

# Drug-eluting stents — today and the future

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## Background history

Since the introduction of percutaneous angioplasty into clinical practice by Andreas Gruentzig in 1977, the efficacy of this treatment modality for coronary artery disease has become progressively established. However, in the early days, balloon angioplasty was limited by 10-20% acute vessel failure necessitating urgent coronary artery bypass grafting (CABG) and by high rates of delayed restenosis (20-40%) necessitating frequent repeat procedures and bypass operations.

The only device that has made a difference was the introduction of the coronary stent in 1987.<sup>1</sup> Initially, bare metal stents were used as a back-up in the event of an acute vessel closure or a dissection/perforation of the coronary artery from the balloon dilation.<sup>2,3</sup> The critical role of platelet inhibition following stent implantation was not known in initial studies and stent thrombosis was a critical determinant of mortality and major cardiac events. Various anticoagulation strategies were initially tried such as warfarin, heparin and dextran with limited success and increased bleeding risk.

After these initial hiccups, it was clearly established that stenting was a good treatment but was also affected by significant restenosis (15-20%), although less than balloon angioplasty (30-40%). This was achieved primarily by eliminating elastic recoil and vascular remodelling, as shown by intravascular ultrasound (IVUS) studies and clinical trials confirmed significant reductions in restenosis compared to balloon angioplasty alone.<sup>4-6</sup>

The two seminal trials establishing the cornerstone role of stenting in the treatment of coronary artery disease were the BENESTENT (Belgian Netherlands STENT) and STRESS (Stent REstenosis Study). These studies randomised patients with focal stenoses in fairly large coronary arteries (3mm) to balloon angioplasty versus stenting using first generation Palmaz-Schatz stents. Although bleeding risk was higher in the stenting arm secondary to use of systemic anticoagulation, the need to re-intervene on the treated vessel (target vessel revascularisation [TVR]) was reduced from 23.3% to 13.5% at seven months in BENESTENT. Restenosis (defined as >50% angiographic restenosis) was

reduced from 42.1% to 31.6% in STRESS.

## Restenosis

Restenosis, however, still remains the Achilles heel of percutaneous coronary intervention and rates between 20% and 40% at six months are reported in the interventional literature.<sup>7,8</sup> Restenosis occurs primarily within the stent and is caused by neointimal hyperplasia.<sup>9</sup> Stents are associated with an increase of neointimal formation compared to balloon angioplasty as a result of excessive injury to the vessel wall and, to a lesser extent, the inflammatory process resulting from the interaction of the metal with the vessel wall. Furthermore, platelet activation, the release of cytokine and matrix production contribute to the process of restenosis following stenting.

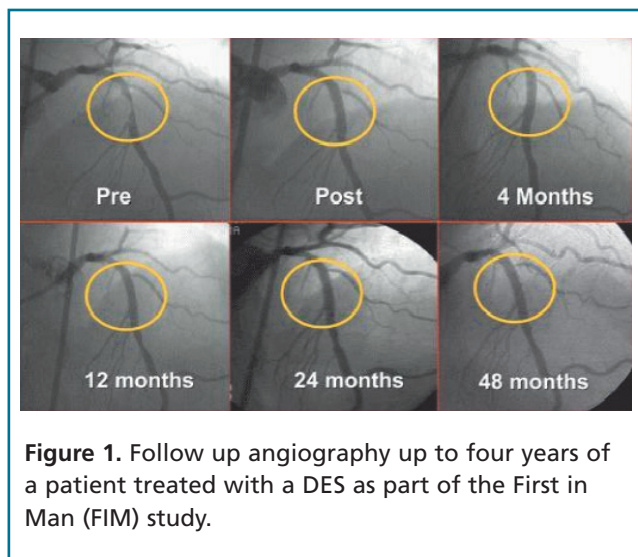
Multiple adjunctive devices have been developed over the years in an attempt to overcome restenosis, such as rotational atherectomy, excimer laser, rotablaters, transluminal extraction catheters (TECs), cutting balloons and heating balloons, with limited success. Numerous adjunctive antiproliferative and antithrombotic agents orally, intravenously and locally delivered have been studied, again without any significant success. The local delivery concept was extended by brachytherapy in the years 1997-2000 and was successful but was limited by logistics, the need for a radiotherapist, the expense of materials and delivery systems, and the limitation of the service to selected centres only. Although the incidence and severity of restenosis was reduced, often it was only delayed by a year or so.

## Significant breakthrough

One of the most significant breakthroughs has been the ability to combine an antiproliferative agent with a stent to allow local delivery and inhibition of the 'healing' process that the stent induces, but without the systemic side effects. Local drug therapy was typically delivered by means of a stent coating or polymer but initial polymers led to significant inflammatory responses in the vessel wall.

Thankfully 'inert' polymer coatings were invented and this led to the use of locally delivered therapies such as sirolimus

in experimental animals and then eventually in humans in the First in Man trial (see Figure 1). This proof of concept trial used the sirolimus stent and was performed in two centres and reported by Sousa et al in 2002.<sup>10</sup> The trial demonstrated the safety and remarkable freedom from restenosis in 45 patients treated with sirolimus-coated stents (Cypher) after four years of follow up.<sup>11-13</sup>



The phenomenal suppression of hyperplasia had never been previously observed and led to the rapid creation of randomised trials to properly evaluate the Cypher stent and, to date, three drug-eluting stents have received Conformité Européenne (CE) and Food and Drug Administration (FDA) approval for clinical use in Europe and in the US, respectively — the Cypher sirolimus-eluting stent (Cordis, Johnson & Johnson, Miami Lake, Florida, USA), the Taxus paclitaxel-eluting stent (Boston Scientific, Natick, Massachusetts, USA) and the Endeavor ABT-578-eluting stent (Medtronic).

### Sirolimus

Sirolimus is a macrolide lactone antibiotic and a potent immunosuppressive agent that inhibits cyclin-dependent kinase complexes and ultimately induces cell cycle arrest in late G1 phase. It inhibits smooth muscle cell proliferation in vitro and reduces intimal thickening in animal models of vascular injury. It also inhibits T-lymphocyte activation and proliferation.<sup>14-16</sup> It is the agent used on the Cypher stent.

### Paclitaxel

Paclitaxel is an antimicrotubule agent initially isolated from the Pacific yew tree (*Taxus brevifolia*),<sup>17</sup> is the active ingredient in the drug Taxol (Bristol-Myers Squibb) and has been widely used in the treatment of cancer, primarily in the breast and ovaries.<sup>18</sup> It has been directly applied to stents bound to polymer as an antirestenosis strategy and an entire programme of clinical trials was inaugurated to examine its efficacy in TAXUS I-VI.

## Trial evidence

### Cypher

The RAVEL trial (randomised study with the sirolimus-eluting Bx Velocity balloon expandable stent) was a pivotal multicentre, randomised trial designed to determine the safety and efficacy of the use of the sirolimus versus bare stent in patients with lesions <15mm long and between 2.5mm and 3.5mm in diameter. It was designed to show significant reductions in restenosis as defined by the degree of restenosis as measured by computer software analysis of coronary angiograms. The sirolimus stent was used in 120 patients and the bare stent in 118 patients. The binary restenosis rate in the sirolimus group was 0 compared with 26.6% of those in the standard stent group ( $p<0.001$ ).<sup>19,20</sup> There were no episodes of stent thrombosis.

At one-year follow up, the overall rate of major cardiac events was 5.8% in the sirolimus stent group and 28.8% for the bare stent, driven by the revascularisation of the target vessel. IVUS performed in a subset of 95 patients from the RAVEL study demonstrated nearly complete abolition of the neointima in the sirolimus group. These remarkable results led to European approval for general use of Cypher stents in daily clinical practice. Despite the increased cost, the use of drug-eluting stents has become widespread and they are used in the 'real world' now for practically all lesions.

The SIRIUS trial was a multicentre, large scale 1,101 randomised, double-blind study of the SIRolImUS-coated Bx Velocity stent for patients with de novo lesions. This pivotal study was designed to examine the efficacy and safety of the sirolimus-coated stent in a more difficult subset of patients than the RAVEL trial; 24.6% had diabetes and longer lesions (15-30mm) located in smaller vessels (2.5-3.5mm). Eight-month follow up performed on 85% of patients detected 10.5% diameter stenosis in the sirolimus and 40.1% in the control stent ( $p<0.001$ ). The binary in-stent restenosis rate in patients receiving the sirolimus-eluting stent was 3.2% versus 35.4% in the control group ( $p<0.001$ ).<sup>21</sup> Clinical events at nine months demonstrated target vessel failure defined as death, myocardial infarction (MI) or repeat percutaneous transluminal coronary angioplasty (PTCA) of treated vessel in the sirolimus group versus 21.0% in the control group ( $p<0.001$ ) and target lesion revascularisation (TLR) rates fell from 19.4% in the bare metal stent group to 6.4% using sirolimus-eluting stents.

The safety of the sirolimus-eluting stent was also demonstrated in the SIRIUS study, with no evidence of late thrombosis and with similar rates of death (0.9%) and MI (2.8%) in the sirolimus group compared to 0.6% and 3.2% in the control group, respectively. The SIRIUS study identified subsets of patients and lesions who continued to experience high rates of restenosis, despite the sirolimus-eluting stent. In particular, insulin-dependent diabetic

patients had 35% of restenosis that was not significantly different from the control stent in this subset of patients. Other subsets of patients with restenosis that varied from 16% to 18% were patients with long lesions and small vessels. Overall, however, the use of the sirolimus-eluting stent led to a 90% relative risk reduction of in-stent restenosis.

Critical endpoints in stenting trials are TVR or TLR and major adverse cardiac events (MACEs) which are death, MI, stroke and TVR. Overall stent thrombosis in these trials is 0.6%. In over 1,200 patients in all trials using Cypher stents, target vessel revascularisation is 5.7% compared to 19.2% using bare metal stent (a reduction of 70%) at nine months.

### Taxus

Taxus stents have been examined in multiple lesion subsets in the TAXUS I-VI clinical trial programme. TAXUS I, like RAVEL, assessed the safety and efficacy of the paclitaxel-coated stent versus bare metal stents in de novo or restenotic focal coronary lesions<sup>22</sup> and, as such, was the first in human clinical assessment of this stent. Restenosis was reduced from 10% to 0%, which was impressive especially given the accepted low restenosis rate in this group of patients (non-diabetic, short focal lesions and vessels >3mm only included). Two year follow up of TAXUS I demonstrated sustained freedom from MACE in the paclitaxel arm over the bare metal stented group (3.3% vs 10.0%).

TAXUS II examined the IVUS findings in de novo focal coronary lesions treated with slow or moderate release Taxus stents versus the bare metal equivalent.<sup>23</sup> Once again, restenosis was significantly lower (2.3% and 4.7%) using paclitaxel versus bare metal (approximately 20%) at six months. As the initial proof of feasibility was shown in TAXUS I and II, longer more complex lesions were treated including in-stent restenosis in the later TAXUS trials<sup>24-26</sup> with similar procedural and clinical success. Taxus, like Cypher, has received CE and FDA approval.

Various other antiproliferative agents such as tacrolimus, everolimus and zotarolimus (Endeavor stent) have been evaluated by other companies for the purposes of applying them to a stent. Recently the Medtronic Endeavor stent has received CE and FDA approval for clinical use. The recently presented ENDEAVOR II trial demonstrated the efficacy of a recent addition to the drug-eluting stent market, the Medtronic Driver stent coated with ABT-578, a novel sirolimus-type analogue. Although angiographic restenosis seemed higher in the ABT-578-coated stent compared to historical restenosis using Cypher or paclitaxel, clinical event rates were no different, which was reassuring.

### Head-to-head data

The SIRTAX trial was one of the first head-to-head trials

evaluating treatment with sirolimus-eluting stents compared with paclitaxel-eluting stents among patients with coronary artery disease, with no exclusions based on presenting syndrome or lesion site, complexity or length. In a prespecified manner, a subset of 600 patients underwent angiographic follow up at eight months. The study was conducted at a single institution and funded by the hospital without industry funding.<sup>27</sup>

The primary endpoint of MACE at nine months was lower in the sirolimus-eluting stent group versus the paclitaxel-eluting stent (6.2% vs 10.8%,  $p=0.009$ ), driven primarily by target vessel revascularisation in the paclitaxel arm (4.8% vs 8.3%,  $p=0.03$ ). The endpoint of target vessel failure was also lower in the sirolimus-eluting stent group (7.0% vs 11.6%,  $p=0.01$ ). Stent thrombosis did not differ by treatment group (2.0% for the sirolimus-eluting stent group and 1.6% for the paclitaxel-eluting stent group). Among the subgroup analysis, the treatment benefit in the primary endpoint for the sirolimus-eluting stent group was notably better in the diabetics (HR 0.31,  $p=0.013$ ) than in the non-diabetics (HR 0.66,  $p=0.110$ ).

The recently completed REALITY trial was presented at the American College of Cardiology (ACC) meeting in Orlando, Florida, in 2005. It compared outcomes of similarly matched patients treated with either Taxus or Cypher stents and showed no significant difference in outcomes whether or not sirolimus or paclitaxel stents had been used. At eight-month clinical follow up, there was no difference in MACEs (9.2% for sirolimus-eluting stent group vs 10.6% for paclitaxel-eluting stent group,  $p=0.41$ ) or any component of MACE (death 1.8% vs 1.2%,  $p=0.50$ ; MI 4.8% vs 5.5%,  $p=0.62$ ; and TLR 5.0% vs 5.4%,  $p=0.81$ , respectively). Stent thrombosis by 30 days was higher in the paclitaxel-eluting stent group (1.8% vs 0.4%).

The findings of the REALITY trial are discordant with the SIRTAX results, both of which demonstrated improvements in the angiographic parameter of late lumen loss with sirolimus-eluting stents, but showed no difference in the primary endpoint of binary restenosis or in clinical MACE rates. In addition, stent thrombosis was significantly higher in the paclitaxel-eluting stent group in the REALITY trial, while no difference in stent thrombosis was observed in the present SIRTAX trial. A recently published meta-analysis of all trials using the two stents sought to examine if there were differences in efficacy and safety.<sup>28</sup> The interesting outcome examined was TLR, which is the primary clinical criteria of interest to a patient, i.e. how likely is the patient to need repeat intervention on the lesion treated. TLR rates for sirolimus were 5.1% vs 7.8% with paclitaxel ( $p<0.01$ ). There were no differences in the rates of death, MI or stent thrombosis.

In contrast, however, Park et al recently presented seven months of MACE data at the Transcatheter Cardiovascular Therapeutics (TCT) 2004 of a non-randomised registry

utilising Taxus and Cypher stents in 294 patients treated during the same period of time. He demonstrated no significant difference in MACE rates between the two stents (3.4% vs 6.0%,  $p=0.387$ ).

### Stent thrombosis

The overall incidence of stent thrombosis is 0.5-2.0%<sup>29,30</sup> and has always been an important clinical issue since the very start of stenting. In the very first stent trials, patients experienced acute or subacute stent thrombosis, defined as complete thrombosis within the stent within 14 days of implantation in 20% of cases in 1991. Stent thrombosis is associated with a mortality rate nearing 50% and an infarct rate of 100%. Factors associated with stent thrombosis include stent underdeployment, malapposition of stent struts, dissection, complex lesion anatomy, undersized stent use and antiplatelet resistance. The choice of bare metal stent versus drug-eluting stent does not seem to affect the incidence of stent thrombosis. With appropriate use of antiplatelet agents (combined aspirin and clopidogrel), the incidence has fallen dramatically.

However, it is of paramount importance to stress to patients not to stop the dual antiplatelet therapy before the designated duration — three months for Cypher, six months for Taxus in stable coronary syndromes, or nine months to a year if stented for an acute coronary syndrome. Consideration for discontinuation should be made on consultation with their cardiologist. Until recently, the incidence of stent malapposition has not been well investigated in the era of drug-eluting stents. Ako et al, however, recently published IVUS findings from patients who underwent serial IVUS studies from the SIRIUS trial.<sup>31</sup> At eight-month follow up, the late incomplete stent strut apposition was observed in 8.7% of patients treated with drug-eluting stents. Although there were no negative clinical events associated with this, it does suggest a potential aetiology for late stent thrombosis in drug-eluting stent-treated patients (see Figure 2).

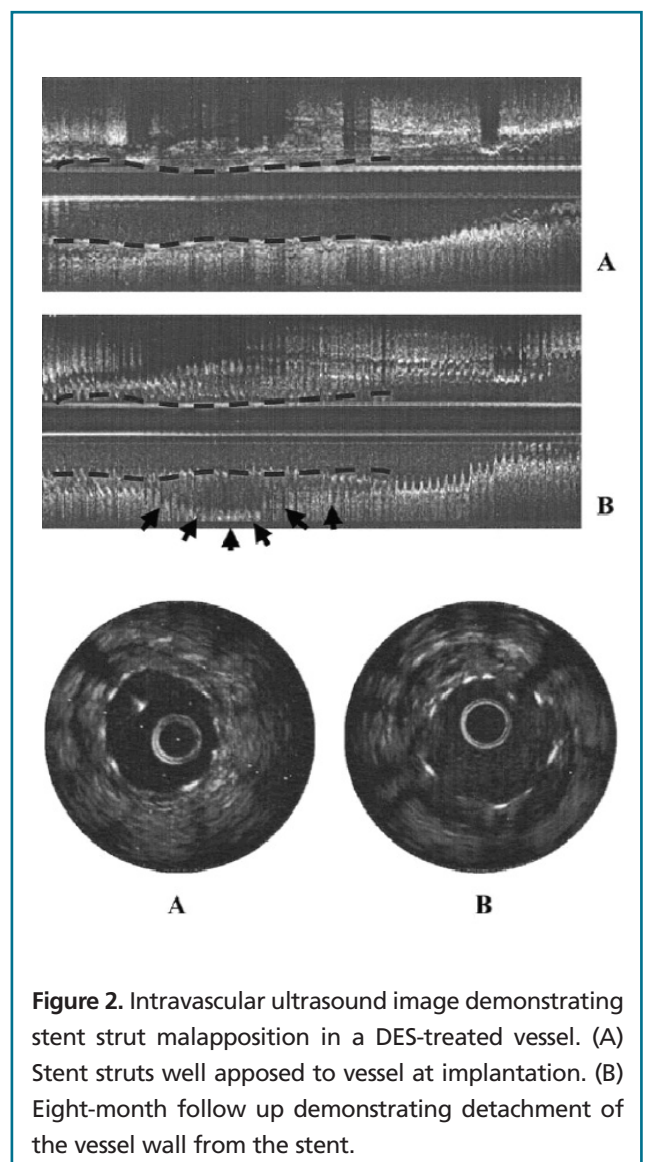
Of note, there were no findings of late stent malapposition in the bare metal stent-treated group in this trial. This further highlights the need to continue dual antiplatelet therapy in drug-eluting stent-treated patients. The absolute duration of dual therapy is the subject of much debate.

### CABG versus drug-eluting stents for left main stem stenosis

CABG has been the gold standard therapy for left main stem (LMS) disease. Clinical need, however, has led to the use of balloon angioplasty, and then stenting in patients at high risk for CABG with excellent early results but significant restenosis. The fantastic angiographic and clinical results achieved with drug-eluting stents in other coronary lesion subsets led to studies of drug-eluting stent use in LMS disease, in patients at high surgical risk or reluctant to undergo CABG. Park et al recently demonstrated that LMS stenting with drug-eluting

stents is safe and feasible with TLR rates of 3.1% vs 19.8% with bare metal stent use at 6/12 and no deaths occurring at 9/12 follow up.<sup>32</sup> The French unprotected LMS registry showed no difference in survival at one year between drug-eluting stents and CABG.

At present, percutaneous coronary intervention for LMS stenosis can be considered a viable alternative to CABG, especially in high risk surgical candidates and a choice can be offered to most patients if the expertise to safely perform the stenting procedure is available. Trials are ongoing to evaluate long-term efficacy of drug-eluting stent treatment for LMS disease. At present, it is reasonable to recommend CABG to patients with unprotected LMS disease, although often when given the choice, patients will opt for percutaneous coronary intervention with drug-eluting stents. In experienced hands, the procedure is safe with excellent clinical outcomes. The literature as to whether or not IVUS should be used routinely to ensure stent apposition and to size the vessel properly is somewhat contradictory. In complex lesions (especially involving bifurcation LMS stenosis), the use of IVUS is advisable.



**Figure 2.** Intravascular ultrasound image demonstrating stent strut malapposition in a DES-treated vessel. (A) Stent struts well apposed to vessel at implantation. (B) Eight-month follow up demonstrating detachment of the vessel wall from the stent.

## CABG versus drug-eluting stents for multivessel disease

Approximately 60% of patients with multivessel disease are candidates for either stenting or CABG.<sup>33</sup> The most appropriate treatment option remains a matter of debate. Studies in the past have shown similar event rates with regard to MI and death between CABG and percutaneous coronary intervention but a greater freedom from reintervention in surgically treated patients. Conclusions, however, made in randomised, controlled trials of percutaneous coronary intervention versus CABG in the present era and, more importantly, before the widespread use of drug-eluting stents cannot be extrapolated to current clinical practice. As reintervention with drug-eluting stents is in single digit percentages nowadays, the recommendation for CABG over percutaneous coronary intervention may not be appropriate.

The ARTS I trial evaluated over 1,200 patients randomised to multivessel percutaneous coronary intervention (using bare metal stents) versus CABG and five-year outcomes have recently been published.<sup>34</sup> The incidence of death, stroke and MI were not significantly different between the two groups, and repeat revascularisation was necessary in 41.7% of the stented group versus 21.8% of the CABG group. There was no difference between the groups in mortality (8.0% stented vs 7.6% CABG), stroke (3.8% stented vs 3.5% CABG) or Q-wave MI (6.7% stented vs 5.6% CABG). Importantly, however, this trial used bare metal stents only and the high repeat revascularisation rates should be expected to be drastically reduced using drug-eluting stents.

Accordingly the ARTS II trial was designed to compare contemporary percutaneous coronary intervention (using drug-eluting stents) with the CABG-treated population in the first ARTS trial. There was significantly better survival from death, cerebrovascular events and MI in the stented group versus the historical CABG group (96.9% drug-eluting stents vs 92% CABG) at one year. Freedom from repeat intervention was 91.5% using drug-eluting stents versus 95.9% for CABG. The freedom from reintervention at one year in ARTS I was only 78.1% using bare metal stents.

If these impressive one year results bear out to the long term, it will be justified that fewer patients will undergo CABG for multivessel disease. Indeed Serruys, in an interview at the ACC in 2005 which was published on theheart.org website, suggested that “with the effectiveness of drug-eluting stent percutaneous coronary intervention on par with that of more invasive CABG for most patients the ranks of patients in whom surgery is preferred is shrinking. These days the patients who should go on to CABG are those with very large numbers of lesions — not three, but four, five or six. The second group that is still very difficult for us to treat are those with chronic total occlusions. Today in our lab, when we see a three vessel disease with a very complex

main stem and chronic total occlusions, we say: that’s for the surgeon.”

A yet unresolved issue is that of multivessel stenting in diabetic patients. Although a formal trial evaluating percutaneous coronary intervention versus CABG in diabetic patients has not yet been completed (although two trials — FREEDOM and CARDIA are ongoing), every post-hoc analysis has shown that the outcome for diabetics is worse following percutaneous coronary intervention than CABG. What has been shown in diabetic patients is that the majority of patients come back not only for in-stent restenosis, but also for new revascularisation due to progression of the atheroma, proximally or distally. This probably explains the superiority of bypass surgery in diabetics because the bypass effectively circumnavigates this region of new disease.

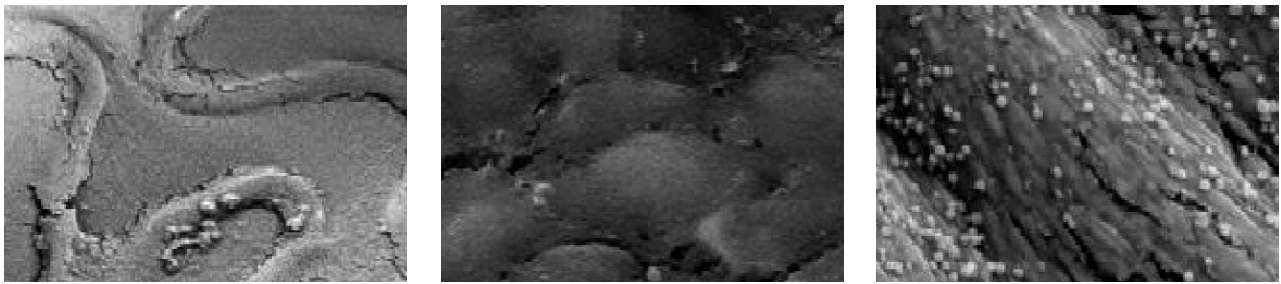
Historical trials have evaluated bare metal stents in multivessel diabetic patients and for now that is the evidence we have to date. FREEDOM and CARDIA will hopefully answer the question as to whether drug-eluting stent implantation in diabetic patients will be as good or better than bypass surgery. These results are many years away and, at present, diabetics with multivessel disease should be recommended to have CABG unless the risk of a CABG is unacceptable.

In summary, the advent of drug-eluting stents has meant that nearly every lesion subset can be effectively treated by percutaneous means with robust clinical and angiographic data on follow up from numerous randomised, controlled trials. Although cost is an issue, as more drug-eluting stents come on to the market costs will fall as competition between manufacturers increases. In fact, the current per unit price has fallen by 30-40% since 2002. A few unanswered questions remain (such as the diabetic issue) but these will be answered in due course. Such minimally invasive techniques to treat coronary artery disease are almost certainly going to continue as the future of revascularisation, especially as newer technologies and operator skills develop further.

## The future

While restenosis has been practically eliminated with the advent of drug-eluting stents, at present two forms of drug-eluting stents are currently in common practice: the Cypher stent and the Taxus stent. Two new additions to the market include the Medtronic Endeavor Stent utilising zotarolimus as the antimitotic agent and the tacrolimus-coated Technic stent. The ENDEAVOR II trial and the Jupiter II trial data were presented at the European Society of Cardiology (ESC) this year and confirmed the marked reduction in restenosis compared to bare metal stents.

As more and more competitors enter the stenting market, costs per stent will have to reduce easing the burden on



**Figure 3.** The Genous stent with a CD34 endothelial progenitor cell coating promoting endothelialisation (healing) within hours to days.

cardiovascular healthcare provision. Outside of drug-eluting stent technology, other companies are assessing different approaches to the prevention of restenosis by promoting faster healing around the stents which may reduce the need for prolonged dual antiplatelet therapies and may reduce the incidence of both stent thrombosis or restenosis in complex lesions and patient subsets (diabetics, long lesions, small vessels etc).

Recently, OrbusNeich received a licence for their new bioengineered R-Stent coated with endothelial progenitor cells. In contrast to antiproliferative drug-eluting stents that minimise excessive healing reactions by indiscriminately inhibiting endothelialisation, the stent promotes rapid and controlled tissue healing at the site of injury. Its antibody coating captures circulating endothelial progenitor cells to provide an intimal luminal surface complete with functional endothelium within minutes to hours, thereby preventing thrombus formation and minimising restenosis (see Figure 3).

The exciting concept of this technology is that it can be used in other areas such as coating for artificial valves, heart-lung machines and vascular conduit prosthesis. By pacifying the reaction to prosthetic heart valves, it may avoid the need for warfarin in the future.

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