Drug-Eluting Stents

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Impressive progress in medical technology has revo-lutionized the field of cardiology over the past 2 decades. Percutaneous interventions have trans-formed cardiac catheterization from a primarily diagnostic procedure into a powerful therapeutic tool. Despite improvements in bare metal stent design and the refinement of intravascular radiation therapy, pre-vention and treatment of restenosis after percutaneous intervention, specifically in-stent restenosis, remains problematic. With new insights in vascular cell biology and greater understanding of the mechanisms under-lying in-stent restenosis, an innovative technology has developed that appears promising for dealing with this predicament. In April 2003, a drug-eluting stent coat-ed with sirolimus (Cypher, Cordis, Miami, FL) was ap-proved for use in the United States. In March 2004, a drug-eluting stent coated with paclitaxel (Taxus Express2, Boston Scientific, Natick, MA) also was ap-proved for use. It remains to be seen whether clinical experience will match the encouraging initial trial results. This review examines the epidemiology of in-stent restenosis, components of drug-eluting stent plat-forms, and the important trials evaluating drug-eluting stents in humans.

IN-STENT RESTENOSIS
Epidemiology

Currently, more than 1 million percutaneous inter-ventions are performed annually in the United States. Of these cases, approximately 90% involve the deploy-ment of a coronary artery stent. Furthermore, 50% of patients either have lesions requiring more than 1 stent or undergo multivessel percutaneous interventions.[1] Even ideal lesions (eg, a focal, short lesion [< 15 mm] in a large diameter vessel [> 3.0 mm]) resulted in angio-graphic binary restenosis (≥ 50% lumen diameter restenosis) rates ranging from 17% to 31%.[2–5] In fact, these "ideal" lesions make up the minority of those stented, and the actual rate of in-stent restenosis is as high as 50%.[6] These statistics have serious implications on health care economics, considering the current high cost of treating restenosis.

Pathogenesis

In-stent restenosis is primarily the result of neointi-mal hyperplasia.[7–12] The development of neointimal hyperplasia begins when the treated plaque fractures during percutaneous transluminal coronary angioplas-ty.[12–17] Immediately, migration and activation of platelets at the site of injury ensue. Activated platelets elaborate numerous substances (including platelet-derived growth factor), which causes the migration of inflammatory cells, primarily monocytes and neutro-phils.[11,12,18,19] These inflammatory cells in turn secrete other growth factors and cytokines.[20–24] The net result of these processes is the proliferation of medial vascu-lar smooth muscle cells at the site of injury.[25–27] These activated vascular smooth muscle cells produce an extracellular matrix resulting in neointimal hyperpla-sia, which ultimately is responsible for in-stent resteno-sis. The hyperplastic process reaches its peak 6 months after stenting. However, the clinical manifestations of in-stent restenosis can occur up to 9 months after the procedure or even longer. The expression of in-stent restenosis may range from asymptomatic angiographic narrowing to recurrent angina/myocardial infarction (MI) and/or total occlusion.

Predictors of In-Stent Restenosis

Several studies have identified angiographic and clinical predictors of in-stent restenosis. **Table 1** depicts the characteristics associated with higher rates of post-procedural restenosis.[28–30] More recently, Farb et al[31] identified morphologic factors that may predict in-stent restenosis. These features include the extent of procedu-ral medial injury and medial fracture length. Features related to the plaque itself also are important: in-stent restenosis increases when the intimal plaque contains

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Table 1. Predictors of Restenosis

Small vessel diameter (< 3 mm)

Long lesions (> 15 mm)

Long stents

Suboptimal stent deployment

Bifurcation lesions

Ostial location of the lesion

Increased number of stents per lesion

Multiple vessels stented

Diabetes

neovessels and when stents are applied to plaques with large lipid cores, which typically contain abundant inflammatory cells. Additionally, there is a growing body of literature suggesting that stent design can influence risk of restenosis.[32–35] Stents with thin struts, as opposed to wide struts, are associated with less inflammation and decreased in-stent restenosis. There is a lack of consensus regarding the benefits of stent implantation in small vessels in comparison to conventional balloon angioplasty.

Existing Treatments for In-Stent Restenosis

Various therapies exist to treat established in-stent restenosis. Unfortunately, most of these modalities do not produce satisfactory long-term results. Systemic drug delivery (statins, angiotensin-converting enzyme inhibitors, corticosteroids, methotrexate, angiopeptin, and others) at the time of angioplasty has been studied and was demonstrated to be of little or no benefit with regard to restenosis.[36–41] These approaches failed because local drug concentrations were inadequate to affect the pathologic process. In addition, most of these drugs were aimed at preventing neointimal hyperplasia and yet were tested in the era in which angioplasty was performed without stenting. Because the restenotic process following conventional balloon angioplasty is a function of recoil and remodeling, these drugs would not be expected to prevent in-stent restenosis resulting from these mechanisms. With this in mind, trials are currently underway to test various systemic drugs in the stent era.

Two proven therapies useful in the treatment of in-stent restenosis are conventional balloon angioplasty and intravascular radiation therapy. Conventional balloon angioplasty can treat focal in-stent restenosis effectively. Intravascular radiation therapy, or brachytherapy, can treat more diffuse in-stent restenosis.[42–44] Brachytherapy results in improved outcome with less angiographic restenosis and decreased target vessel revascularization.[45–49] However, there are a number of

important limitations to its use. Brachytherapy requires the assembly of a multidisciplinary team, including radiation therapists, radiation oncologists, and interventional cardiologists. Additionally, in early incarnations of this technology, late thrombosis was documented in up to 10% of patients.[50,51] This complication has been reduced dramatically with the use of prolonged dual antiplatelet therapy and the avoidance of new stent deployment at the time of brachytherapy. Restenosis at the edges of the treated segment, or "edge effect," is another problem associated with intravascular radiation therapy.[52–54] Radiation exposure is another limiting factor.

Diffuse restenosis also can be treated with coronary artery bypass grafting. Total occlusion, the worst-case scenario for restenosis, remains problematic and sometimes requires referral to cardiac surgery.

DRUG-COATED STENT PLATFORMS

A drug-coated stent has several putative advantages over a bare metal stent. The drug-coated stent addresses both the remodeling/recoil and hyperplasia mechanisms of restenosis in one device. It maximizes the drug effect locally, while it minimizes the potential for systemic toxicity. Furthermore, drug release can be manipulated using a polymer coating.

There are 2 major subtypes of coated stents: biocompatible-coated and drug-coated. Biocompatible coatings line the abluminal surface of the metal stent in an attempt to decrease the inflammatory response. Several biocompatible coatings have been investigated in humans with equivocal or negative results.[55–67] Additionally, heparin has been investigated as a drug coating. Although heparin-coated stents are reported to have lower rates of subacute thrombosis, they do not appear to have a significant impact on restenosis or major adverse cardiac events (MACE) rates, which were defined as death, MI, or target vessel revascularization.[5,68–70] To date, the stents coated with antiproliferative agents (ie, sirolimus and paclitaxel) show the most promise.

The drug-coated stent platform is made up of several components. Specifically, it contains the metal stent and the drug with or without a polymer. In drug-coated stents containing a polymer, the polymer serves as the vehicle for drug delivery. The polymer and drug are mixed together and directly cover the abluminal surface of the metal stent. In drug-eluting stents, a topcoat, consisting of another thin layer of polymer, is placed over the base coat to serve as a diffusion barrier. This topcoat allows for controlled drug delivery via creation of a concentration gradient from stent to artery.
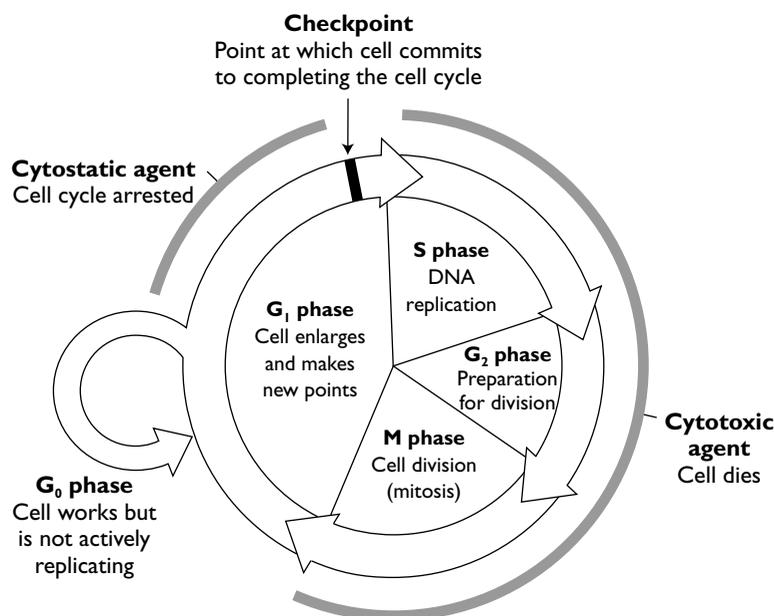
Figure. Interruption of the cell cycle by pharmacologic agents found in drug-eluting stents. Sirolimus arrests vascular smooth muscle cells in the G_1 phase. Paclitaxel kills vascular smooth muscle cells in the G_2 phase. (Reprinted with permission of the Cordis Corporation. Available at www.jnjgateway.com/images/CYPHER/SOR.pdf. Accessed 8 Jul 2004.)

Sirolimus

Sirolimus (rapamycin) was first discovered in 1973 when it was isolated from the soil of Easter Island. In 1980, its chemical structure was elucidated and found to have a similar impact on T cells as its relative compound, tacrolimus. Both agents inhibit growth factor and cytokine-stimulated, T-cell proliferation. In 1988, Gregory et al[71] noted that rats that received allografted hearts and were treated with sirolimus did not develop the usual intimal thickening associated with allograft vasculopathy. This significant discovery led to the hypothesis that if sirolimus prevented arteriopathy in the allograft model, perhaps it also could prevent restenosis in the animal balloon-injury model.[71] This premise was confirmed in a series of key experiments.

The basis for using sirolimus in a drug-eluting stent platform derives from its cytostatic effect on vascular smooth muscle cells (**Figure**). Sirolimus binds to the FKBP (FK506 binding protein), and this complex subsequently binds to the receptor designated *target of rapamycin* (TOR). Through a cascade of cellular events, the vascular smooth cell is restricted in the G_1 phase of the cell cycle, and consequently, migration and proliferation is inhibited, without destroying the cell or injuring the vessel (Figure).[72,73]

Paclitaxel

Paclitaxel is the other dominant agent that has been tested in drug-eluting stent platforms. It is a naturally-occurring plant derivative extracted from the Pacific yew, *Taxus brevifolia*, and is well known for its utility as an antineoplastic agent. It works as a microtubule-stabilizing agent and thereby inhibits the cell cycle at the G_2/mitosis phase transition (Figure). Paclitaxel inhibits smooth muscle cell migration and proliferation and, because of its highly lipophilic characteristic, has the potential for long-lasting effects by residing in the arterial vessel wall for extended periods and by being delivered without a polymer.[74]

DRUG-ELUTING STENT TRIALS
Sirolimus—Clinical Feasibility Trial

The first human experiences with a drug-eluting stent were observational studies with a sirolimus-eluting stent[75–77] (**Table 2**).These trials enrolled 45 patients with lesions at low risk of restenosis (short lesions in large vessels); 30 in Sao Paulo and 15 in Rotterdam. The Sao Paulo patients were further subdivided into 2 groups of 15 patients. One group received a fast-release (sirolimus eluted over 15 days, with the majority over 48 hours) and the other group received a slow-release (sirolimus eluted over 30 days) stent. The patients were followed clinically, angiographically, and by intravascular ultrasound (IVUS). The results in the Rotterdam group at 2 years were excellent, with an average sustained in-stent late loss of nearly zero and a binary restenosis rate of 0% in both groups.[78] Serious late complications attributed to the drug-eluting stent were virtually absent with the exception of a single case of late thrombosis. Evaluation of MACE rates revealed a 92% event-free survival at 2 years.[78]

Table 2. Drug-Eluting Stent Trials

Stent Platform/ Drug Agent	Trials	Study Design (N)
Bx Velocity Stent platform/ sirolimus	Pilot studies[75,76]	Observational study (45)
CYPHER stent/sirolimus	RAVEL[79]	RCT (238)
CYPHER stent/sirolimus	SIRIUS[81]	RCT (1101)
Supra-G stent platform/ paclitaxel (directly bound)	ASPECT[84]	Pilot RCT (177)
V-Flex Plus stent platform/ paclitaxel (nonpolymeric)	ELUTES[82]	Pilot RCT (192)
QuaDS-QP2 stent platform/ QP2 (7-hexanoyltaxol) polymer sleeves	SCORE[85,86]	Pilot RCT (266)
NIRx (bare metal) stent platform, TAXUS stent/ paclitaxel (polymer)	TAXUS I[87]	Safety and efficacy/ RCT (61)
	TAXUS II[88]	Efficacy/RCT (536)
	TAXUS III[89]	Pilot to treat in-stent restenosis (28)
	TAXUS IV[90]	RCT (1314)

RCT = randomized, controlled trial.

RAVEL Trial

The encouraging results from pilot studies led to RAVEL, a randomized study of the Cypher stent (a sirolimus-coated balloon expandable stent) in the treatment of patients with de novo native coronary artery lesions.[79] This study was the first randomized, double-blind, controlled trial testing drug-eluting versus bare metal stents. The investigators examined 238 patients with single de novo lesions (< 18 mm long, 2.5–3.5 mm) in 19 centers in Europe and Latin America. The protocol called for a 6-month angiographic follow-up and 1-, 6-, 12-month, and annual clinical follow-up to 5 years. As with most current studies investigating drug-eluting stents, the investigators excluded patients with long lesions, ostial lesions, significant calcium, and/or presence of thrombus angiographically. The results at 1 year demonstrated a binary restenosis rate of 0% versus 26% ($P < 0.001$) and MACE-free survival of 94% versus 71% ($P < 0.001$) in the sirolimus-coated group and the bare metal stent group, respectively. The angiographic results were confirmed in a subset of 120 patients evaluated with IVUS. IVUS revealed essentially no volume obstruction in the stent and no evidence of edge restenosis. This virtual elimination of neointimal hyperplasia translated clinically into the absence of repeat percutaneous interventions.[80]

SIRIUS Trial

After the excellent results achieved in lesions at low risk for in-stent restenosis studied in RAVEL, the same drug-eluting stent platform was tested in more complex lesions. A US multicenter, randomized, double-blind study of the sirolimus-eluting stent in de novo native coronary lesions randomized 1101 patients with de novo coronary lesions with reference diameters of 2.5 to 3.5 mm and lesion lengths of 15 to 30 mm to receive either an uncoated versus a sirolimus-eluting stent.[81] These more complex lesions required an average of approximately 1.6 stents per patient. The follow-up included clinical assessment (death, MI, or target vessel revascularization) as well as both angiographic and IVUS substudies to determine target vessel failure.

Initial results from SIRIUS were encouraging, including MACE-free survival at 9 months of 7.1% versus 18.9% ($P < 0.001$) and target vessel failure 8.6% versus 21.0% ($P < 0.001$) in the sirolimus-coated group and the bare metal stent group, respectively. There also was a 91% relative risk reduction in in-stent restenosis— 3% in the sirolimus-eluting stent group versus 35% in the bare metal stent group ($P < 0.001$). When examining "in-segment restenosis" (defined as the area within the stent plus the 5 mm proximal and distal to the stent), however, the results, while still robust, were less encouraging. Overall, in-segment restenosis rates were 9% in the sirolimus-eluting stent group versus 36% in the bare metal stent group ($P < 0.001$). Furthermore, there was a direct linear relationship between reference vessel diameter and in-segment restenosis rates. The in-segment restenosis rates for small (median, 2.30 mm), medium (median, 2.79 mm), and large (median, 3.0 mm) vessels were as follows: 15.5% versus 34.6% ($P < 0.027$), 7.5% versus 39.6% ($P < 0.001$), and 2.4% versus 25.0% ($P < 0.002$) in sirolimus-coated versus bare metal stents, respectively. Although in-stent restenosis in these more "real world" lesions was not influenced by vessel size, clearly in-segment restenosis was proportionally higher in smaller vessels. This result likely reflects the nonspecific arterial response to balloon injury outside the margins of the drug-eluting stent, which stresses the importance of developing an optimal stent-delivery platform and strategy that minimizes arterial trauma outside the confines of the stent in small vessels.

ELUTES Trial

ELUTES was a pilot trial that examined the treatment of de novo coronary lesions (diameter, 3.0–3.5 mm; length, 16 mm) with a paclitaxel-eluting stent.[82] This trial served as a dose-finding study to determine the safety and efficacy of a platform containing directly bound paclitaxel by comparing 4 different dose densities with

uncoated control stents. The protocol was designed as a prospective, multicenter, randomized, triple-blind design with 5 treatment arms and enrolled 192 patients with low-risk lesions. All of the efficacy endpoints, including 6-month percent diameter stenosis, late loss, and binary restenosis, were significantly reduced with the paclitaxel-coated stent versus the bare metal stent. However, there was no difference in the 6-month MACE rates between the paclitaxel-coated and control stents (11% in both). One patient treated with the highest paclitaxel dose had a subacute thrombotic event.[83]

ASPECT Trial

ASPECT was a prospective, multicenter, double-blind study that compared a bare metal stent versus the same stent coated with two different concentrations of paclitaxel.[84] The investigators noted a direct linear relationship of paclitaxel dose with a decrease in binary restenosis rates at 6 months (27% control, 12% low-dose, and 4% high-dose paclitaxel). Not only did paclitaxel virtually eliminate binary in-stent restenosis but also reduced percent diameter stenosis from 39% (control) to 14% (high-dose paclitaxel) ($P < 0.0001$) at 6 months. In patients treated with conventional antiplatelet therapy (aspirin plus thienopyridine), no thrombotic complications were noted. However, a small number of patients (n = 37) were treated with aspirin plus cilostazol. In this subgroup, 4 patients receiving paclitaxel-coated stents suffered thrombotic complications versus zero patients who received a bare metal stent. Based on this finding, the authors concluded that locally delivered paclitaxel exhibited an important anti-restenotic effect but may in fact delay re-endothelialization and healing and thereby predispose to stent thrombosis.

Thus, based on the ELUTES and ASPECT studies, a near linear relationship exists between the dose density of paclitaxel and the rate of in-stent restenosis, percent diameter stenosis, and late loss. Based on the results, a minimum effective dose density of approximately 3 µg/mm^2 was identified.

SCORE Trial

SCORE was a pivotal trial that compared a polymer-based paclitaxel derivate (7-hexanoyltaxol, QP-2)– coated stent to a bare metal stent in de novo coronary artery stenoses. The inclusion criteria dictated that the lesions be 20 mm or less in length and be present in vessels of 3.0 to 3.5 mm.[85,86] The study was designed to enroll 400 patients. However, after the randomization of 266 patients, the study had to be terminated early due to safety concerns. The high 10.2% MACE rate at

Table 3. Stent Thrombosis Found in the SCORE Trial

Timing of Thrombotic Event	Control (Bare Metal Stent)	Drug-Eluting Stent
Periprocedural	0	1
Discharge (d 30)	0	3
1–6 mo	0	4
≥ 6 mo	0	4

Data from Grube[85] and Kataoka et al.[86]

30 days in the QP-2–coated stent group was attributed to late stent thrombosis[86] (**Table 3**). Despite the safety issues, this trial once again demonstrated the efficacy of drug-eluting stents with an 83% relative risk reduction of binary restenosis (36.9% bare metal stent versus 6.4% QP-2–coated stent; $P < 0.001$).[86]

The SCORE trial was the first study evaluating a polymer sleeve stent delivery system. It demonstrated a significant reduction in restenosis observed at 6-month follow-up (0% restenosis in the treatment group versus 52% in the control group). However, this benefit came at the cost of late thrombotic complications (MI/death) in 12 patients (9.4%; $P < 0.01$) of those treated with the QP-2–eluting stent versus 0% who received a bare metal stent (Table 3). The thrombotic complications with the QP-2–eluting stent (up to 16 months) were ascribed to both the mechanical disruption and degradation of the stent polymer sleeves and excessively high drug dosing. Based on these findings, the authors recommended long-term clopidogrel treatment after the implantation of this specific drug-eluting stent platform.[86]

TAXUS Trials

The TAXUS studies comprise 6 individual investigations examining populations with lesions ranging from low- to high-risk de novo lesions to treatment of manifest in-stent restenosis. This series utilized polymer-based paclitaxel-eluting stents, specifically a nonerodible polymer-coated stent. The following will focus on TAXUS I, which investigated the safety and efficacy of the paclitaxel-eluting stent platform; TAXUS II, which investigated the efficacy of a slightly different platform with slow-release and moderate-release polymer coatings; TAXUS III, which evaluated this technology in the setting of restenosis; and TAXUS IV, a recent study comparing the paclitaxel-eluting stent platform with a bare-metal stent.

TAXUS I. TAXUS I was a prospective, double-blind, randomized, controlled, multicenter trial comparing the paclitaxel-eluting (n = 31) versus the same design bare metal stent (n = 30).[87] Lesion lengths were less

Table 4. Comparison of the SIRIUS and TAXUS IV Trials

	SIRIUS	TAXUS IV
Drug	Sirolimus	Paclitaxel
Patients (N)	1101	1314
Vessel diameter (mm)	2.5–3.5	2.5–3.75
Lesion length (mm)	15–30	10–28
Follow-up (mo)	9	9
In-stent restenosis (%)	3	5.5
In-segment restenosis (%)	9	7.9
Target vessel failure (%)*	8.6	7.6

Data from Moses et al[81] and Stone et al.[90]

*Target-vessel failure was defined by death, myocardial infarction, or ischemia-driven revascularization related to the target vessel.

than 12 mm and reference vessel diameters were 3.0 to 3.5 mm. At 1-year follow-up, both MACE rates as well as binary restenosis were reduced, though neither reached statistical significance. MACE rates were 3% versus 10% ($P = 0.612$) and binary restenosis was 0% versus 10% ($P = 0.112$) in the paclitaxel-coated and bare metal stent groups, respectively. Unlike the problems of in-segment restenosis seen in SIRIUS, there was no evidence of in-segment restenosis seen with the drug-coated stent at 6 months. In fact, IVUS results demonstrated efficacy with the paclitaxel-eluting stent, with 6-month neointimal hyperplasia volume reduced in the drug-coated stent group (14.8 ± 1.8) versus the bare metal stent control group (21.6 ± 10.7) ($P < 0.026$). In conclusion, TAXUS I showed evidence of safety with low MACE rates, 0% stent thrombosis, 0% binary restenosis, and 1-year target lesion revascularization of 0% using a paclitaxel-coated stent.

TAXUS II. TAXUS II was an international, randomized, multicenter, triple-blind trial of 536 patients, testing slow-release and moderate-release paclitaxel-eluting stents with polymer coatings.[88] The patients had standard risk de novo lesions 12 mm or shorter, with reference vessel diameters of 3.0 mm to 3.5 mm. The primary endpoint of in-stent net volume obstruction assessed by IVUS at 6 months was significantly reduced in both the slow-release and moderate-release cohorts (relative risk reduction, 62% for both; [$P < 0.0001$]). The 6-month angiographic restenosis rates also were significantly reduced (drug-eluting slow-release group, 2.3% versus control 17.9%; drug-eluting moderate-release group 4.7% versus control 20.2% [$P < 0.0001$]). Both cohorts also displayed significantly reduced MACE and target lesion revascularization rates. Thus, this trial demonstrated the safety and efficacy for both slow- and moderate-

release formulations with concordant improvements in clinical, IVUS, and angiographic parameters. In both the slow-release and moderate-release cohorts, there was no evidence of edge restenosis.

TAXUS III. TAXUS III examined the feasibility and safety of using slow-release TAXUS paclitaxel-eluting stent for the treatment of in-stent restenosis.[89] Twenty-eight patients with in-stent restenosis of a native coronary artery (3.0–3.5 mm in diameter and < 30 mm in length) and objective evidence of ischemia underwent restenting with the TAXUS platform. There were no Q-wave MIs, stent thromboses, or deaths at 12-month follow-up. MACE at 6 months occurred in 29% of the patients. The binary restenosis rate was 16%, and in 3 of the 4 cases, restenosis occurred in an area where there was no delivery of paclitaxel (1 distal edge dissection and 2 in a gap between stents). The investigators concluded that the polymer-based paclitaxel-eluting stent is a safe and potentially efficient treatment alternative for patients with in-stent restenosis. The fact that there were no episodes of late stent thrombosis is encouraging, although 1 patient had late total occlusion and all patients were treated with 6 months of clopidogrel. This study has several limitations including small sample size; single-arm, open-label design; and incomplete follow-up. Further studies are ongoing for additional confirmation.

TAXUS IV. TAXUS IV, which compared a slow-release paclitaxel-eluting stent with a bare metal stent of the same model, was published recently.[90] The trial showed that at 9 months, target vessel revascularization, the primary endpoint of the study, and target lesion revascularization were reduced (by 61% and 73%, respectively) in patients who received the TAXUS stent compared with the bare metal stent. Further, the coated stent reduced in-stent restenosis from 24.4% to 5.5% and in-segment restenosis rates from 26.6% to 7.9%. While the in-stent restenosis rate of 5.5% for the TAXUS stent is slightly higher than the 3.2% reported at 9 months by the SIRIUS trial investigators,[81] the in-segment restenosis rate was a full percentage point below that reported in the SIRIUS trial. The TAXUS stent brought about important reductions in restenosis across a wide range of patient characteristics and coronary lesions. Clinical benefit was noted in diabetics as well as in patients with small vessels and long lesions. These results differ slightly from the SIRIUS trial outcomes (**Table 4**).

CONCLUSION

In-stent restenosis has an incidence near epidemic proportions, with approximately 250,000 new cases

annually. Current treatments for in-stent restenosis are cumbersome, costly, and of limited efficacy. Therefore, prevention is the key. The preliminary results of drug-eluting stent trials are exciting because these new stents appear to be effective in reducing in-stent restenosis. Long-term data (up to 3 years) from trials of sirolimus-coated stents suggest unprecedented efficacy in the prevention of in-stent restenosis in low-risk lesions.[91] However, there are many unresolved issues. Concerns include cost, long-term effects, efficacy in complex lesions, in-segment restenosis rates in smaller vessels, and ideal antiplatelet therapy. In addition, the application of this technology to saphenous vein grafts, noncoronary vasculature, and nonobstructive, vulnerable plaques has not been determined. Experience with vascular brachytherapy as a treatment for in-stent restenosis has shown that restenosis may be delayed and not entirely eliminated.[44] A similar "catch-up" phenomenon may occur with the drug-eluting stent technology as the concentration of the drug in the stent and vascular intima and media decline over time.

A number of clinical trials are being designed or already are in progress to answer many of these questions. In the meantime, brachytherapy probably will maintain a role in the cardiac catheterization lab for the treatment of in-stent restenosis and drug-eluting stent failures. Improved bare metal stent technology and future generation stents will keep "plain old stenting" an option in certain subsets of patients. Despite the many unanswered questions, the findings to date mark an exciting advance in the percutaneous management of patients with symptomatic coronary artery disease. **HP**

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