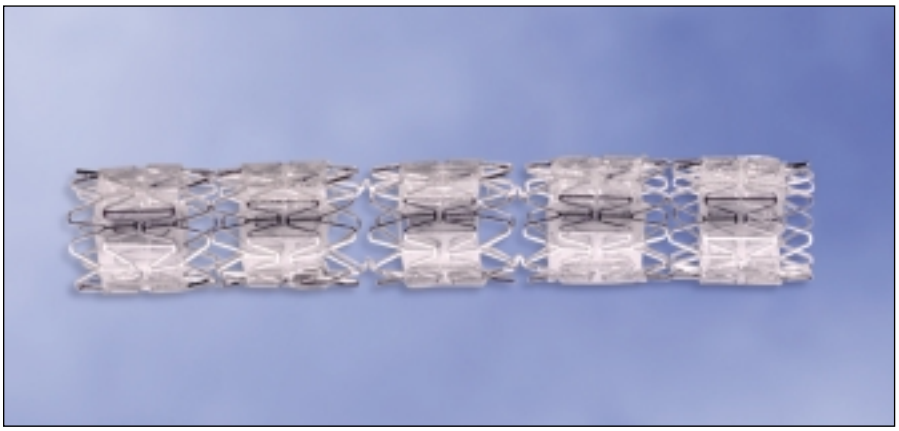

Figure 2. *The Quanam Taxol-derivative stent.*

stent preparation is to coat the stent with a thin layer (10 μ) of a nonerodable methacrylate and ethylene-based co-polymer, which contains the drug. The total drug and polymer weight is approximately 500 μg, and the ratio of drug to polymer is approximately 30%.

Experimental Data

Thus far, experimental data has revealed that drug-coated stents achieve a very high local drug concentration and can be effective in inhibiting intimal proliferation. Most investigations have utilized the sirolimus-coated stent. Gallo and colleagues recently demonstrated a reduction in postangioplasty restenosis in a porcine model with prolonged systemic sirolimus therapy.[12]

Sirolimus is a hydrophobic drug that has low solubility in aqueous solutions.[13,14] Its lipophilicity allows sirolimus to pass easily though cell membranes, which enables intramural distribution and prolonged arterial tissue retention.[14] In addition, cellular uptake is enhanced by the drug's binding to the cytosolic receptor, FKBP-12, which may also improve its chronic tissue retention.

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Pharmacokinetic studies. The benefit of a local drug delivery using a stent-based platform is illustrated by pharmacokinetic studies. One hour after a sirolimus-coated stent was deployed in a porcine coronary artery, the whole blood concentration of sirolimus was at its peak (2.6 ± 0.7 ng/mL). The level of sirolimus declined below the lower limit of detection (0.4 ng/mL) within 3 days. The total arterial tissue level of sirolimus was 35 times the whole blood concentration at 3 days, and the residual stent content was 71 ± 10 μg (43% of the initial stent dose).[15] Thus, stent-based systems have the ability to deliver a drug locally, achieving potentially therapeutic arterial tissue concentrations without prolonged significant systemic exposure.

Efficacy studies. Preclinical effi-

Table 1
Summary of Preclinical Data at 28 Days After Placement of Sirolimus-Coated Stents

Study	Model	Drug Load	Neointimal Area (mm^2)		Reduction
			Control	SRL Coated	
Carter et al[16]	Porcine coronary	125 μg	4.57 ± 0.46	2.84 ± 0.31	38%
Suzuki et al[17]	Porcine coronary	185 μg	5.24 ± 0.58	2.47 ± 0.33	53%
Carter et al[18]	Porcine coronary	155 μg	2.94 ± 0.43	1.40 ± 0.11	52%
Klugherz et al[19]	Rabbit iliac	64 to 196 μg	1.20 ± 0.07	0.66 ± 0.12	45%

Data is expressed as mean ± SE.

cacy studies demonstrated a 35% to 50% reduction in in-stent neointimal hyperplasia with sirolimus-coated stents compared to bare-metal stents in porcine and rabbit models at 28 days (Table 1).[15,16] Moreover, compared to bare-metal stents, sirolimus-coated stents significantly reduced strut-associated inflammation.[15] An histological assessment revealed the presence of typical neointimal cellular components and a similar endothelialization for both the sirolimus- and the bare-metal stents. The arterial-wall morphology at 28 days for the sirolimus-coated and the bare-metal stents are demonstrated in Figure 3. The morphology of nonstented, reference, arterial-wall sections, including the vessel area, neointimal area, and percent area stenosis, was similar for the metal and the three dosing regimens of the drug-coated stents.[15] In general, the neointima of the sirolimus-coated stents consisted of smooth muscle cells (SMC), matrix proteoglycans, and scant focal regions of residual fibrin adjacent to the stent struts. Focal medial necrosis or intimal hemorrhage was not observed within any of the

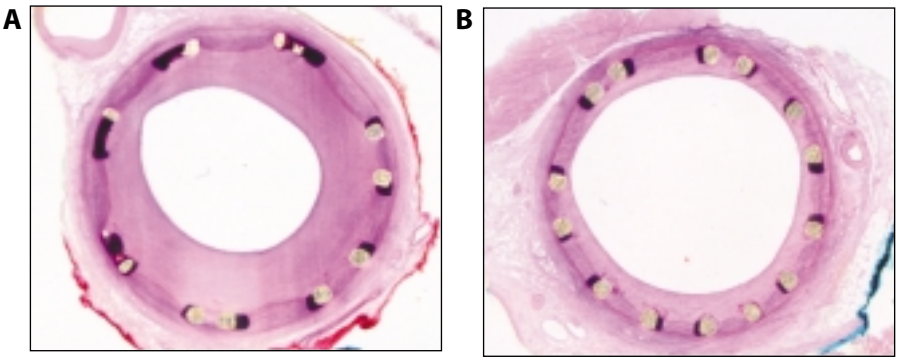


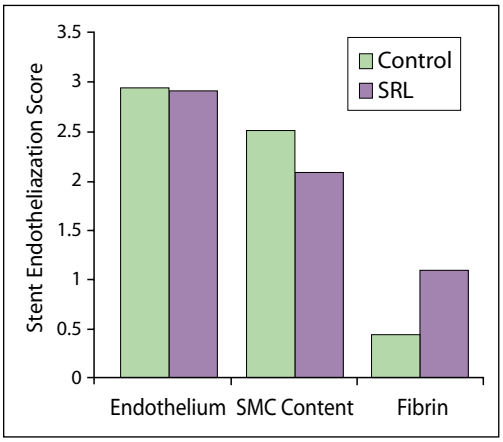
Figure 3. *Low-power photomicrographs at 28 days after oversized stent placement in normal porcine coronary arteries.* ***(A)*** *A bare-metal stent with moderate neointimal formation encroaching the lumen.* ***(B)*** *The sirolimus-coated stent has significantly less neointimal hyperplasia than the bare-metal stent has, despite a similar degree of vessel injury. The photomicrograph of the sirolimus-eluting stent demonstrates minimal neointimal formation consisting of smooth muscle cells and matrix proteoglycans. (H&E, 2.1 X magnification)*

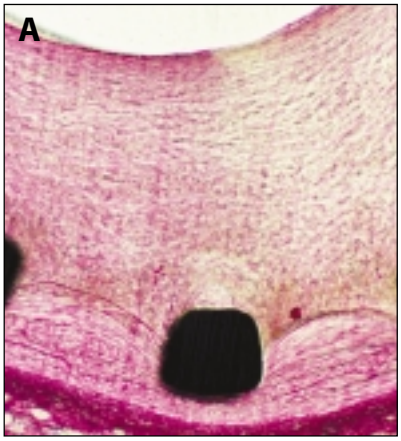
bare-metal or drug-coated stents.[17]

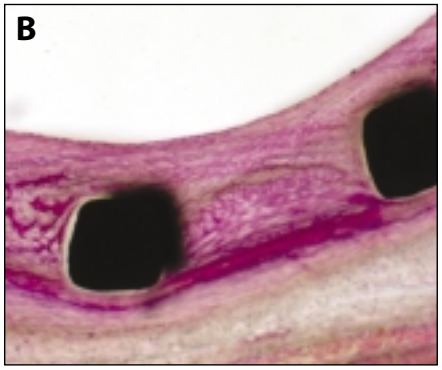
A semiquantitative histological grading system demonstrated less SMC colonization and more residual fibrin deposition for the sirolimus-eluting stents compared to those for the bare-metal stents. In addition, there was a greater reduction in the SMC content score for the drug-coated stents than for the bare-metal stents. The endothelialization scores, however, were identical for the metal and sirolimus stents (Figure 4). This demonstrates that critical reparative events, such as endothelialization and SMC colonization of the neointima, occur in a similar temporal sequence with both sirolimus-eluting and bare-metal stents.[17]

Mechanisms that inhibit neointimal hyperplasia. Arterial-wall protein expression at 7 days suggests that the mechanism by which stent-based sirolimus delivery reduces in-stent neointimal hyperplasia is similar to that for systemic treatment with the agent. Western blot analysis demonstrated a profound reduction in proliferating cell nuclear antigen (PCNA) expression

Figure 4. *The bar graph demonstrates the effects of bare-metal and drug-coated stents on arterial repair. The smooth muscle cell (SMC) content score was lower for the drug-coated stents than it was for the bare-metal stents (P < .0001). Intimal fibrin scores were 2-fold greater for the sirolimus (SRL) versus metal stents (P < .0001). The stent endothelialization scores were identical for the metal and sirolimus stents. High-power photomicrographs of bare-metal* ***(A)*** *and sirolimus-coated* ***(B)*** *stents demonstrate some of the morphologic features of the arterial wall at 28 days after implant. The neointima of the sirolimus-coated stent contains smooth muscle cells with grade 1 residual fibrin deposition.*







in the vessel wall at 7 days for the sirolimus-eluting stents, as well as reduced phosphorylation of pRb protein; this is consistent with the drug's proven effects on cell cycle signaling and proliferation. In addition, a significant reduction in strut-associated inflammation was observed at 28 days with the sirolimus-coated stent, suggesting that there is a potential for additional mechanisms that inhibit neointimal hyperplasia.[17] Vessel-wall, protein-expression analysis documented a 70% reduction in the inflammatory cytokine MCP-1 with sirolimus-eluting stents.[17] Unlike cyclosporine and tacrolimus, other oral immunosuppressive agents, sirolimus is a weak inhibitor of cytokine production. Its potent immunosuppressive effect arises from its inhibition of T-cell proliferation by blocking IL-2 activation of $p70^{s6}$ kinase.[14] The observed reduction of MCP-1 may be secondary to the effects of sirolimus on cellular proliferation and on the production of cytokines by activated SMC.

Taxol and its derivative have also been extensively studied in experimental models. Similar local drug retention has been demonstrated both in the sheath as well as in the coated version of the Taxol stents. Drachman and colleagues have demonstrated that effective inhibition of neointimal formation can be achieved by the Taxol-coated stent without delaying endothelialization (Figure 5).[18]

Clinical data. A German pilot study for safety, the first clinical study performed, used the Quanam-Taxol "semicovered" stent. The study was performed in 34 patients using a 3.0 mm or 4.0 mm Taxol-coated or bare-metal stent. No major adverse clinical event was observed in 30 days, nor did in-stent restenosis or late thrombosis occur. Quantitative angiography after the deployment of the stent revealed a minimum luminal diameter (MLD) of 2.9 mm in both groups and a 6-month MLD of 0.9 mm and 2.2 mm in the bare-metal and drug-coated stent groups, respectively.[11] A larger, multicenter, randomized study has been completed, and the results will soon be available for analysis.

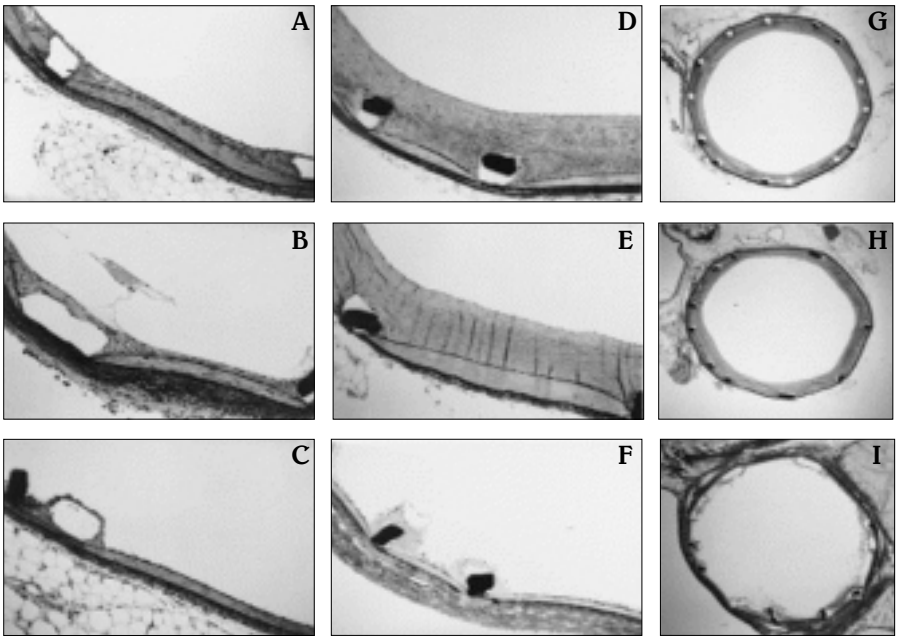


Figure 5. *Photomicrographs show rabbit iliac arteries stained with Verhoeff's tissue elastin stain after balloon denudation and stent implantation. Seven days after stenting, a thin cellular neointima separates the lumen from the internal elastic lamina in uncoated stents* ***(A)*** *and stents coated with poly(lactide-co-sigma-caprolactone)* ***(B)****. In arteries receiving stents coated with poly(lactide-co-sigma-caprolactone) containing paclitaxel* ***(C)****, no intimal thickening is seen although the media retains its cellularity. Fifty-six days after balloon denudation and stent implantation, neointimal thickening had progressed in uncoated stents* ***(D, G)*** *and stents coated with poly(lactide-co-sigma-caprolactone)* ***(E, G)*** *but remained almost undetectable in stents coated with poly(lactide-co-sigma-caprolactone) releasing paclitaxel* ***(F, I)****. Original magnifications: A to F = 150×; G to I = 18×. Reproduced from Drachman et al.*[18] J Am Coll Cardiol. *2000;63:2325–2332, with permission from the American College of Cardiology.*

The safety and feasibility of a sirolimus-coated stent were evaluated in a phase I clinical trial in which 45 patients with stable angina were electively treated with a 3.0 mm or 3.5 mm diameter stent, 18 mm long. Plavix was given for 60 days, and at 6 months no patient had restenosis. Intravascular ultrasound revealed minimal intimal hyperplasia without significant edge effects. At 12 months, one patient developed late stent thrombosis, which was attributed to plaque rupture proximal to the stent (Figure 6).[11]

The randomized study with the sirolimus-coated Bx velocity, balloon-expandable stent in the treatment of patients with de novo native coronary lesions (RAVEL) is a prospective, multicenter, randomized, double-blind clinical trial comparing bare-metal and sirolimus-coated stents. A total of 220 patients will be randomized to a single sirolimus-coated stent (140 $\mu g/cm^2$) or the bare-metal Bx Velocity stent. The primary clinical endpoints are target lesion revascularization and angiographic restenosis at 6 months.

[*Editor's note: as this article was going to press, resuslts of the RAVEL study were announced at The European Society of Cardiology XXIII Congress. These results will be reported in the next issue of* Reviews in Cardiovascular Medicine.]

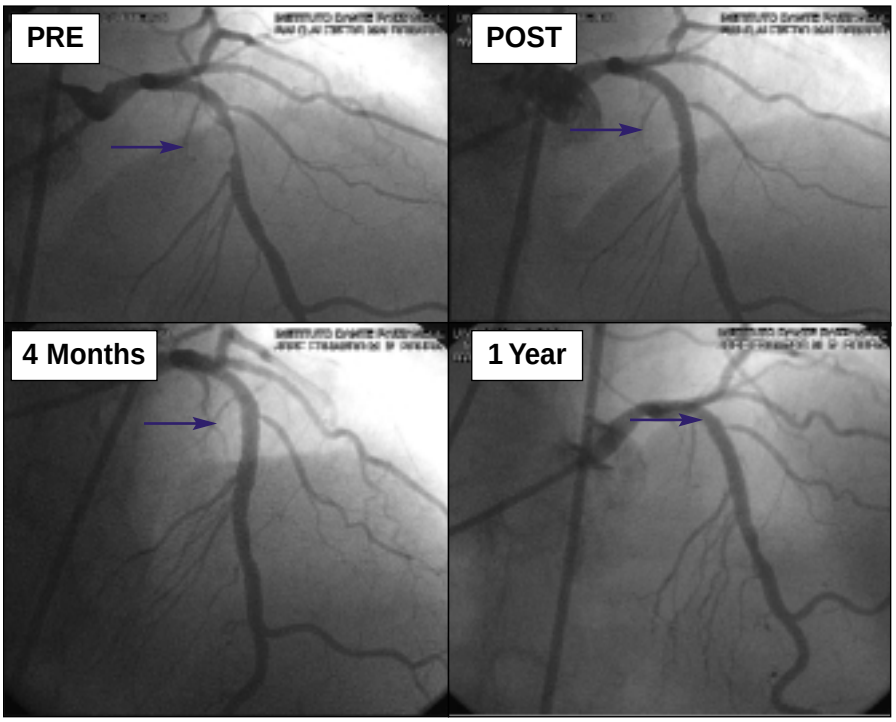


Figure 6. *Serial angiographic images of an LAD lesion treated with a sirolimus-1X-coated Bx Velocity stent demonstrating complete patency at 1 year. (Courtesy of J.E. Sousa.)*

The SIRIUS (Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with De Novo Coronary Artery Lesions) trial is a prospective, multicenter, randomized, double-blind clinical trial that will be conducted in 55 centers in the United States. A total of 1100 patients with focal de novo, native, coronary arterial lesions (2.5 mm to 3.5 mm in diameter, 15 mm to 30 mm long) will be randomized to treatment with sirolimus-coated (109 mg/cm^2) or bare-metal Bx Velocity stents. The primary endpoints of the SIRIUS trial are target vessel failure (death, myocardial infarction, or target lesion revascularization) at 9 months. Additional core laboratory analysis of angiographic and intravascular ultrasound data will be performed to determine what effects treatment has on neointimal hyperplasia and in-stent restenosis. The clinical follow-up will extend to 3 years in order to assess for late events. Enrollment in this trial began in March 2001 and is expected to be completed by the summer of 2001. In addition, the Taxol- and actinomycin D-coated stent studies are currently ongoing and are not available for analysis at this time.

The Future

The technology of the drug-eluting stent has matured and established itself as a promising method to reduce further the incidence of restenosis. It is a simple adaptation of known stent technology, because it is deployed in the same fashion as is a conventional bare-metal stent. To date, no major adverse clinical event has been observed in small clinical studies. The drug does not have a paradoxical effect of inducing intimal hyperplasia at low doses, as has been seen in radiation therapy, and thus far no edge effect (ie, restenosis at the edges of treatment) has been observed. One clinical case of late thrombosis has been observed, however, but it is too early to determine if this is attributable to the drug-eluting stent.

Will the drug-eluting stent be the Holy Grail interventional cardiologists have been seeking to overcome restenosis? It is probably the best candidate found thus far. Will there be a "dark side" to this technology? As with all new technology, initial enthusiasm is tampered by some drawbacks, and longer-term therapy will be needed to determine what these may be. Can restenosis rates really be zero? This can be possible, when measured by the binary restenosis rate, as long as the angiographic % stenosis stays below 50%. In the clinical trials performed to date, treated lesions have been in vessels 3.0 mm or greater; therefore, the expected restenosis rate would be low regardless of whether the stent therapy were drug-eluting or bare-metal. With the RAVEL and SIRIUS trials soon to be completed, we expect to find the answers to these questions very soon. If these randomized trials confirm the initial findings of the pilot studies, then this indeed may be the Holy Grail for which we have been looking. The next questions to ask will then be how much will this Holy Grail cost, and can our strained

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health care system bear this additional cost? ■

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Main Points

- The angiographic restenosis rate of coronary stenting is 10% to 20% in patients with short lesions and large vessels, but increases to 30% to 60% in patients with diabetes or lesions that are diffuse, in small vessels, or at a bifurcation.
- Although stenting initially creates a larger lumen size, it results in a later 56% to 75% loss in area because of increased intimal hyperplasia.
- Currently, the only effective treatment for restenosis is brachytherapy.
- Drug-eluting stents are simple to use and help prevent negative remodeling and intimal hyperplasia. Current investigational drugs include sirolimus (Rapamycin), Taxol and its derivative, paclitaxel, and actinomycin.
- Most drug-eluting studies have used a stent coated with sirolimus, a lipophilic drug that binds to the cytosolic receptor FKBP-12, is rapidly deployed, and is retained longer in arterial tissue. Sirolimus is a potent inhibitor of cytokine and growth-factor–mediated cell proliferation and has been approved by the FDA as an immunosuppressive agent.
- In studies comparing sirolimus-coated and bare-metal stents, the sirolimus-coated stents resulted in less smooth muscle cell colonization, more residual fibrin deposition, a significant reduction in strut-associated inflammation, minimal intimal hyperplasia, and no edge effect.
- Trials of sirolimus-coated stents have also shown no adverse clinical events at longer-term follow-up.
- Ongoing, prospective, multicenter, randomized trials of drug-eluting stents are expected to clarify whether treatment with these stents can prevent restenosis without adverse effects.