

# New stent technologies: coated, covered and bifurcated stents

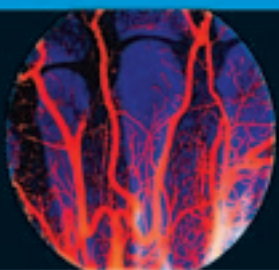
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## Abstract

Specific anatomic challenges and in-stent restenosis have been the impetus for new designs in stent technology. Drug-eluting stents, particularly the sirolimus-coated and paclitaxel-coated stents have shown efficacy in clinical trials. Ongoing studies involve the application of these stents in saphenous vein grafts, bifurcation lesions, and for in-stent restenosis. Other medications, especially everolimus, have also shown preliminary efficacy.

Stents covered with polytetrafluoroethylene are indicated for coronary perforations, and are being investigated for saphenous vein graft lesions.

A randomised trial with a self-expanding polytetrafluoroethylene-covered stent in saphenous vein graft lesions is underway. Specialised stent designs for bifurcation lesions are also in development, and early safety data are promising for this challenging anatomic subset.

Recent advances in stent technology have improved clinical outcomes in percutaneous coronary intervention. Current technology aims to upgrade applications for percutaneous revascularisation, by reducing the incidence of restenosis and improving long-term prognosis in patients with complex coronary artery disease.

## Introduction

Following the first clinical application of a coronary stent in 1986, the implantation of coronary stents has become an integral part of more than 80% of percutaneous coronary interventions. Multi-centre trials have demonstrated sustained benefit combined with effective anti-platelet therapy, which has led to the widespread use of coronary stents.<sup>1</sup> Coronary stents are evolving in both composition and design. For example, alloys such as cobalt-chromium may offer advantages over stainless steel in terms of strength, biocompatibility and radio-opacity.

New stent technology is driven by clinical requirements, and particular influences are restenosis and anatomical challenges. Specialised designs for bifurcation lesions and saphenous vein grafts are being developed. However, the most widely applicable advance has been with drug-eluting stents (Table 1) for the prevention of in-stent restenosis (ISR). This review will focus on the latest stent technology for specific anatomic lesion subsets and the prevention of ISR, including coated, covered and dedicated bifurcation stents (Table 2).

**Table 1. Summary of clinical outcomes from major trials in drug-covered stents**

Study Patient n	RAVEL 238		SIRIUS 1101		TAXUS I 61		TAXUS II 700		FUTURE 1 42	
	Sirolimus	Bare metal	Sirolimus	Bare metal	Paclitaxel	Bare metal	Paclitaxel	Bare metal	Everolimus	Bare metal
RVD (mm)	2.60	2.64	2.78	2.81	2.99	2.94	2.78 (SR) 2.72 (MR)	2.75	3.10	2.96
Late loss (mm)	0.00	0.80	0.17	1.00	0.36	0.71	0.31 (SR) 0.30 (MR)	0.78	0.10	0.83
Angiographic restenosis incidence (%)	0	26.6	3.2	35.4	0	10.3	2.3 (SR) 4.7 (MR)	19	0	9.1
TLR incidence (%)	0	22	4.1	16.6	0	6.7	4.6 (SR) 3.1 (MR)	13.3	3.8	8.3
MACE incidence (%)	3.3	27.1	7.1	18.9	0	6.7	8.5 (SR) 7.8 (MR)	19.8	7.7	8.3

**Abbreviations/definitions:** MACE, major adverse cardiac event; restenosis, luminal narrowing of  $\geq 50\%$ ; RVD, reference vessel diameter; TLR, target lesion revascularisation. TAXUS II had two experimental arms: slow release (SR) and moderate release (MR).



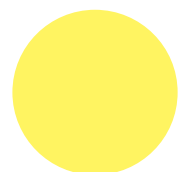
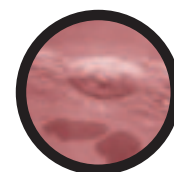
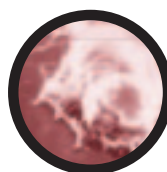
**Table 2. Summary of lesion types, stents and outcomes**

Lesion type	Stent	†Outcomes/benefits	Level of evidence
<i>De novo</i> lesion 15–30 mm long, 2.5–3.5 mm diameter	Sirolimus-coated Bx Velocity stent	<ul style="list-style-type: none"> <li>•Inhibits late lumen loss and restenosis</li> <li>•Reduces MACE and TLR</li> </ul>	Randomised, controlled trials
<i>De novo</i> lesion <12 mm long, 3.0–3.5 mm in diameter	Moderate or slow-release, paclitaxel polymer-coated NIRx stent	<ul style="list-style-type: none"> <li>•Inhibits neointimal proliferation and restenosis</li> <li>•Reduces MACE and binary restenosis</li> </ul>	Randomised, controlled trials
<i>De novo</i> lesion <25mm long, 2.5– 4.0 mm in diameter	Paclitaxel (not polymer)-coated Achieve stent	<ul style="list-style-type: none"> <li>•Inhibits late lumen loss</li> <li>•No significant reduction in binary restenosis</li> </ul>	Randomised, blinded and controlled trial
<i>De novo</i> Lesion <18 mm long, 2.75– 4.0 mm in diameter	‡Everolimus-eluting stent	<ul style="list-style-type: none"> <li>•Inhibits late lumen loss</li> </ul>	Randomised, single-blinded, single centre controlled trial
Perforation, aneurysm	PTFE-covered Jostent, coronary stent graft	<ul style="list-style-type: none"> <li>•May be successful for perforation.</li> </ul>	Patient registry data
SVG lesion	Symbiot-covered self-expanding nitinol stent encased in PTFE	<ul style="list-style-type: none"> <li>•May reduce the incidence of distal embolisation and angiographic restenosis</li> </ul>	Non-randomised study Ongoing randomised, blinded and controlled trials
Bifurcation lesion	SLK-View bifurcated stent	<ul style="list-style-type: none"> <li>•Allows alignment of the stent while maintaining access to side branch vessel</li> </ul>	Non-randomised European registry, ongoing US registry study
Bifurcation lesion	Cypher stent with T-stenting technique	<ul style="list-style-type: none"> <li>•May reduce restenosis rates for the main artery</li> </ul>	Non-randomised study

**Abbreviations:** MACE, major adverse cardiac events; TLR, target lesion revascularisation; PTFE, polytetrafluoroethylene; SVG, saphenous vein graft.

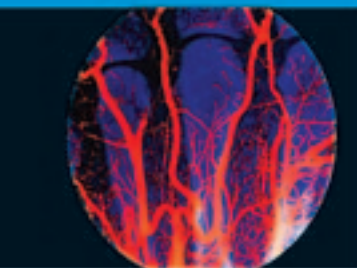
†In the controlled studies, outcomes are as compared with the uncovered or uncoated stent

‡Everolimus is an analogue of sirolimus



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## Drug-eluting stents

The most significant limitation of current coronary stenting is the need for repeat procedures. Trials comparing multi-vessel stenting and coronary artery bypass surgery have found a 16% absolute increase in the risk of requiring repeat revascularisation at 1-year follow-up, due primarily to ISR.<sup>2</sup> While brachytherapy has been developed to prevent repeat restenosis, local pharmacological treatment with drug-eluting stents has been shown to prevent initial neointimal proliferation. The most widespread clinical experience has been established with the sirolimus-eluting Bx Velocity™ stent (Cypher, Cordis, Johnson & Johnson) and the paclitaxel-eluting NIR™ (Medinol) and Express™ (Boston Scientific) stents.

### *Sirolimus-eluting stent*

Sirolimus (rapamycin), which is an immunosuppressive agent used to prevent transplant rejection, has potent anti-proliferative and anti-migratory effects on smooth muscle cells. Clinical trials have determined that sirolimus is an effective local inhibitor of restenosis. The RAVEL study, conducted in Europe, randomised 238 patients with *de novo* native coronary lesions of 2.5–3.5 mm in diameter that could be covered by a single 18 mm stent, to treatment with either a bare metal or a sirolimus-eluting Bx Velocity stent. At 6 months, no late lumen loss was observed in the sirolimus-stent group. In addition, none of the patients in the sirolimus-stent group, compared with 27% in the bare metal group, developed angiographic restenosis of  $\geq 50\%$  of the luminal diameter ( $p < 0.001$ ). At 12 months, there was a significantly higher rate of major cardiac events in the bare stent cohort compared with the sirolimus group, due to target vessel revascularisation.<sup>3</sup>

The SIRIUS trial, conducted in the United States, randomised 1101 patients with *de novo* lesions of 15–30 mm in length and 2.5–3.5 mm in diameter, to treatment with either a sirolimus-eluting stent, or an uncoated stent (control). At nine months, major

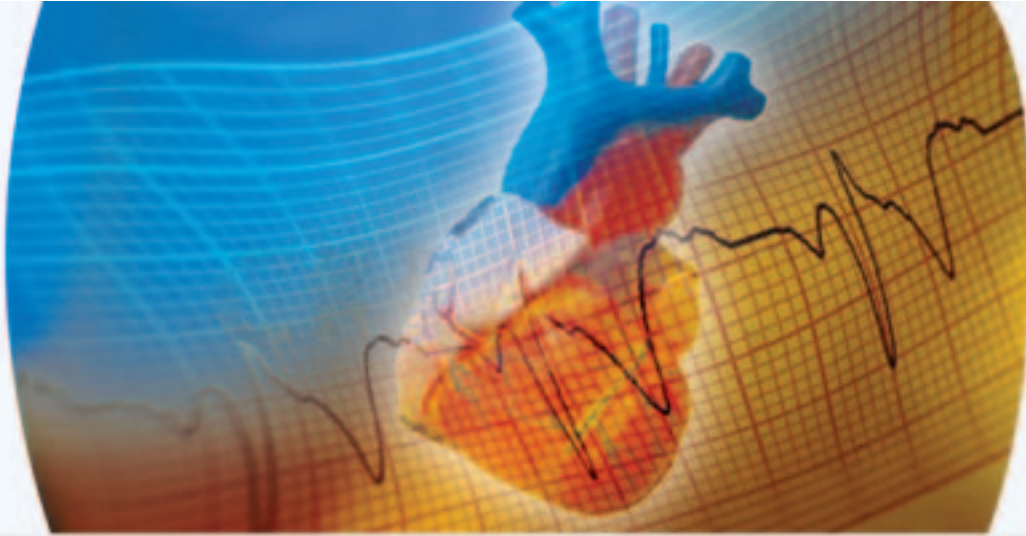
adverse cardiac events (MACE) including target lesion revascularisation occurred in significantly less patients in the sirolimus-eluting stent arm (7.1%) compared with the control arm (18.9%). A significant reduction in these events for the sirolimus-eluting stent group was also observed in all subgroups, including diabetics and patients with long lesions or small vessels.<sup>4</sup>

Ongoing studies are evaluating the use of sirolimus-eluting stents for the treatment of ISR. The first report of the use of sirolimus-eluting stents in ISR was in 16 patients with severe recurrent restenosis in native coronary arteries. In this cohort, one patient died and three had restenosis at 4 months.<sup>5</sup> Another trial investigated 25 consecutive patients with ISR who were treated with a sirolimus-eluting stent of 18 mm in length and 2.5–3.5 mm in diameter. Only one patient (4%) had recurrent angiographic restenosis at 12 months.<sup>6</sup>

Additional trials are evaluating the efficacy of sirolimus-eluting stents for the prevention of non-target lesion revascularisation events. The FREEDOM trial is a prospective randomised trial comparing multi-vessel, sirolimus-eluting stents with coronary artery bypass grafts in patients with diabetes mellitus. Five-year endpoints include mortality, cognitive function and cost-effectiveness.

### *Paclitaxel-eluting stent*

Paclitaxel (Taxol™) is a microtubule-stabilising agent used in the chemotherapy of many common solid tumours, and has activity in preventing neointimal proliferation. Initial clinical experience with the local delivery of paclitaxel by the drug-eluting Express stent was in the TAXUS I trial. Sixty-one patients with lesions that were <12 mm long, in vessels of 3.0–3.5 mm in diameter, were randomised to receive a bare metal stent or a slow release paclitaxel-eluting stent. At 6 months, there was no case of restenosis in the paclitaxel arm compared with a 10% rate in the control arm.<sup>7</sup>



The TAXUS II trial investigated 700 patients with *de novo* lesions in vessels of 3.0–3.5 mm in diameter, who were randomised to receive either a control NIR bare metal stent or a slow- or moderate-release paclitaxel-coated NIR stent. At a 6-month angiographic and clinical follow-up, the paclitaxel-coated stent, when compared with the control stent, gave a statistically significant reduction in target lesion revascularisation MACE (8% vs. 20%) and binary restenosis (3% vs. 19%). A clinical reduction in MACE was also observed at 12 months and in the subgroups of diabetic patients and patients with long lesions (>10 mm) or small vessels (<2.75 mm). Results were similar for both the slow- and moderate-release paclitaxel-eluting stents.<sup>8</sup>

The largest trial of the paclitaxel-eluting stent is the recently completed TAXUS IV trial. This was a multi-centre, randomised trial, which evaluated 1326 patients with *de novo* lesions of 10–28 mm in length and 2.5–3.5 mm in diameter. Patients were randomised to receive either a slow-release paclitaxel-eluting Express stent, or a bare metal Express stent. At 30 days, primary success and safety outcomes were similar for the bare and paclitaxel-eluting Express stents.<sup>9</sup> Nine-month primary and secondary endpoint data will be released in Q3 2003.

For the treatment of ISR with paclitaxel-eluting stents, only uncontrolled data are available. In the TAXUS III trial, 28 patients with ISR were treated with one or more paclitaxel-eluting NIR stents. The angiographic restenosis rate was 16% at 6-months, and tended to occur at gaps between paclitaxel-eluting stents.<sup>10</sup>

The TAXUS V trial is an ongoing prospective trial of the paclitaxel-eluting Express stent compared with beta brachytherapy for the treatment of ISR.

#### *Other drug-eluting stents*

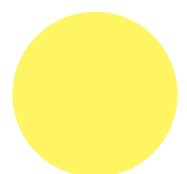
Other stents that have been studied include the everolimus (sirolimus analogue)-coated stent, the dexamethasone-coated Dexamet™ stent (Abbott

Laboratories), and the paclitaxel-coated Achieve™ stent (Guidant). The FUTURE I trial was a randomised, blinded study of the everolimus-eluting stent compared with a bare metallic stent. Late lumen loss at 6 months was significantly lower for the everolimus-eluting stent compared with the bare stent (0.1 mm vs. 0.8 mm,  $p < 0.0001$ ).<sup>11</sup> The STRIDE trial was a non-randomised trial of the dexamethasone-coated Dexamet stent for *de novo* lesions. At 6 months, two patients (3%) required target lesion revascularisation, but there were no other MACE, and the late lumen loss was 0.45 mm.<sup>12</sup> The DELIVER trial, in 1023 patients, was a randomised, blinded evaluation of the paclitaxel-coated Achieve stent compared with the MULTI-LINK™ PENTA™ bare metal stent (Guidant). There was a small but statistically significant decrease in late lumen loss with the paclitaxel-coated Achieve stent compared with the bare metal stent (0.8 mm vs. 1.0 mm,  $p < 0.003$ ). However, binary restenosis was not significantly reduced. No polymer was used with this paclitaxel stent coating, which may account for the better outcomes observed in the TAXUS trials than in the DELIVER trial.

#### **Covered stents**

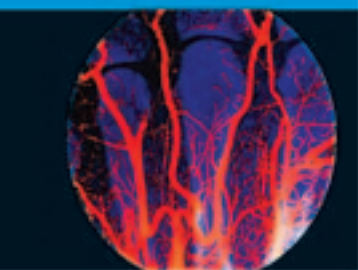
Biocompatible, covered stents were first used in peripheral arterial disease, mainly for aneurysms or vascular repair following perforation. Many different coverings have been studied including autologous venous and arterial grafts. However, the most widely studied covered stent is the polytetrafluoroethylene (PTFE)-covered Jostent™ (Jomed). The Jostent coronary stent graft has a thin layer of PTFE placed between two stainless steel stents and was initially introduced to treat native coronary artery aneurysms and coronary perforations. A case series of 12 patients with coronary perforations demonstrated effective sealing with a PTFE-covered stent after failed prolonged balloon inflation and reversal of anticoagulation.<sup>13</sup>

In coronary aneurysms, a case series of seven patients reported successful placement of



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PTFE-covered stents without complication. At 3 years, six patients were free of symptoms, and one required repeat percutaneous coronary intervention.<sup>14</sup>

The largest clinical experience with the Jostent covered stent graft is derived from a registry of 70 patients who had this device implanted to treat perforation (n=3), aneurysm (n=6), Saphenous vein graft lesions (n=7), complex lesions (n=24) and ISR (n=32).<sup>15</sup> The primary success rate of Jostent covered stent graft implantation was 96%. In the three cases of perforation, the lesion was sealed. Overall, the side branch occlusion rate was 19%, causing seven non-Q wave myocardial infarctions, two Q-wave myocardial infarctions, and one episode of successfully treated ventricular fibrillation. Four patients (5.7%) had sub-acute stent thrombosis. The overall restenosis rate was 32%, manifested mainly as edge restenosis. This high-risk lesion registry demonstrated that Jostent covered stent graft implantation is feasible if side branches can be reliably avoided; however, sub-acute stent thrombosis and restenosis rates are high.

Covered stents have also been investigated for saphenous vein graft disease, the treatment of complex ulcerated plaques and for ISR. The hypothesis is that the PTFE covering prevents debris and neointimal hyperplasia from protruding through the stent struts. A study of five patients, each with two lesions in different vein grafts, evaluated the placement of a PTFE-covered stent in one graft and a conventional stent in the other. Four of the five conventional stents required angioplasty for restenosis, whereas no covered stents needed repeat intervention.<sup>16</sup>

The BARRICADE and RECOVERS trials are ongoing multi- and single-centre randomised trials of the Jostent covered stent graft in *de novo* saphenous vein graft lesions, and are monitoring angiographic and clinical outcomes. The SYMBIOT series of trials assessed the Symbiot™-covered stent (Boston Scientific) (Figure 1), which is a self-expanding nitinol stent encased in a



Figure 1. Symbiot™-covered stent (Boston Scientific, Natick, MA)

PTFE membrane specifically designed for saphenous vein graft interventions. The SYMBIOT II trial was a non-randomised trial of 77 patients with saphenous vein graft disease and it reported a low incidence of distal embolisation and angiographic restenosis.<sup>17</sup> The SYMBIOT III trial is an ongoing, randomised, controlled trial in 700 patients with *de novo* saphenous vein graft disease, comparing the Symbiot-covered stent with a bare metal stent.

### Bifurcated stents

Coronary artery disease commonly occurs at bifurcations, secondary to flow patterns. These lesions are technically challenging and commonly result in side-branch occlusion and a higher rate of restenosis.<sup>18</sup> Several techniques use conventional stents in bifurcation lesions and include: T-stenting, Y-stenting, and the culotte method. These methods have variable success and often require further intervention. Stents designed specifically for bifurcation lesions increase access to side branches, decrease procedure time and potentially improve clinical outcomes.

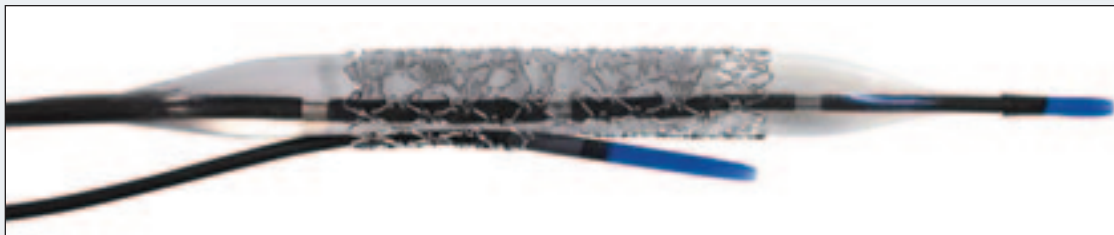


Figure 2. SLK-View stent (Advanced Stent Technologies, Pleasanton, CA)

Dedicated bifurcation stents are in development and they require wiring both the main vessel and the side branch to align a stent side-hole. The SLK-View™ stent (Advanced Stent Technologies) (Figure 2) allows alignment of the stent while maintaining access to the side branch vessel. Preliminary 6-month angiographic and clinical data in 81 patients indicate 99% procedural success, including 100% side branch access following stent deployment. The incidence of in-hospital MACE was 1%, and 6-month angiographic restenosis rates were 30%, which compares favourably to historical controls for bare metal stenting of bifurcation lesions.<sup>19</sup>

The MULTI-LINK FRONTIER™ stent (Guidant) and NIRSIDE™ stent (Medinol) are other dedicated bifurcation stents that are being assessed in non-randomised, safety studies. In addition to the specialised designs for bifurcating stents, 85 patients have been treated with one or two CYPHER™ stents (Johnson & Johnson), the majority of which were T-stents. Six-month angiographic restenosis rates were 3.1% for the main artery and 20% for the side branch.<sup>20</sup>

Advances in coronary stent technology have markedly improved procedural success, safety, and both acute and chronic outcomes. Evolving technology in stent design will lead to expanded indications and better prognosis. Ongoing trials will address the impact of newer stent technologies on the treatment of complex lesions, bifurcation lesions, small-diameter vessels, multi-vessel disease, ISR and left main disease.

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