ABSTRACT

Cardiovascular disease is the leading cause of death in the United States, and atherosclerosis is a major contributor. Vessels that are constricted, or stenosed, due to arteriosclerosis can be revascularized via methods such as percutaneous transluminal coronary angioplasty and coronary artery bypass grafting. The vast majority of percutaneous procedures are coupled with the placement of a stent. Restenosis, the renarrowing of an artery, is a serious medical phenomenon that occurs in about one third of patients 6 months postangioplasty. This renarrowing is characterized by elastic recoil, negative remodeling, and neointimal hyperplasia. The mechanical stent can prevent vascular contraction and recoil; however, the rate of in-stent restenosis ranges from 15% to 40% as neointimal proliferation in the stent remains a problem after stent placement. Brachytherapy has been investigated as treatment of stent restenosis with success. Drug-eluting stents have been studied in an effort to achieve even lower restenosis rates while maintaining good clinical outcomes. Sirolimus, a cytostatic macrolide agent, and paclitaxel, a well-known cytotoxic cancer treatment, are the 2 antiproliferative agents most extensively evaluated as drug-eluting stents in coronary artery disease. Sirolimus-eluting stents have demonstrated very low restenosis rates and low incidences of major adverse cardiac events (MACE) in 2 prospective, randomized, blinded, controlled clinical trials. Some formulations of stents coated with paclitaxel are effective in preventing restenosis, but other formulations are associated with unacceptably high MACE rates. The single-digit restenosis rates reported in clinical trials of drug-eluting stents is a major milestone in the fight against cardiovascular disease and therefore a cause for excitement in the medical community.

The leading cause of death for both men and women in the United States is cardiovascular disease (CVD), accounting for almost twice as many deaths as all forms of cancer. Coronary heart disease (CHD) represents the overwhelming majority (54%) of these CVD deaths. Importantly, CHD is a leading cause of death in adults who are at the peak of their productive lives. Atherosclerosis, resulting in coronary artery disease (CAD), is a leading cause of deaths from myocardial infarction (MI) and stroke. In fact, nearly 75% of all CVD deaths are due to atherosclerosis. Arteriosclerosis, a type of atherosclerosis, is a slow and progressive disease characterized by the thickening and hardening of arteries. This condition involves deposits of fatty substances, cholesterol, cellular waste products, calcium, and other substances on the inner lining of an artery. This plaque usually affects large- and medium-sized arteries. Plaques can grow large enough to significantly reduce blood flow through an artery, resulting in the constriction or narrowing of an artery, or stenosis.

Arteriosclerosis can start to form when the endothelium of an artery is damaged. Three proven causes of such damage include hypercholesterolemia and hypertriglyceridemia, hypertension, and smok-
Recent evidence suggests inflammation in the blood may play a role in triggering MI and stroke. Thrombosis, which is triggered by the inflammation, can transiently or permanently occlude a vessel or can become detached, resulting in embolism at a distant site.

Revascularization is indicated in severe CAD, and the most frequently applied technique to treat stenosed arteries is percutaneous transluminal coronary angioplasty (PTCA). This procedure has increasingly been performed in recent years due to the longer life expectancy of the population and, thus, the growing incidence of CAD. From 1987 to 2000, the number of PTCA procedures increased by 262% and the number of patients undergoing this procedure increased by 260%. Based on recent figures from the American Heart Association, in the year 2000, PTCA was performed an estimated 561,000 times in the United States. Of these, 64% were performed on men and 50% were performed on patients aged 65 years or older. Most PTCA procedures are performed with stents, wire-mesh tubes. Unfortunately, stents can be compromised by scar tissue ingrowth, a process called restenosis.

Coronary artery bypass grafting (CABG), another common procedure for the treatment of arteriosclerosis, allows the rerouting of blood around clogged arteries and thereby improves the supply of blood and oxygen to the heart. An estimated 519,000 CABG procedures were performed in the United States in the year 2000.

The purpose of this paper is to review in-stent restenosis and currently approved therapy for its treatment. In addition, drug-eluting stents will be described, including anticipated benefits in reducing restenosis.

**Restenosis**

Once PTCA or CABG has been performed, CAD may still progress. Restenosis, the narrowing of vessels, is a serious event that occurs in approximately one third of patients 6 months postprocedure and generally requires another revascularization procedure. New stenoses may also occur in grafts or native vessels following CABG. In an effort to reduce restenosis associated with angioplasty, a stent is typically used; this form of therapy now represents 70% to 90% of all angioplasty procedures. Two prospective, randomized controlled trials that compared conventional coronary balloon angioplasty with stent implantation in patients with stable and unstable angina with single de novo stenosis demonstrated significant reductions in restenosis with the use of the stent. Although the use of stents is associated with a reduced rate of restenosis compared with balloon angioplasty alone, in-stent restenosis remains an important risk in this patient population.

**In-stent Restenosis**

The process of restenosis after balloon angioplasty is characterized by elastic recoil, negative remodeling, and neointimal hyperplasia at the site of injury. The placement of a mechanical stent prevents negative recoil and remodeling; therefore, restenosis in patients with a stent is primarily caused by ingrowth of tissue. This neointimal proliferation is a product of physiological and pathological responses marked by platelet activation, inflammation, and proliferation of smooth muscle cells. Pathological migration and proliferation of smooth muscle cells in the vessel wall can be stimulated by balloon angioplasty and stent placement.

The rate of in-stent restenosis ranges from 15% to 40%, and is highest in patients with diabetes or complex lesions. Similar to that observed after routine angioplasty, the time course of in-stent restenosis is within 6 to 9 months of the procedure. The best method to treat in-stent restenosis is unclear, but most patients receive repeated balloon angioplasty with
either the same size or a larger balloon. Unfortunately, recovery of the lumen size achieved during initial stent implantation is generally not obtained. Furthermore, stented patients who develop restenosis have an increased risk of further restenosis after repeated coronary intervention.

**TREATMENT OF RESTENOSIS**

**ROTABULATION**

One option for attempting to achieve larger lumen size following in-stent restenosis is rotational atherectomy (rotablation). Results of the first multicenter, prospective, randomized trial that compared rotablation followed by adjunctive low-pressure PTCA (rotational atherectomy; n = 152) with PTCA alone (n = 146) were recently published. Patients with in-stent restenosis were eligible to participate in this study. The primary clinical outcome was minimal luminal diameter (MLD) at 6 months after treatment. No significant differences in MLD were observed between treatment groups before or immediately after intervention. However, at 6 months, PTCA was associated with significantly greater net gain in MLD compared with rotational atherectomy (0.67 ± 0.54 mm vs 0.45 ± 0.57 mm; P = .0019). More rotational atherectomy patients presented with restenosis of greater than 50% compared with PTCA patients at the 6-month end-point (65% vs 51%, P = .039). These results demonstrate that better long-term outcome was achieved with PTCA alone compared with rotational atherectomy with adjunctive low-pressure PTCA. Other atherectomy devices, such as laser or directional atherectomy, have not proved to be more effective than rotablation for this indication.

**BRACHYTHERAPY**

Currently, brachytherapy is the only approved method of treating established in-stent restenosis. Vascular radiation using γ- or β-rays prevents restenosis by inhibiting the proliferation of smooth muscle cells in response to injury. Line sources, liquid sources, gas and membrane sources, and stent-based delivery are among the various delivery mechanisms that have been or are currently under investigation. Preliminary studies evaluating the efficacy of coronary stenting plus catheter-based intracoronary γ-radiation demonstrated significant reductions in angiographic, ultrasonographic, and clinical indexes of restenosis in patients with previous coronary restenosis. The composite clinical endpoint (death, M1, stent thrombosis, and revascularization of the target lesion) was reached by significantly fewer patients treated with radiation (15%) compared with patients treated with placebo (48%; P = .01; Figure 1). The Proliferation Reduction with Vascular Energy Trial (PREDICT) study was a randomized trial comparing coronary stenting plus intracoronary radiation with placebo. The primary endpoint of this study was the composite clinical endpoint. The results of the PREDICT study demonstrated a significant reduction in the composite clinical endpoint in patients treated with radiation compared with placebo [P = .01; Figure 2]. These findings suggest that brachytherapy is an effective treatment for restenosis after coronary stenting.

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Figure 2: SIRIUS: All Clinical Events to 9 Months of Follow-up

![Figure 2: SIRIUS: All Clinical Events to 9 Months of Follow-up](image)

MACE = major adverse cardiac event; SIRIUS = (please add); TVR = target vessel revascularization; TVF = target vessel failure. Adapted with permission from Moses JW. SIRIUS 1 study slides: Clinical and angiographic outcomes, Slide #31 and #32.
(PREVENT) was a prospective, randomized, sham-controlled study evaluating intracoronary β-radiation in 105 patients with de novo or restenotic lesions. Results of this study show β-radiation of de novo or restenotic lesions to be a safe and effective treatment measure for hindering the development of restenosis following stent or balloon angioplasty.

As briefly described below, more recent trials using radiotherapy confirmed the results observed in these smaller initial studies, leading to the widespread acceptance of endovascular radiation therapy for in-stent restenosis.

The durability of radiation as treatment for restenosis was evaluated in the Scripps Coronary Radiation to Inhibit Proliferation Post-stenting Study (SCRIPPS), a double-blind randomized trial that compared 192Ir (n = 26) with placebo (n = 29) in patients with restenosis after coronary angioplasty. Patients were followed up for 36 to 46 months. Target lesion revascularization occurred significantly less often with 192Ir (15.4%) compared with placebo (48.3%; P < .01). 192Ir was associated with significantly lower incidence of the composite clinical endpoint of death, MI, or target lesion revascularization (23.1%) compared with placebo (55.2%; P = .01).

Patients with in-stent restenosis were followed up for 9 months after receiving 192Ir (n = 131) or placebo (n = 121) in the Gamma-1 trial. Radiation was associated with significant reductions in the composite endpoint of death, MI, and need for repeated revascularization of the target lesion; however, because of late thrombosis in the radiation group, this benefit was due to a reduced need for revascularization and not a decrease in death or MI. This late thrombosis was observed only in patients who received a new stent and had already discontinued oral antiplatelet therapy.

Despite the beneficial effects observed with brachytherapy, late thrombosis or edge failure is found at the treatment edges in one third to one half of patients. The cause of this finding is unknown but may be due to a dropoff of radiation or "geographic miss." Geographic miss is an inadequate coverage by the radioactive source of the target region. Due to limitations associated with brachytherapy and the desire to reduce clinical events to a greater degree, investigations into preventing restenosis with drug therapy have been conducted.

**Drug-Eluting Stents**

Systemic administration of immunosuppressive or antiproliferative drugs in the treatment of CAD is complicated by the need to achieve adequate local concentrations of the drug without systemic toxicity. The use of a pharmacologic agent that inhibits cellular proliferation coupled with a mechanical prosthesis to withstand remodeling forces was the thinking behind the use of drug-eluting stents to prevent restenosis.

**Sirolimus-Coated Stents**

Sirolimus is a macrolide antifungal agent with immunosuppressive properties similar to cyclosporine A and tacrolimus that prevents smooth muscle proliferation after vascular injury. The agent is cytostatic—not cytotoxic—and thereby prevents cells from dividing without destroying them; thus, cells are left in a quiescent state. This novel cell-cycle inhibitor was initially used to prevent rejection of renal transplants. Sirolimus exerts its antiproliferative activity by binding
to specific cytosolic proteins, immunophillines. G1 to S cell-cycle progression is blocked by the inhibition of mammalian target of rapamycin protein. Sirolimus prevents T-cell proliferation as well as the proliferation and migration of smooth muscle cells.

The First in Man (FIM) study involved 45 patients at 2 centers. At one site in this initial pilot study, patients with angina were treated with a slow-release sirolimus-coated stent (n = 15) or a fast-release sirolimus-coated stent (n = 15). No in-stent or edge restenosis was found at 4- and 6-month follow-up. Additionally, 1 year after stent placement, neointimal hyperplasia was minimal and similar to that shown at 4 months. No repeated revascularizations, stent thromboses, or MACE occurred at 1 year. This small study demonstrates the efficacy and safety of sirolimus-coated stents in humans.

At the second site for the FIM study, 15 patients with single-vessel CAD were treated with slow-release sirolimus-coated stents and were followed up for 6 months. Neither in-stent restenosis nor changes in minimal lumen diameter were observed. No evidence of an edge effect was observed in the segments proximal and distal to the stents. Additionally, quantitative intravascular ultrasound showed negligible intimal hyperplasia.

These promising initial results with sirolimus-eluting stents were verified in the Randomized Study with the Sirolimus-Eluting Velocity Balloon-Expandable Stent in the Treatment of Patients with De Novo Native Coronary Artery Lesions (RAVEL) trial. RAVEL was a randomized, double-blind trial that compared 2 types of stents for revascularization of single, primary lesions in native coronary arteries: sirolimus stent (n = 120) vs standard stent (n = 118). Patients were followed up for 1 year. The primary angiographic endpoint was in-stent luminal late loss; secondary endpoints were percentage of in-stent stenosis of the luminal diameter, rate of restenosis, and the minimal luminal diameter of the stented segment and of the 5-mm segments proximal and distal to the stent at 6 months. A composite of MACE, death, MI, CABG, and revascularization of the target lesion or vessel served as the primary clinical endpoint.

At follow-up, late luminal loss at both the proximal and distal edges of the active stent and at the stented segment was significantly less with active therapy than in the control stent group (P < .001 for all 3 comparisons). Additionally, the mean minimal luminal diameter of the stented segment was greater in the sirolimus-stent group compared with control (2.88 ± 0.48 mm vs 2.23 ± 0.50 mm; P < .001). Sirolimus-stent therapy was associated with significantly less neointimal hyperplasia and volume obstruction compared with standard-stent therapy (P < .001 for both comparisons). After 1 year of follow-up, a significantly lower rate of overall MACE was observed with sirolimus therapy compared with control (5.8% vs 28.8%, P = .001; Table 1). None of the sirolimus-treated patients required percutaneous revascularization of the target lesion compared with 22.9% of the standard-stent group. Additionally, no adverse events were attributable to the sirolimus coating. The results of this randomized controlled study indicated that sirolimus-eluting stents demonstrated efficacy in the prevention of neointimal proliferation, restenosis, and associated clinical events in patients with CAD.

Table 1. Cardiac Events in the Hospital and During 12-month Follow-up in the RAVEL Study

<table>
<thead>
<tr>
<th>Event</th>
<th>Sirolimus Stent (n = 120)</th>
<th>Standard Stent (n = 118)</th>
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<tr>
<td>Before discharge</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death (n)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Myocardial infarction (n)</td>
<td>3</td>
<td>3</td>
</tr>
<tr>
<td>Q-wave</td>
<td>2</td>
<td>1</td>
</tr>
<tr>
<td>Non-Q-wave</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Coronary artery bypass grafting (n)</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>After discharge</td>
<td></td>
<td></td>
</tr>
<tr>
<td>Death (n)</td>
<td>2</td>
<td>2*</td>
</tr>
<tr>
<td>Myocardial infarction (n)</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Q-wave</td>
<td>0</td>
<td>0</td>
</tr>
<tr>
<td>Non-Q-wave</td>
<td>1</td>
<td>2</td>
</tr>
<tr>
<td>Coronary artery bypass grafting</td>
<td>1†</td>
<td>1†</td>
</tr>
<tr>
<td>Percutaneous revascularization of target lesion (n)</td>
<td>0</td>
<td>27</td>
</tr>
<tr>
<td>Total, n (%)</td>
<td>7 (5.8)</td>
<td>34 (28.8)‡</td>
</tr>
<tr>
<td>Cumulative event-free survival (%)</td>
<td>94.1†</td>
<td>70.9‡</td>
</tr>
</tbody>
</table>

* Both patients had had previous myocardial infarctions.
† Coronary artery bypass grafting was performed to treat progressive disease of the left main coronary artery and the ostium of the anterior descending coronary artery, not the target lesion.
‡ P < .001 for the comparison between the 2 groups with the use of Fisher’s exact test.
§ P < .001 for the comparison between the 2 groups with the use of the log-rank test.
Reprinted with permission from Morice et al. N Engl J Med. 2002;346(23). ©2002 Massachusetts Medical Society. All rights reserved.
Recently, preliminary results of the largest randomized, double-blind, controlled study involving a drug-eluting stent were released. In the CYPHER™ Sirolimus-Eluting Stent in Coronary Lesions (SIRIUS) study, the sirolimus-eluting stent (n = 533) was compared with a bare-metal stent (n = 525) in patients with a de novo native coronary lesion. In order to more closely follow everyday practice, the patient population in this study included those with diabetes (26.4%), long lesions (average 14.4 mm), hyperlipidemia (73.6%), hypertension (67.7%), and multivessel disease (41.6%) and patients with previous PTCA or CABG (34.2%).

Angiographic data at 8-month follow-up demonstrated minimal in-stent late lumen loss (0.17 mm) in patients treated with the active stent. Sirolimus therapy was associated with a 3.2% rate of angiographic in-stent restenosis compared with 35.4% observed with control (P < .001)—a 91% reduction compared with bare-stent therapy (Table 2). Angiographic in-lesion restenosis (including a 5-mm area at both ends of the stent) occurred at a rate of 8.9% with the sirolimus-eluting stent and 36% in the control group (P < .001). This represents a 75% reduction compared with the control group. Over one fourth (27.7%) of patients had lesions that required placement of overlapping stents. The sirolimus-treated patients experienced a significantly improved event-free survival rate (92.7%) compared with control (80.7%; P < .001; Figure 2).

Despite the discontinuation of antiplatelet therapy at 3 months postprocedure, the rate of thrombosis in the active stent group was 0.4%, a rate that was indistinguishable from the control stent. After 9 months of follow-up, a 75% reduction in the target lesion revascularization rate was observed in the sirolimus-eluting stent group compared with the bare-metal stent group. These results support the beneficial effects of the sirolimus-eluting stent observed in the earlier studies in preventing restenosis in CAD patients. Follow-up is planned to extend for 5 years in order to evaluate long-term efficacy and safety.

Based on the beneficial effects observed in clinical studies, the sirolimus-eluting stent was approved in Europe in April 2002 and is currently available in more than 50 countries. In October 2002, the Food and Drug Administration (FDA) advisory panel voted to recommend approval of the sirolimus-eluting stent to reduce restenosis of de novo coronary artery lesions in patients with CAD. The stent was finally approved on April 24, 2003.

### Table 2. SIRIUS: Quantitative Coronary Angiography Peri-Stent Analysis—Late Loss

<table>
<thead>
<tr>
<th></th>
<th>Sirolimus (%)</th>
<th>Control (%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>In-stent</td>
<td>0.17</td>
<td>1.00</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Proximal margin</td>
<td>0.17</td>
<td>0.33</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>Distal margin</td>
<td>0.04</td>
<td>0.24</td>
<td>&lt;.001</td>
</tr>
<tr>
<td>In-segment</td>
<td>0.24</td>
<td>0.81</td>
<td>&lt;.001</td>
</tr>
</tbody>
</table>


**Paclitaxel-Coated Stents**

QP-2–Coated Stents. One of the first agents investigated in drug-eluting stents was the well-known cancer treatment, paclitaxel. This cytotoxic drug is a diterpenoid that interferes with cell microtubule function. Paclitaxel is highly lipophilic and is therefore able to readily pass through the hydrophobic barrier of cell membranes. Depending on the duration of drug delivery and dosage, paclitaxel has profound inhibitor effects on neointimal thickening. At high doses, this agent leads to inflammatory vessel response, cell loss, medial thinning, and increased risk of stent thrombosis; therefore, tissue pharmacokinetics, dose control, and delivery profile are essential when using paclitaxel.

The first human trial evaluating a taxane analogue (QP-2) in a drug-eluting stent was a small pilot study in 14 patients. The dose of QP-2 was 800 µg/stent and patients were followed up for 8.3 months. No significant in-stent or edge stenosis was observed during follow-up. Lumen narrowing in the vessel segments immediately adjacent to the stent ends was similar to narrowing observed with conventional stents and was mainly due to plaque formation. Due to these favorable results with QP-2–eluting stents, further study was pursued.

The Study to Compare Restenosis (SCORE) was a randomized multicenter study that evaluated the efficacy and safety of the QP-2–coated stent. The stent delivered 3 g/sleeve, and patients were to receive concomitant ticlopidine for 30 days. The enrollment goal of this study was 400 patients from 17 sites. At follow-
up, QP-2-coated stents were associated with a marked reduction in restenosis (6.4%) compared with the bare stents (36.9%). These beneficial effects were observed at least 5 mm past the proximal and distal stent edges. Despite this dramatic reduction in restenosis, QP-2-coated stents were associated with frequent stent thromboses and side-branch occlusions. The 30-day MACE incidence was 10.2% and the rate of periprocedural MI was 7.1% in patients treated with the QP-2-coated stent. Due to these unacceptable safety findings, the study was ended prematurely after 266 patients had been enrolled. Extended follow-up revealed a late catch up in restenosis with the QP-2-coated stent.

Paditaxel Polymer-Coated Stents Seven Paclitaxel-Eluting Stent for Prevention of In-Stent Restenosis (TAXUS I-VII) studies have been designed to evaluate a polymer paclitaxel-coated stent (1 µg/mm²) as a slow release or as a moderate-release stent.20-32 The TAXUS I study was the first clinical trial to investigate the safety and efficacy of the TAXUS NIRX stent system (n = 31) compared with a bare-metal stent control (n = 30) in patients with de novo or restenotic lesions.31 No significant difference in 6-month angiographic restenosis rates were observed between active treatment and control groups (0% vs 10%). No patients experienced MACE at 30-day follow-up. After 1 year, the rate of MACE was 3% in the paclitaxel group and 10% in the control group. Compared with the bare-metal stent, paclitaxel-coated stents were associated with significant improvements in: minimal lumen diameter (2.60 ± 0.49 vs 2.19 ± 0.65), diameter stenosis (13.56 ± 11.77 vs 27.23 ± 16.69), and late lumen loss (0.36 ± 0.48 vs 0.71 ± 0.48; P < .01).

Based on these beneficial effects of the TAXUS stent in CAD, additional insight into the safety and efficacy of this drug-eluting stent is being sought via the TAXUS II-VII studies. The results of TAXUS II, a multinational, randomized, controlled, triple-blind study, have recently been made available.21,32 The TAXUS II study was the first clinical trial to investigate the safety and efficacy of this drug-eluting stent is being sought via the TAXUS II-VII studies. The results of TAXUS II, a multinational, randomized, controlled, triple-blind study, have recently been made available.31 No significant difference in 6-month angiographic restenosis rates were observed between active treatment and control groups (0% vs 10%). No patients experienced MACE at 30-day follow-up. After 1 year, the rate of MACE was 3% in the paclitaxel group and 10% in the control group. Compared with the bare-metal stent, paclitaxel-coated stents were associated with significant improvements in: minimal lumen diameter (2.60 ± 0.49 vs 2.19 ± 0.65), diameter stenosis (13.56 ± 11.77 vs 27.23 ± 16.69), and late lumen loss (0.36 ± 0.48 vs 0.71 ± 0.48; P < .01).

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These results of TAXUS II demonstrated reproducibility of results observed in TAXUS I. No differences between slow- and moderate-release stents were observed; therefore, the slow-release stent was selected as the minimum effective formulation in standard-risk de novo lesions. Results of TAXUS III have recently been made available, while TAXUS IV is to be completed by September 2003 and will address the optimum formulation for high-risk lesions.

Nonpolymer Paclitaxel-Coated Stents The Evaluation of Paclitaxel Eluting Stent (ELUTES) trial, a dose-finding study, evaluated the efficacy of different dosages of paclitaxel-coated stents in 192 CAD patients.22 Four drug dosages were used ranging from 0.2 µg/mm² to 2.7 µg/mm². At follow-up, a clear dose-response relationship was observed. Patients who received a higher dose of paclitaxel experienced a lower rate of restenosis. Binary restenosis rates were 20%, 12%, 14%, and 3% for the ascending paclitaxel dose groups compared with 21% for the bare-metal stent control group.

These beneficial effects of the paclitaxel-eluting stent were verified in the triple-blind, randomized, placebo-controlled Asian Paclitaxel-Eluting Stent Clinical Trial (ASPECT).33 Patients with single de novo lesions were randomized to low-dose paclitaxel (1.28 µg/mm², n = 28), high-dose paclitaxel (3.0 µg/mm², n = 28), or bare-metal stent (n = 25). Higher doses of paclitaxel were associated with greater reductions in intimal hyperplasia within the stented segment (13 ± 14 mm² in high-dose group, 18 ± 15 mm² in low-dose group, 31 ± 22 mm² in control; P < .001). This finding held true when low- and high-dose groups were analyzed separately compared with control; however, no differences between the 2 paclitaxel dose groups were observed. Restenosis rates at 6-month follow-up were lower with paclitaxel therapy (4% high-dose, 12% low-dose) compared with control.
Despite the lower rate of restenosis with high-dose paclitaxel, this group of patients experienced a high rate of MACE (up to 11.7%) due to an increased rate of stent thrombosis.

The Rx Achieve™ Drug-Eluting Coronary Stent System in the Treatment of Patients with De Novo Native Coronary Lesions (DELIVER) study, another study evaluating the efficacy of paclitaxel-coated stents, is currently under way. This trial is a prospective, randomized, parallel-group study in the setting of de novo native coronary artery lesions. Efficacy will be assessed by target-vessel failure at 270 days. Over 1000 patients are enrolled in DELIVER: 522 to receive paclitaxel-coated stents and 522 to receive bare stents. Preliminary results have reported restenosis in 22% of control and 17% of paclitaxel-coated stent patients.

**Other Drug-Eluting Stents**

Several other pharmacologic agents have been or are currently being investigated as drug-eluting stents in the setting of CAD. One such agent, actinomycin, did not demonstrate any clinical benefit in the Actinomycin Eluting Stent Improves Outcomes by Reducing Neointimal Hyperplasia (ACTION) study. Tacrolimus-coated stents are being evaluated in the Endovascular Investigation Determining the Safety of New Tacrolimus-Eluting Stent Grafts (EVIDENT) and Preliminary Safety Evaluation of Nanoporous Tacrolimus-Eluting Stents (PRESENT) studies; however, preliminary results are disappointing. The Evaluation of 9a-F-16 Methylprednisone (Dexamethasone)-Eluting Stents on the Reduction of Restenosis (EMPEROR) trial is studying the efficacy and safety of dexamethasone-coated stents. Finally, everolimus is being evaluated as a stent coating in the First Used to Underscore Reduction in Restenosis with Everolimus (FUTURE) study with encouraging early results (Table 3).

**Limitations of Drug-Eluting Stents**

The promising beneficial effects observed in the clinical investigations of drug-eluting stents appear to offer a panacea for treating CAD. However, there are some limitations associated with this form of therapy to consider. To date, only a relatively small sample size has been investigated in clinical trials. The largest such trial was the SIRIUS study, which involved over 1000 patients. As is the case in most clinical trial designs, patients with

<table>
<thead>
<tr>
<th>Study Name</th>
<th>Drug-Eluting Stent Evaluated</th>
</tr>
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<tbody>
<tr>
<td>FIM</td>
<td>Sirolimus</td>
</tr>
<tr>
<td>RAVEL</td>
<td>Sirolimus</td>
</tr>
<tr>
<td>SIRIUS</td>
<td>Sirolimus</td>
</tr>
<tr>
<td>SCORE</td>
<td>Q P-2</td>
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<tr>
<td>TAXUS I-VII</td>
<td>Paclitaxel</td>
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<td>Paclitaxel</td>
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<td>ELUTES</td>
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<td>PRESENT</td>
<td>Tacrolimus</td>
</tr>
<tr>
<td>EVIDENT</td>
<td>Tacrolimus</td>
</tr>
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Data from Grube et al. Minerva Cardioangiol. 2002;50:469-473.
complicating concurrent medical conditions were generally excluded from participation in the drug-eluting stent evaluations.\textsuperscript{8,12,30} In clinical practice, CAD patients with confounding factors, such as diabetes, bifurcated lesions, occlusions, calcified vessels, degenerative vein grafts, unprotected left main stem lesions, or acute M I are perhaps more common than the 'uncomplicated' patient usually enrolled in clinical trials. It is important to note that clinical experience with such complex patient subtypes is growing per the SIRIUS and TAXUS IV studies. Additionally, long-term efficacy and safety data with drug-eluting stents are lacking. The FDA approval recommendation for the sirolimus-eluting stent came with a request for 5-year follow-up on all patients enrolled in the 3 principal studies to date. Therefore, long-term data will be forthcoming.

**Conclusion**

CAD is a significant contributor to morbidity and mortality in the United States. Unfortunately, current treatment measures available for clinical use today are associated with a relatively high rate of restenosis. The major therapeutic goal in the treatment of CAD is to further reduce, and hopefully eliminate, the need for repeated intervention due to restenosis.\textsuperscript{10} There are 2 main parts important to any revascularization strategy: the provision of a safe and durable treatment of flow-limiting coronary obstructions and prevention of future morbidity and mortality from ongoing coronary atherosclerosis in nontreated coronary segments.\textsuperscript{35}

Vessels can re-narrow following intervention via 2 basic mechanisms: vascular contraction and neointimal proliferation.\textsuperscript{16} Vascular contraction is effectively blocked with the typical stent. On the other hand, neointimal proliferation may occur due to coronary interventions, such as balloons, stents, and atherectomy catheters. Late lumen loss after stent placement is primarily a result of intimal hyperplasia.\textsuperscript{9} The initiation of neointimal tissue proliferation within and around the stent is therefore the major limitation to stent implantation.

Currently, brachytherapy is the only approved treatment for in-stent restenosis. Significant reductions in M A CE are observed with radiation treatment; however, restenosis is still problematic with this therapy. The use of locally administered immunosuppressive or antiproliferative drugs in drug-eluting stents provides a biological and mechanical approach to prevent in-stent restenosis. Drug-eluting stents provide efficient prevention of restenosis by addressing remodeling and intimal proliferation in one device and maximize drug effect at the target lesion with minimal systemic toxicity.\textsuperscript{22}

Why all the excitement surrounding drug-eluting stents? Clinical trial evidence suggests that we have reached the day when single-digit restenosis rates coupled with acceptable clinical outcomes can be achieved when treating de novo lesions (Figure 3).\textsuperscript{30} The approval of the sirolimus-eluting stent by the FDA for the prevention of restenosis is cause for further excitement in the medical community. Currently, the sirolimus-eluting stent is the only drug-eluting stent whose efficacy and safety have been established in 2 large-scale, randomized, double-blind, controlled, clinical studies (RAVEL and SIRIUS). However, results from the TAXUS IV study evaluating paclitaxel-coated stents should be reported in the near future.

**References**


