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# Drug-eluting stents: The beginning of the end of restenosis?

## ABSTRACT

In multiple clinical trials, patients who received drug-eluting stents instead of plain stents during percutaneous coronary interventions had rates of restenosis that were lower by roughly one half to three fourths, depending on how restenosis was defined and on the population studied. These stents will likely be used more and more as their indications evolve.

## KEY POINTS

In-stent restenosis is due to exaggerated neointimal proliferation. Patients at higher risk include those with diabetes mellitus, longer lesions, and lesions in smaller vessels.

Two drug-eluting stents are approved by the US Food and Drug Administration: the Cypher stent, which releases sirolimus, and the TAXUS stent, which releases paclitaxel.

Whether drug-eluting stents should be used to treat complex lesions, in-stent restenosis, or acute coronary syndromes is under investigation.

Drug-eluting stents are expensive but may ultimately prove cost-effective.

**D**RUG-ELUTING STENTS are here, and they are better than ordinary stents. But how much better? What situations justify their added expense? Might they be associated with new side effects (eg, increased risk of thrombosis)? And could it be that they delay the onset of restenosis but do not prevent it?

*See related editorial, page 825*

The recent introduction of drug-eluting stents has been met with great enthusiasm. The prospect of safely implanting a stent in de novo coronary lesions with minimal risk of restenosis has generated well-deserved optimism.

This enthusiasm must be tempered, however, with the knowledge that patients and lesions come in many different forms, and that many questions regarding the effectiveness, safety, and economic implications of drug-eluting stent use in these various groups remain unanswered.

Randomized controlled studies support the use of drug-eluting stents in short de novo coronary lesions. To date, data are lacking (but studies are under way) for the use of these stents in other situations: left main trunk lesions, saphenous vein graft lesions, multivessel disease, acute myocardial infarction, bifurcation lesions, insulin-dependent diabetes mellitus, small vessels (< 2.25 mm diameter), in-stent restenosis, and chronic total occlusions.

In this article, we address the mechanisms by which drug-eluting stents prevent restenosis, and which patients are most likely to benefit from their use.

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This paper discusses therapies that are experimental or that are not approved by the US Food and Drug Administration for the use under discussion.

## ■ FROM BALLOONS TO STENTS

The number of percutaneous coronary interventional procedures performed in the United States has steadily increased over the past 10 years and now exceeds 1 million per year. Thanks to advances in procedural techniques, tools, and drugs, the success rate for these procedures now approaches 99%.

Stenting, introduced in 1993, was one of the advances that significantly reduced the procedural complication rates of balloon angioplasty. Stents mitigate the complications of acute and subacute vessel closure, intimal dissection, and elastic recoil of the vessel wall, and reduce angioplasty-related restenosis rates.

Despite these advantages, early enthusiasm for stents was somewhat diminished by the complications of stent thrombosis and in-stent restenosis.

Early studies demonstrated that the risk of stent thrombosis was related to technical factors such as inadequate stent expansion, low-pressure deployment, deployment in small-caliber vessels, poor distal coronary flow, and inadequate antithrombotic and antiplatelet regimens. This experience led to the development of practices that make stent thrombosis infrequent today. However, the problem of in-stent restenosis has been more difficult to overcome and continues to make percutaneous intervention a less than definitive treatment.

Rates of restenosis vary dramatically and depend on many clinical and angiographic characteristics of the patient population. The landmark trials of coronary stent implantation, the Stent Restenosis Study (STRESS)<sup>1</sup> and the Belgium Netherlands Stent (BENESTENT) trial,<sup>2</sup> enrolled patients with discrete stenoses in large-caliber vessels. Angiographic restenosis rates were 31.6% and 22%, respectively, and rates of in-stent restenosis as defined by the need for repeat revascularization of the target vessel were 10.2% and 13.5%, respectively.<sup>1,2</sup> Although general estimates of in-stent restenosis rates range between 10% and 20%, rates as high as 70% have been reported in certain high-risk subsets.<sup>3</sup>

## ■ MECHANISMS OF RESTENOSIS

The primary mechanism driving in-stent

restenosis is an exaggerated neointimal proliferative response. The process begins immediately after a stent is deployed, when the endothelium is injured. When the metal struts are embedded against the vessel wall, mechanical stress results in dissection of the tunica media and exposure of the subendothelial matrix. Exposure of collagen, fibronectin, von Willebrand factor, and laminin stimulates platelet activation and leukocyte infiltration at the site of injury.

Subsequently, a complex cascade of inflammatory mediators, including growth factors and various cytokines, are stimulated and released, triggering migration, activation, and proliferation of vascular smooth muscle cells at the site of stent deployment.<sup>4</sup>

In-stent restenosis usually occurs within weeks to months after stent deployment. Although acute injury triggers the vascular smooth muscle cell response, chronic wall stress after stent deployment may potentiate vascular smooth muscle cell migration and proliferation. It has been suggested that the chronic stimulus for vascular smooth muscle cell proliferation is the presence of the metallic stent itself, with consequent low-grade inflammation.

Vascular smooth muscle cell activation is a complex intracellular process, ultimately resulting in expression of mRNA responsible for translation and synthesis of proteoglycans and collagen, components of the extracellular matrix that represent the bulk of in-stent restenosis tissue.<sup>5-8</sup>

## ■ CHALLENGES IN DEVELOPING A DRUG-ELUTING STENT

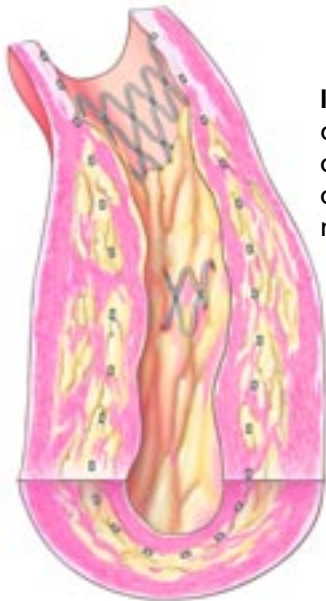
Drug-eluting stents were designed to prevent in-stent restenosis by inhibiting leukocyte infiltration and smooth muscle cell activation and proliferation. Many agents with anti-inflammatory or antineoplastic properties have been tried (TABLE 1).

The ideal agent must safely exert sufficient antirestenotic effects while maintaining a wide enough therapeutic index at the site of implantation to allow eventual stent endothelialization and adequate vessel healing. It must also have negligible or no systemic effects. Also, the drug must be compat-

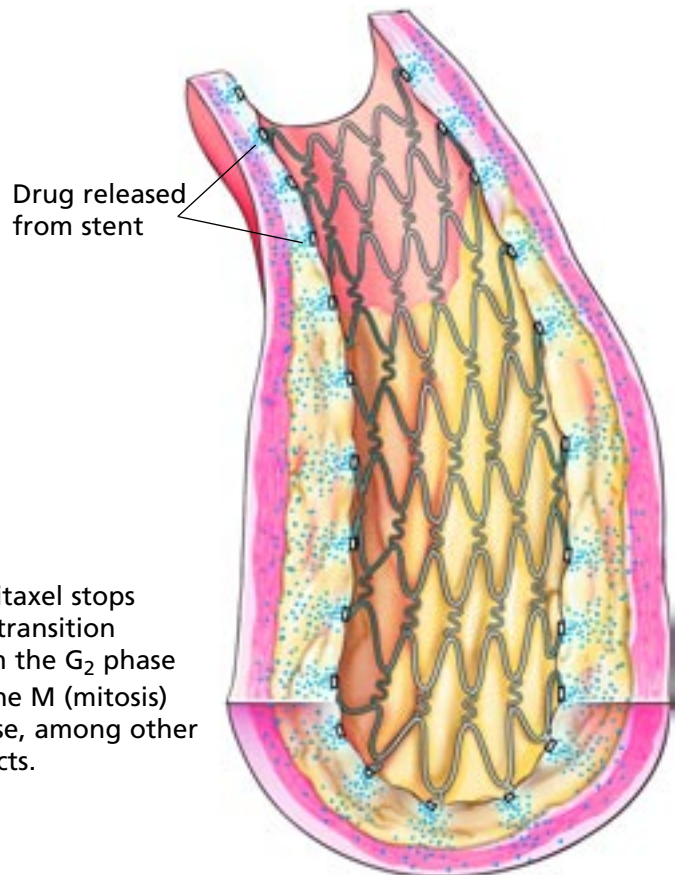
**Restenosis rates as high as 70% have been reported with plain stents**



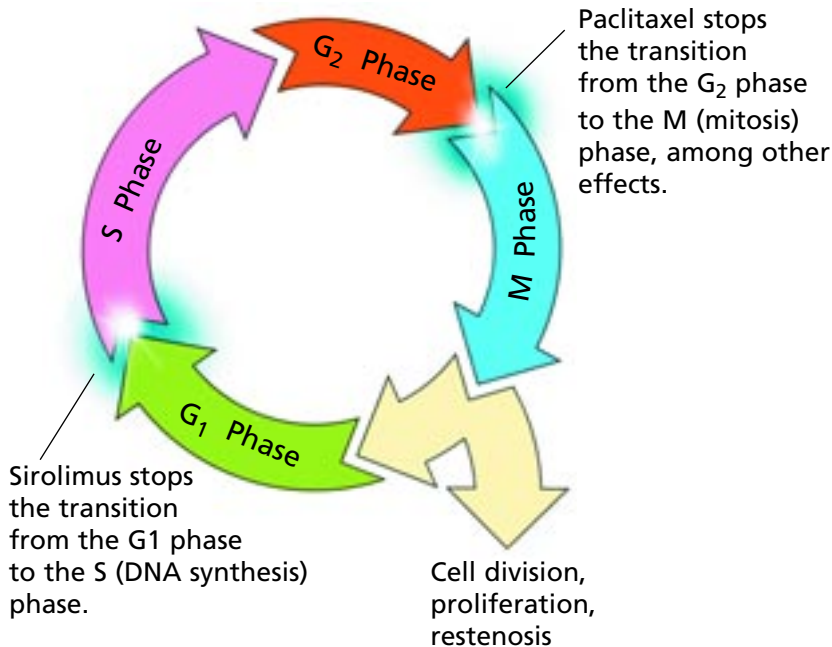
## Drug-eluting stents



**In-stent restenosis**, with migration and proliferation of vascular smooth muscle cells and white blood cells, complicates a considerable proportion of percutaneous coronary intervention procedures performed with bare-metal stents.



The cell cycle can be blocked at different phases to prevent the exaggerated cell division and proliferation in the stented artery.



**Drug-eluting stents** dramatically reduce the rate of in-stent restenosis by slowly releasing antiproliferative agents (sirolimus or paclitaxel in the two stents available in the United States) that interrupt the cell cycle and prevent cell division.

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FIGURE 1

TABLE 1

### Agents studied in drug-eluting stents

#### Antiproliferative agents

Sirolimus  
 Paclitaxel, other taxanes  
 Tacrolimus  
 Everolimus  
 Vincristine  
 Vinblastine  
 HMG-CoA reductase inhibitors  
 Doxorubicin  
 Colchicine  
 Actinomycin D  
 Mitomycin C  
 Cyclosporine  
 Mycophenolic acid

#### Immunomodulators

Dexamethasone  
 Methylprednisolone  
 Gamma interferon

#### Antithrombotics

Heparin  
 Abciximab

#### Antioxidant

Probucol

#### Estrogen

17-beta estradiol

#### Growth factor inhibitors

Tranilast  
 Trapidil  
 Angiopeptin

#### Antisense oligonucleotides

c-myc  
 c-myb

#### Collagen inhibitors

Halofuginone  
 Batimistat

Restenosis begins immediately after a stent is deployed

ible with the stent it is bonded to, so that an adequate dose can be uniformly delivered in adequate concentrations to the target tissue.

Some agents can be bonded directly to a metal stent. Others must be bound to a matrix polymer to ensure drug retention and uniform distribution on the stent. By altering the physiochemical properties of the matrix polymer, one can in theory control the kinetics of the drug elution so that the drug is released in a sustained fashion over a period of weeks after implantation.<sup>9-11</sup>

The two agents studied most extensively in human clinical trials are sirolimus and paclitaxel.

#### ■ SIROLIMUS

Sirolimus (formerly called rapamycin) was discovered in 1977. An antifungal macrolide antibiotic, it also has potent immunosuppressive effects, and it was not developed for antibiotic use. It has since been approved and used to prevent solid organ transplant rejection.

Sirolimus prevents in-stent restenosis primarily by preventing activation and proliferation of both vascular smooth muscle cells and leukocytes, which are critical to the restenosis process.<sup>12-15</sup>

Sirolimus inhibits cell growth and proliferation by arresting the mitotic cell cycle. Being a lipophilic molecule, it diffuses readily across the cell membranes of vascular smooth muscle cells and leukocytes. Once in the cytoplasm, it binds with high affinity to the FKBP-12 binding protein. The tightly bound FKBP-12/sirolimus complex ultimately inhibits down-regulation of the *p27kip1* tumor-suppressor gene, blocking the transition in the mitotic cell cycle from the G1 to the S phase.<sup>16,17</sup>

The sirolimus-eluting Cypher stent (Cordis, Miami, FL) is approved by the US Food and Drug Administration (FDA) and was introduced in the United States in April 2003. The drug is blended with a nonerodible polymer that is bonded to the stainless steel stent. The drug is released slowly over 4 to 6 weeks; approximately 80% is released by 4 weeks, and 100% by 6 weeks.

#### ■ CLINICAL TRIALS OF THE SIROLIMUS-ELUTING STENT

##### Initial proof of concept

The initial clinical trial demonstrating feasibility of the sirolimus-eluting stent enrolled 30 patients with angina pectoris. Of these, 15 received a fast-release sirolimus-eluting stent (which released the drug over < 15 days), and 15 received a slow-release sirolimus-eluting stent (which released the drug over > 28 days). All stents were 3.0 to 3.5 mm in diam-



eter and 18 mm long. All patients received clopidogrel at the time of the procedure and for 60 days thereafter. Quantitative coronary angiography and intravascular ultrasonography (IVUS) were performed at the time of the procedure and at 4, 12, and 24 months later.<sup>18</sup>

At 4 months, no patient in either group had more than 50% restenosis. Moreover, the percentage of neointimal hyperplasia (by volume) was significantly less than that observed after plain stent implantation in previous studies. At 8 months, there were no major adverse clinical events (stent thrombosis, repeat revascularization, myocardial infarction, or death).<sup>19</sup> The lack of angiographic restenosis was sustained at 12 months.

At 2 years,<sup>20</sup> the average volume of neointimal hyperplasia measured by IVUS remained minimal. Of the initial 30 patients enrolled, only 1 had angiographic restenosis (52% diameter obstruction), and only 3 had undergone target-vessel revascularization.

### **RAVEL: Effective in simple lesions**

The Randomized Comparison of a Sirolimus-Eluting Stent with a Standard Stent for Coronary Revascularization (RAVEL) trial compared the sirolimus-eluting Cypher stent with the Bx Velocity stent (which is the same as the Cypher stent but without the drug) in single, primary lesions of native coronary arteries.<sup>21,22</sup>

Two hundred thirty-eight patients with angina were randomized in 19 centers in South America and Europe. The primary target lesions were 2.5 to 3.5 mm in diameter and less than 18 mm long. Clinical characteristics of the two patient groups were comparable, as was the angiographic complexity of their treated lesions.

Patients received clopidogrel or ticlopidine at the time of the procedure and for 60 days thereafter. Clinical follow-up was at 30 days, 6 months, and 1 year. Repeat angiography was performed at 6 months.

Remarkably, at 6 months, none of the patients in the sirolimus stent group had angiographically significant binary restenosis (> 50% narrowing), vs 26.6% in the plain

stent group ( $P < .001$ ). At 1 year, the overall combined major cardiac end point (death, myocardial infarction, coronary artery bypass grafting, or target lesion revascularization) had occurred in 5.8% of the sirolimus stent group vs 28.8% in the plain stent group ( $P < .001$ ). This difference was due entirely to fewer target-vessel revascularizations. There were no episodes of stent thrombosis in the sirolimus stent group.

### **SIRIUS: Effective in higher-risk lesions**

Although the first two studies established proof of concept for the potential safety and efficacy of sirolimus-eluting stents, neither trial enrolled a significant number of patients at particularly high risk for restenosis or with complex anatomic features.

The Sirolimus-eluting Stent in Coronary Lesions (SIRIUS) trial<sup>23</sup> was a US multicenter, randomized, double-blind study of the sirolimus-eluting Cypher stent in native de novo coronary lesions. In all, 1,058 patients were randomized between February 2001 and August 2001 to receive either sirolimus-eluting Cypher stents or plain Bx Velocity stents. Compared with previous studies, SIRIUS enrolled a greater proportion of patients with high-risk features for restenosis, including diabetes, smaller vessels, and long lesions requiring overlapping stents. The primary end point was target-vessel failure (cardiac death, myocardial infarction, or target-vessel revascularization) at 9 months.

The overall target-lesion revascularization rate was 4.1% in the sirolimus stent group vs 16.6% in the plain stent group ( $P < .001$ ). The target-vessel failure rate was 8.6% with sirolimus stents vs 21% with plain stents, a 58% risk reduction ( $P < .001$ ).

Target-lesion revascularization rates were significantly lower with the sirolimus stent than with the plain stent in various high-risk subgroups:

- Patients with small vessels (about 2.3 mm): 7.3% vs 20.6% ( $P < .001$ )
- Patients with long lesions requiring overlapping stents: 4.5% vs 17.7% ( $P < .001$ )
- Patients with diabetes: 6.9% vs 22.3%. ( $P < .001$ ), although the results for patients with type 1 diabetes mellitus were not as impressive.

**Patients with type 1 diabetes may benefit less from drug-eluting stents**

TABLE 2

### Planned or ongoing trials of sirolimus-eluting stents

TRIAL	POPULATIONS, COMMENTS
E-SIRIUS	Lesions in small vessels, long lesions, patients with diabetes mellitus
C-SIRIUS	Lesions in small vessels, long lesions, patients with diabetes mellitus
ARTS II	Multivessel percutaneous coronary intervention vs coronary artery bypass graft surgery
SISR	In-stent restenosis
DECODE	Patients with diabetes mellitus

### Major questions remain about the use of drug-eluting stents in acute coronary syndromes

#### E-SIRIUS: Further corroboration

The European SIRIUS (E-SIRIUS) trial further corroborated the efficacy of the Cypher stent in reducing restenosis rates.<sup>24</sup> Patients in this multicenter, randomized, double-blind study had de novo coronary stenoses with a reference-vessel diameter of 2.5 to 3.0 mm and lesion length of 15 to 32 mm, and were randomized to receive either a sirolimus-eluting stent or a plain stent.

The primary end point was the minimum lumen diameter in the stent, measured angiographically at 8 months. Secondary angiographic end points included in-stent and in-segment binary restenosis, and in-lesion minimum lumen diameter. Secondary clinical end points were major adverse clinical events and target-lesion revascularization rates at 9 months.

At 9 months, the in-stent minimum lumen diameter was 2.22 mm in the sirolimus stent group vs 1.33 mm in the plain stent group ( $P < .0001$ ). Rates of the secondary end points were also significantly lower with the sirolimus stent:

- Binary restenosis 5.9% vs 42.3% ( $P = .0001$ )
- Major adverse clinical events 8.0% vs 22.6% ( $P = .0002$ )
- Target-lesion revascularization 4.0% vs 20.9% ( $P = .0001$ ).

#### OTHER POSSIBLE APPLICATIONS FOR THE SIROLIMUS-ELUTING STENT

**Treating complex lesions.** The sirolimus-eluting stent has been used successfully in complex atherosclerotic lesions such as bifurcations,<sup>25</sup> chronic total occlusions, very long lesions, and left main stenoses.<sup>26</sup> Large-scale trials of its use in these lesions are either planned or ongoing (TABLE 2).

**Treating in-stent restenosis.** Once in-stent restenosis has occurred, it is likely to recur, and after subsequent percutaneous interventions to treat it, recurrence rates are between 30% and 70%. Currently, intravascular brachytherapy is the only treatment proven to reduce rates of recurrent in-stent restenosis.

Two recent reports of the use of sirolimus-eluting stents for in-stent restenosis suggest they are a viable treatment option.<sup>27,28</sup> In this procedure, the old stent is left in place, and the new stent is inserted within the old stent and expanded. To date, the FDA has not approved the use of drug-eluting stents to treat in-stent restenosis. The sirolimus-eluting Stent for In-stent Restenosis (SISR) trial, a randomized study comparing the sirolimus-eluting stent with brachytherapy, is currently enrolling patients throughout the United States.

**Treating acute coronary syndromes.** Patients with acute coronary syndromes are another challenging population who may benefit from drug-eluting stents. However, major questions remain about safety and efficacy.

The hallmark characteristics of the “culprit” lesion in acute coronary syndromes include a ruptured plaque, disrupted endothelium, platelet aggregation, and fibrin deposition; therefore, inhibition of local vascular healing with a drug-eluting stent may in theory predispose to adverse thrombotic events. In vitro, sirolimus reduces endothelial function and enhances platelet aggregation<sup>29,30</sup>; whether these proaggregatory effects have clinical relevance is not established. It is also unclear whether sirolimus causes less platelet aggregation when combined with the stent polymer.

Despite these theoretical concerns, outcomes were similar in 198 consecutive patients with acute coronary syndromes who received



sirolimus-eluting stents compared with a similar cohort of patients who received plain stents in a registry at a single medical center.<sup>31</sup> At 30 days, the rate of major adverse clinical events was 6.1% with sirolimus-eluting stents vs 6.6% for plain stents ( $P = .8$ ). Similarly, stent thrombosis occurred in 0.5% of the sirolimus stent group vs 1.7% with plain stents ( $P = .4$ ). In multivariate analysis, the incidence of major adverse clinical events was not influenced by sirolimus stent use (odds ratio 1.0, 95% confidence interval 0.4–2.2,  $P = .97$ ).

These findings suggest that sirolimus-eluting stents are safe to use in acute coronary syndromes, but no general conclusions can be made at this time. Randomized controlled trials are warranted.

### ■ SIROLIMUS STENT RESTENOSIS IN THE REAL WORLD

The reasons that sirolimus-eluting stents fail to prevent all cases of in-stent restenosis are not completely understood.

Despite attempts to broaden the inclusion criteria, randomized controlled trials thus far have failed to enroll sufficient numbers of the very broad spectrum of patients treated in most contemporary clinical practices. For instance, patients with diseased saphenous vein grafts, bifurcation lesions, and prior restenosis have not yet been well studied. It has therefore been difficult to restrict use of the sirolimus-eluting stent to patients specifically matched to inclusion criteria in the randomized trials.

In an attempt to define better the morphological and clinical features of in-stent restenosis after sirolimus-eluting stent implantation in the “real world,” Lemos et al<sup>32</sup> recently reported follow-up angiographic or IVUS results in a registry of 121 consecutive patients with complex coronary stenosis features receiving sirolimus-eluting stents. These cases of drug-eluting stent implantation included treatment for in-stent restenosis, lesions at bifurcations, left main coronary artery occlusions, chronic total occlusion, very small vessels, long segments, and acute myocardial infarction.

Observations from this registry and others<sup>33</sup> suggest that restenosis after drug-eluting

**TABLE 3**

### Complete or ongoing trials of paclitaxel-eluting stents

TRIAL	POPULATIONS, COMMENTS
TAXUS I	Short (< 15 mm), de novo coronary lesions
TAXUS II	Short (< 15 mm), de novo coronary lesions
TAXUS III	In-stent restenosis
TAXUS IV	Slow-release stents, long (10–28 mm), de novo coronary lesions
TAXUS V	Slow-release stents, long (10–46 mm), complex de novo coronary lesions
TAXUS VI	Moderate-release stents, long (18–40 mm), complex de novo coronary lesions

stent implantation is usually focal and occurs most frequently at stent edges, stent strut fracture sites, or regions of vessel trauma receiving inadequate drug concentrations. Systemic drug resistance has not been observed.

### ■ PACLITAXEL

Paclitaxel is an antineoplastic drug that had been used to treat solid organ cancer before its application in coronary intervention was explored. It is a lipophilic molecule that readily diffuses across cell membranes.

The primary action of paclitaxel that makes it an effective inhibitor of restenosis is that it is a potent stabilizer of microtubules, by polymerizing the alpha units and subunits of tubulin. Since microtubule disassembly is essential for the transition from the G2 to the M phase in the mitotic cell cycle, stabilization arrests mitosis and cell proliferation. Microtubule dysfunction also inhibits cell migration, reducing the infiltration of vascular smooth muscle cells and leukocytes into the zone of injury caused by stents.<sup>34</sup>

### ■ CLINICAL TRIALS OF PACLITAXEL-ELUTING STENTS

Clinical trials of paclitaxel-eluting stents have been encouraging. Early studies were performed using a variety of stent platforms,

**Sirolimus and paclitaxel inhibit proliferation by stopping mitosis**

matrix polymers (or no polymer at all), and drug concentrations.<sup>35,36</sup> Although the first studies of stents coated with paclitaxel derivatives implanted in human coronary arteries had mixed results,<sup>37–42</sup> more recent results from the paclitaxel-eluting stent (TAXUS) trials (TABLE 3) have been very promising.

TAXUS I, performed in Europe, demonstrated the feasibility of using a slow-release paclitaxel-eluting stent to treat coronary artery lesions.<sup>43</sup>

Both TAXUS II<sup>44</sup> (done in Europe) and TAXUS IV<sup>45</sup> (done in the United States) showed significant reductions in binary restenosis compared with plain stents.

TAXUS IV included 1,326 patients with single de novo lesions 2.5 to 3.75 mm in diameter and less than 28 mm long, who were randomized to receive the slow-rate release paclitaxel-eluting TAXUS stent (Boston Scientific, Natick, MA) or the uncoated Express 2 stent from the same company. At 1 year, the rate of the primary end point (ischemia-driven target-vessel revascularization) was 4.7% with the paclitaxel stent vs 12% with the plain stent ( $P < .001$ ). Angiographic follow-up was prespecified in a subset of 732 patients and was complete in 559. Among these patients, binary restenosis occurred in 5.5% with the paclitaxel stent vs 24.4% with the plain stent, a 77% difference ( $P < .0001$ ).<sup>45</sup>

A potential bias of routine angiographic follow-up is that patients may undergo target-vessel revascularization on the basis of angiographic findings alone, and not symptoms. This would be especially true in the plain stent group, as one would expect to find higher rates of binary restenosis in this group. This was confirmed in the TAXUS IV trial at 1 year. In the plain stent group, a significantly higher percentage of patients who underwent routine angiography had target lesion revascularization compared with those who did not have routine angiography (18.4% vs 12.8%,  $P = .04$ ). This was not the case in the paclitaxel stent group (5.7% vs 3.3%,  $P = .18$ ).

Despite this shortcoming, the reduction in both target-lesion revascularizations and binary restenosis in the TAXUS IV trial remains impressive. Subgroup analyses revealed significant reductions in angiographic restenosis rates for patients with small vessels (reference-

vessel diameter  $< 2.5$  mm), diabetes (including insulin-dependent diabetes), and long lesions ( $> 20$  mm).

Of note, although angiographic restenosis rates were reduced for patients with insulin-dependent diabetes, the more clinically relevant end point of target lesion revascularization was not significantly improved in this subset (5.9% with the paclitaxel stent vs 13.0% with the plain stent,  $P = .32$ ). Neither the TAXUS IV nor the SIRIUS trial demonstrated a significant reduction in clinical target-vessel revascularization rates with drug-eluting stents vs plain stents in patients with type 1 diabetes.

Paclitaxel-eluting stents have been available in Europe, Asia, Australia, and South America for some time, and the TAXUS stent was approved in the United States in March 2004.

TAXUS V and TAXUS VI are both randomized, controlled, double-blind trials of the slow-release and moderate-release TAXUS stents, respectively. Both trials have enrolled patients with long (10–46 mm) and complex de novo lesions. The results of the TAXUS VI trial were recently presented but have not yet been published. At 9 months, the in-segment binary restenosis rate was 12.4% in the paclitaxel stent group vs 35.7% in the plain stent group ( $P < .0001$ ). Late lumen loss was also significantly lower in the paclitaxel stent group (0.24 mm vs 0.66 mm,  $P < .0001$ ).

One of the most striking findings in this trial was a dramatic reduction in rates of binary restenosis in diabetic patients: 10.8% in the paclitaxel stent group vs 47.6% in the plain stent group ( $P = .0005$ ).

The TAXUS V in-stent restenosis trial will study the efficacy of paclitaxel stents for the treatment of in-stent restenosis.

## ■ OTHER DRUGS

Trials are under way to study other drug-stent combinations, most notably everolimus and other rapamycin analogues.

A trial of the Endeavor drug-eluting stent (ENDEAVOR I) is a nonrandomized registry of 100 patients with de novo lesions, studying the rapamycin analogue ABT-578 (Abbott Laboratories, Abbott Park, IL) on the cobalt-

**Critics warn that drug-eluting stents may merely delay stenosis, not prevent it**





alloy Driver stent platform. The results were recently presented at the 2004 Paris Course on Revascularization. Angiographic in-stent late lumen loss was found to be 0.33 mm at 4 months. One-year follow-up results, however, while clinically excellent with very low target-vessel failure rates, showed an increase in in-stent late lumen loss to 0.58 mm.

Critics of drug-eluting stents have warned that adding drugs to stents may not prevent restenosis, but may merely delay it. The results from ENDEAVOR I add some credibility to this argument.

### ■ PROBLEM OF SUBACUTE STENT THROMBOSIS

After the Cypher sirolimus-eluting stent was introduced in the United States in April 2003, reports of subacute stent thrombosis caused some concern. These reports remain anecdotal, and rates of subacute thrombosis were not higher than in controls in the randomized trials discussed earlier. By November 2003, the FDA had received more than 360 reports of subacute stent thrombosis associated with the Cypher stent. Considering that more than 575,000 Cypher stents were distributed in this time, this rate is comparable to estimated historical rates with plain stents.

Prospective registries are being organized to understand this issue more clearly. Since subacute stent thrombosis carries significant rates of myocardial infarction and death, the clinical benefit of drug-eluting stents in complex interventional procedures should be considered, but based on current evidence, this potential detriment should not preclude their use.

### ■ WHEN ARE THEY WORTH THE ADDED COST?

The question of who should receive drug-eluting stents is complex. Medical, financial, and ethical considerations should be evaluated in

each case. Since restenosis has not been shown to affect mortality rates, the theoretical advantages of reducing restenosis rates are in improving quality of life and reducing use of limited financial and hospital resources.

Undoubtedly, the immediate procedural cost of drug-eluting stent implantation will be higher than with plain stents. These costs may be mitigated by reductions in future interventional procedures, prescriptions for antiangiogenic medications, and time away from work.

Current drug-eluting stents are charged to hospitals at \$2,500 to \$2,700 per stent, which is about three to four times the cost of a plain stent. For patients receiving a single drug-eluting stent, on average, this cost is recouped by reduction in need for future treatments. Due to fixed reimbursement patterns, implantation of more than one or two stents is generally done at a financial loss to the hospital, and sometimes to society as whole, depending on the risk of target-vessel revascularization without them.

Also unknown is whether reductions in restenosis will make percutaneous coronary intervention a more favorable strategy than coronary artery bypass surgery. The question warrants further study.

Currently, randomized controlled studies support the use of the sirolimus-eluting Cypher stent and the paclitaxel-eluting TAXUS stent in short de novo coronary lesions, but data for their use in longer, more complex lesions is accruing. Whether selective use of drug-eluting stents for patients at higher risk for in-stent restenosis with plain stents will be the most effective strategy is being debated.<sup>46,47</sup>

With each day that drug-eluting stents are implanted throughout the world, we learn more about their safety, efficacy, and new technical challenges. As with most advances in medicine, the true impact and degree of benefit of drug-eluting stents will be evident only after they have been used over a long time.

**Restenosis has not been shown to affect mortality rates**

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