Advances in coronary stent technology: current expectations and new developments

William M Wilson
Nicholas LM Cruden
Edinburgh Heart Center, Royal Infirmary of Edinburgh, Edinburgh, United Kingdom

Abstract: The field of percutaneous coronary intervention has witnessed many advances over the last few decades that have served to make it a safe and effective treatment for patients with angina due to coronary artery disease. Although the development of drug eluting stents has significantly reduced the need for repeat revascularization procedures, in-stent restenosis, stent thrombosis, and an increase in bleeding events related to the prolonged use of dual antiplatelet therapy remain important issues. The quest for the optimal coronary stent continues with numerous recent developments that are designed to further improve clinical outcomes following percutaneous coronary intervention. This review will focus on recent advances in coronary stent technology, including bioabsorbable stents and dedicated bifurcation stents, and discuss developments on the horizon.

Keywords: coronary stent, bioabsorbable stent, bifurcation stent

Background
Balloon angioplasty of the coronary arteries was first developed in the 1970s as an alternative means of revascularization to coronary artery bypass surgery. A major drawback with balloon angioplasty alone was the high rate of abrupt vessel closure resulting from acute arterial recoil and coronary artery dissection. The introduction of bare metal stents (BMS) in the early 1990s revolutionized percutaneous coronary intervention (PCI), and reduced rates of acute vessel closure associated with balloon angioplasty from >5% to <1%.1 With the resultant reduction in periprocedural myocardial infarction and the need for emergency coronary artery bypass surgery, coronary stent implantation rapidly became the standard of care for patients undergoing PCI such that balloon angioplasty alone was reserved for situations where stent insertion could not be achieved or was not practical. Indeed, in 2008 coronary stents were implanted in >96% of 800,000 PCI procedures performed in the US.2 Although effective at preventing abrupt closure, the introduction of the BMS has led to the emergence of two important complications, namely stent thrombosis (abrupt thrombotic occlusion) and in-stent restenosis (luminal narrowing due to neointimal proliferation).3

Stent thrombosis is a rare but serious complication that results in myocardial infarction or sudden death in >70% cases. The incidence of stent thrombosis is highest in the first month following stent implantation, reducing thereafter as the stent becomes incorporated in the vessel wall. Factors associated with an increased risk of stent thrombosis include delayed endothelialization, hypersensitivity reactions to drugs or to the polymer coating of the stent, stent malapposition, and significant disruption to the architecture and integrity of the stent scaffold.4 In contrast, clinically significant in-stent restenosis usually
presents within 6–12 months of stent implantation, manifesting more frequently as recurrent angina. Early studies with first generation BMS reported angiographic restenosis rates of 22%–32%.8 Factors associated with in-stent restenosis include longer lesion and stent length, smaller vessel diameter, ostial lesion location, target lesion bifurcation, significant disruption to the architecture or integrity of the stent scaffold, and the presence of diabetes.7,8

Evolution of stent scaffold design combined with the local delivery of antiproliferative agents, such as sirolimus, and the concomitant use of dual antiplatelet therapy have reduced, but not abolished, rates of stent thrombosis and restenosis. In a recent large scale randomized trial comparing clinical outcomes at 2 years with two contemporary drug eluting stents (DES), 1%–2% of patients experienced a stent thrombosis and 5% of patients required repeat revascularization for target lesion failure.9 Clearly, these two important complications remain as concerns for the interventional cardiologist and continue to drive advances in coronary stent design and technology.

Bleeding events in patients treated with coronary stents are also a major concern. Bleeding is the most common complication following coronary stent implantation and is associated with adverse clinical outcomes.10 Predisposing factors include the need for dual antiplatelet therapy,10 the concomitant use of anticoagulants for coexisting conditions, and the fact that almost 5% of patients will undergo major noncardiac surgery in the 12 months following coronary stent implantation.11 Besides optimizing pharmacological strategies,12 it is hoped that advances in coronary stent technology designed to reduce thrombotic potential and limit the need for dual antiplatelet therapy may lead to a reduction in bleeding events and improved clinical outcomes.

This review will focus on recent developments in coronary stent technology that have been designed to address the issues of stent thrombosis, in-stent restenosis, and the need for prolonged dual antiplatelet therapy.

**Stent scaffold structure**

The key concerns in early coronary stent development were restenosis and deliverability. A reduction in stent strut thickness was associated with a lower incidence of periprocedural myocardial infarction13 and restenosis, possibly related to less vascular trauma.14 Switching from stainless steel to cobalt alloys for balloon expandable stents allowed for thinner stent struts to be employed without compromising radial strength (as used in the Multilink Vision [Abbott Vascular, Santa Clara, CA, USA; strut thickness of 91 µm] and Driver [Medtronic Inc, Minneapolis, MN, USA; strut thickness 81 µm] coronary stents which have been demonstrated as comparable platforms).15 Thinner stent struts can be less radio-opaque, which compromises angiographic visibility; however, previous attempts to improve radio-opacity using gold markers were associated with higher rates of restenosis.16 More recently, a novel alloy comprising stainless steel and platinum has been developed (Element stent [Boston Scientific, Natick, MA, USA]; strut thickness 81 µm); radial strength is preserved and the platinum allows for increased radio-opacity which facilitates stent positioning within the coronary artery.

Thinner stent struts, along with a lower metal:artery ratio, and the reduction in the number of fixed connectors between cells, have served to enhance flexibility and conformability, facilitating delivery of longer stents even where marked tortuosity or calcification are present. However, previous attempts enhanced deliverability may come at a price, namely a reduction in radial and longitudinal strength, which can predispose to longitudinal deformation. This can manifest as a change in stent length, strut overlap, strut separation, malapposition, or luminal obstruction and may predispose patients to stent thrombosis.17 The recently released Promus PREMIER DES (Boston Scientific) was designed specifically to address this issue and incorporates additional connectors at the proximal end of the stent to improve longitudinal integrity without compromising stent flexibility (Figure 1).

**Bioabsorbable stent scaffolds**

Theoretically, bioabsorbable stents afford all the benefits of conventional metallic coronary stents by providing a rigid...
scaffold to prevent vessel recoil and negative remodeling, and a vehicle that permits local drug delivery to inhibit neointimal hyperplasia. Proponents argue that the disappearance of the stent scaffold over time is beneficial for a number of reasons including: recovery of vessel compliance and local endothelial function, avoidance of permanent “jailing” of side branches and “overhang” at coronary ostia, compatibility with subsequent cardiac computed tomography and magnetic resonance imaging (lack of artifact from stent struts), and the ability to undergo subsequent coronary bypass grafting, even at the original site of stent implantation. Whether these benefits translate into a reduction in the risk of stent thrombosis remains to be determined.

Potential drawbacks of bioabsorbable stents include embolization of a partially degraded stent scaffold, difficulties in delivering or deploying the bulky polymer stents (thicker struts are required to maintain radial force), and the lack of radio-opacity. Care must be taken when implanting bioabsorbable stents to ensure target lesions are adequately prepared as aggressive postdilatation can cause strut fracture and should be avoided. Extensive calcification and marked proximal tortuosity may limit the successful delivery of current generation bioabsorbable stents.

The duration and process of stent resorption also requires careful attention. If resorption is too rapid, recoil may occur and compromise long-term patency. If resorption is too slow, patients remain exposed to the risk of restenosis and stent thrombosis. As a result, it has been suggested that the optimal duration for the presence of a stent scaffold following balloon dilation of a coronary artery is 6 months. Table 1 summarizes the potential advantages and disadvantages of bioabsorbable stents. An outline of contemporary bioabsorbable stents is provided in Table 2.

Constructed from poly-L-lactic acid (PLLA) monofilament with no antiproliferative drug coating, the Igaki-Tamai stent (Kyoto Medical Planning Co, Kyoto, Japan) was the first biodegradable stent to undergo clinical evaluation in humans, and demonstrated comparable clinical outcomes to contemporary BMS. Unfortunately, delivery and deployment necessitated the use of an 8F guiding catheter and prolonged exposure to heated contrast medium, respectively, thus limiting clinical use. A second generation stent, delivered via a 6F guide catheter without the need for heat application, is currently undergoing preclinical evaluation.

The bioabsorbable vascular solutions (BVS) everolimus eluting stent (Abbott Vascular) is the first bioabsorbable stent to become commercially available (Figure 2). Made from a bioabsorbable polymer backbone of PLLA with a polymer coating of poly-D,L-lactide that contains and controls the release of the antiproliferative drug, everolimus, it is the first bioabsorbable stent to yield clinical and imaging outcomes comparable to conventional DES implantation. The stent has undergone a series of revisions to address concerns regarding mechanical integrity. Clinical data from the recent ABSORB B study in 101 patients demonstrated late loss and minimal luminal area at 6 months, comparable with current generation everolimus eluting stents. Complete bioresorption of the implant occurred by 2 years with no compromise of luminal area and restoration of pharmacologic vasomotion at the site of implantation. The ABSORB II clinical trial, a randomized head to head comparison with a metallic everolimus eluting stent, is currently ongoing.

The DREAMS bioreosorbable stent (Biotronik, Berlin, Germany) is the only fully bioreosorbable metallic stent to undergo clinical evaluation in humans. Coated with a bioabsorbable polymer and the antiproliferative drug, paclitaxel,
this magnesium-based stent exhibits mechanical properties that are similar to conventional metallic stents, and this permits thinner strut size to facilitate delivery. Modification of the magnesium alloy addressed the issue of early recoil that was observed with the first generation stent. In the recent BIOSOLVE-1 trial, use of the DREAMS stent was associated with low rates of target lesion failure at 6 and 12 months (4% and 7%, respectively) with no safety concerns.27

Comprised of a polyanhydride ester and salicylic acid, the IDEAL BDS stent (Bioabsorbable Therapeutics, San Jose, CA, USA) is a fully absorbable sirolimus eluting stent that releases salicylic acid and is promoted as possessing both antiproliferative and anti-inflammatory properties.28 While a pilot study has confirmed safety with no evidence of recoil, insufficient neointimal suppression was an issue. A second generation stent is now in development.

The Rezolve bioabsorbable stent (Reva Medical Inc, San Diego, CA, USA) is a sirolimus coated radio-opaque stent constructed from a tyrosine poly(desamino tyrosyl-tyrosine ethyl ester) carbonate. It is currently undergoing clinical assessment in the RESTORE trial, with plans for a larger clinical study comparing outcomes with a conventional metallic DES already well advanced.

While early results with biodegradable stents show promise, challenges remain in developing a stent that maintains sufficient radial strength for an appropriate duration without overly thick struts, or that can be used as a drug vehicle, and whose degradation does not incite an inflammatory response. The goal is for a healed, normally functioning vessel with no residual foreign material, and no ongoing risk of restenosis or stent thrombosis.

**Self-expanding stent scaffolds**

The self-expanding coronary nitinol Wallstent (Boston Scientific) was the first stent used in the coronary circulation, but it had issues with deliverability and high restenosis rates.29 This concept was soon abandoned with the arrival of balloon expandable stents. More recently, however, the use of self-expanding scaffolds has been revisited, in particular to tackle bifurcation lesions.

The STENTYS (STENTYS, Paris, France) self-expanding nitinol stent, developed both as a BMS and as a DES coated with a bioabsorbable polymer eluting paclitaxel, is approved for use in Europe (Figure 3). While its use has been promoted in the setting of bifurcation lesions,30 its real

---

### Table 2 Bioabsorbable stents: examples

<table>
<thead>
<tr>
<th>Stent</th>
<th>Characteristics</th>
<th>Clinical evidence</th>
</tr>
</thead>
<tbody>
<tr>
<td>Igaki-Tamai stent</td>
<td>First stent to undergo clinical evaluation in humans</td>
<td>50 patients (84 stents) with long-term follow-up</td>
</tr>
<tr>
<td></td>
<td>PLLA monofilament with no drug coating</td>
<td>Rates of target vessel revascularization comparable with BMS (18% at 5 years, 28% at 10 years)22</td>
</tr>
<tr>
<td></td>
<td>Requires 8F delivery guide and prolonged exposure to heated contrast medium</td>
<td></td>
</tr>
<tr>
<td></td>
<td>Currently only used in peripheral vessels</td>
<td></td>
</tr>
<tr>
<td>Bioabsorbable vascular solutions stent</td>
<td>PLLA backbone with a polymer coating (poly-D,L-lactide) that contains and controls delivery of everolimus</td>
<td>ABSORB B study: 101 patients, 6 months results (late loss, MLA) comparable with current generation DES24</td>
</tr>
<tr>
<td>IDEAL BDS stent</td>
<td>Made from salicylic acid derivatives</td>
<td>Pilot study demonstrated no acute recoil but insufficient neointimal suppression</td>
</tr>
<tr>
<td></td>
<td>Releases sirolimus and aspirin to provide antiproliferative and anti-inflammatory effects</td>
<td>Second generation stent in development</td>
</tr>
<tr>
<td>DREAMS stent</td>
<td>Magnesium stent with bioabsorbable polymer and paclitaxel coating</td>
<td>BIOSOLVE-I: Target lesion revascularization occurred in 7% patients at 1 year27</td>
</tr>
<tr>
<td>Rezolve stent</td>
<td>Sirolimus coated radio-opaque stent constructed from a tyrosine polylactyl-coated carbonate</td>
<td>Currently undergoing clinical trials (RESTORE)</td>
</tr>
</tbody>
</table>

**Abbreviations:** BMS, bare metal stent; DES, drug eluting stent; MLA, minimum lumen area; PLLA, poly-L-lactic acid.

---

Figure 2 The bioabsorbable vascular solutions everolimus eluting stent (Abbott Vascular, Santa Clara, CA, USA) is made from a bioabsorbable polymer backbone of poly-L-lactic acid with a polymer coating of poly-D,L-lactide that contains and controls the release of the antiproliferative drug, everolimus.
strength probably lies in the treatment of acute myocardial infarction where vessel sizing due to thrombus and vascular constriction may be ambiguous. In the recently published APPOSITION II (Randomized Comparison between the STENTYS Self-Expanding coronary Stent and a Balloon-Expandable Stent In Acute Myocardial Infarction) study, use of the STENTYS stent was associated with significantly less early strut malapposition (0.58% versus 5.46%, P < 0.001) when compared to a conventional BMS. It remains to be determined whether these benefits will translate into improved longer term clinical outcomes.

Delivered via a 0.014 inch guide wire based platform rather than conventional balloon expandable technology, the Cardiomind Sparrow (Biosensors International, Singapore) is an ultra-thin, self-expanding nitinol stent developed for the treatment of small vessels. Like the STENTYS stent, it has been developed both as a bare metal and drug eluting scaffold, which is coated with a polylactic acid based biodegradable polymer and elutes the antiproliferative agent, sirolimus. With a strut thickness that is approximately 50% of conventional DES, radial strength remains a concern but early reports are promising.

**Micromesh covered stent**

Aimed primarily at patients presenting with an acute ST elevation myocardial infarction, the MGuard stent (InspireMD, Tel Aviv, Israel) is a novel BMS covered with a polyethylene terephthalate micronet mesh designed to trap thrombus and limit distal embolization. Results from a recent randomized study of 433 patients presenting with acute ST elevation myocardial infarction demonstrated that complete resolution of ST segment elevation occurred more frequently (57.8% versus 44.7%) and angiographic surrogates of myocardial blood flow improved with the MGuard stent when compared with commercially available BMS. Data on medium- to long-term clinical outcomes are awaited.

**Dedicated bifurcation stents**

The optimal management of percutaneous revascularization involving coronary bifurcation lesions remains to be established. For the majority of bifurcation lesions, a provisional strategy to stent the main vessel and “rescue” the side branch only where perfusion is threatened is generally accepted as the treatment of choice. Where side branch stenting is mandated, controversy remains regarding the optimal technique using conventional stents. The major limitations of conventional stenting techniques for bifurcation lesions include an inability to scaffold the side branch ostium completely, distortion of the main branch stent following side branch dilation, the potential loss of a jailed side branch, and the inability to rewire the side or main branch. Furthermore, clinical outcomes following stenting of bifurcation lesions remain inferior to clinical outcomes following treatment of non-bifurcation lesions, irrespective of which approach is used. These issues have led to the development of a number of dedicated bifurcation stents. These stents vary widely in the type of material used for construction (nitinol versus various metallic alloys), the method of delivery (balloon expanding versus self-expanding), the presence of antiproliferative drug coating, and the principles behind the design. Although a number of smaller studies have highlighted the potential of dedicated bifurcation stents (Table 3), clinical benefit has yet to be demonstrated in large scale randomized clinical trials.

Dedicated bifurcation stents can be largely grouped under three headings: those designed to treat the side branch first (eg, Tryton [Tryton Medical, Durham, NC, USA] or Sideguard [Cappella Medical Devices, Galway, Ireland]); those that facilitate provisional side branch stenting while maintaining direct access to the side branch after main vessel stenting (eg, Xience Side Branch Access [SBA] [Abbott Vascular]); and conical stents (eg, Axxess stent [Biosensors International, Singapore]).

The Tryton Side Branch stent system is a cobalt chromium BMS (strut thickness 83 µm), which is deployed in the side branch artery first using a standard single wire balloon expandable delivery system. A conventional DES is then deployed in the main vessel through the scaffolding extending proximally into the main branch. The Tryton stent provides minimal strut coverage in main vessel, full strut coverage at the side branch ostium, and the ability to adapt to a wide spectrum of bifurcation angles and sizes. The bare
<table>
<thead>
<tr>
<th><strong>Table 3</strong> Dedicated coronary bifurcation stents</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Guide size required</strong></td>
</tr>
<tr>
<td>Tryton (Tryton Medical)</td>
</tr>
<tr>
<td>Xience SBA (Abbott Vascular)</td>
</tr>
<tr>
<td>Taxus Petal (Boston Scientific)</td>
</tr>
<tr>
<td>Sideguard (Cappella Medical Devices)</td>
</tr>
<tr>
<td>Axxess (Biosensors)</td>
</tr>
<tr>
<td>Stentys (stentys)</td>
</tr>
</tbody>
</table>

**Abbreviations:** BMS, bare metal stent; DES, drug eluting stent; FIM, first in man; MACE, major adverse cardiac events; MI, myocardial infarction; ST, stent thrombosis; TLR, target lesion revascularization; TVR, target vessel revascularization; CoCr, cobalt chromium; PtCr, platinum chromium; DIVERGE study, drug-eluting stent intervention for treating side branches effectively.
struts in the side branch do not seem to predispose to side branch in-stent restenosis.\textsuperscript{43–45} The Tryton IDE study, a randomized comparison of a dedicated two stent strategy using the Tryton stent with a conventional provisional bifurcation stenting strategy in over 700 patients, has recently completed enrolment.

The Sideguard stent is a novel nitinol self-expanding BMS (64 \textmu m strut thickness) that flares proximally at the ostium of the side branch into a trumpet shape to facilitate full ostial side branch coverage. It is usually used in combination with a conventional DES in the main branch. This stent appears attractive for use in lesions with bifurcation angles greater than 70 degrees, but should be avoided in shallow angle bifurcations (less than 40 degrees). Its feasibility as a bifurcation stent was demonstrated in a first-in-man study of eleven patients\textsuperscript{46} (no significant restenosis was seen at 6 month follow-up) and in a small single center UK study\textsuperscript{47} (successful deployment in 20 patients; major adverse cardiac events in 5\% of patients at 6 months). Longer term efficacy data are awaited.

Multiple stents with preformed side ports to facilitate access to the side branch exist. The Xience SBA stent is an everolimus eluting stent that provides wire access into the side branch regardless of the planned treatment strategy. A single inflation deploys the stent in the main branch and opens a portal into the side branch.

The Axxess stent is a self-expanding, drug eluting (Bilimimus A9), conical shaped nitinol stent, which is deployed by withdrawal of a covering sheath (Figure 4). It should be deployed at the level of the carina, thus providing scaffolding to the bifurcation and ostia of both side branches while leaving the true carina free of metal and affording easy access to both distal branches, which can be treated with conventional stents as required, although this stent can stand alone. It performs best in shallow angle bifurcation lesions, and is not recommended for bifurcation angles of >70 degrees. As with any self-expanding device, adequate lesion preparation is critical prior to stent deployment. The device was tested in the DIVERGE (Drug eluting Stent Intervention for Treating Side Branches Effectively) study where 302 patients had bifurcation lesions treated with the Axxess stent; 22\% patients required additional stenting of one branch and 65\% required stenting of both branches, while rates of major adverse events, target lesion revascularization, and stent thrombosis were 7.7\%, 6.4\%, and 1\%, respectively, at 9 month follow-up.\textsuperscript{48}

\section*{Drug delivery systems}

The realization that stent scaffolds can be used as vehicles to target local drug delivery directly to the vessel wall revolutionized PCI. Following the emergence of DES in 2002, the antiproliferative agents sirolimus (and its metabolites) and paclitaxel have been the predominant drugs eluted by DES. Polymer coatings were developed to deliver these antiproliferative drugs in a controlled and uniform manner. The polymer can either be applied over the drug or the drug can be dispersed within the coat, with the pharmacokinetics of drug release affected by altering physical or chemical properties of the polymer coating.

In early generation DES, the polymers used to deliver antiproliferative drugs (on Cypher [Cordis, Bridgewater, NJ, USA] and Taxus [Boston Scientific] stents) were not designed for vascular compatibility and were linked to inflammation and stent thrombosis.\textsuperscript{49–52} This led to efforts to develop biologically inert (but nonerodable) polymers. Several trials have demonstrated a very low incidence of stent thrombosis with these newer agents when compared to the first generation DES.\textsuperscript{52–54}

More recently, fully biodegradable polymer coatings have been developed. These afford drug delivery through loading and elution of a lipophilic drug from a biocompatible polymer (to prevent restenosis early poststent insertion), which is slowly degraded into inert organic monomers, thereby removing the risk associated with persistent polymer residue in the vessel wall. Numerous biodegradable polymer stents have been evaluated in clinical trials and appear non-inferior to permanent polymer stents. These include the Nobori biolimus A9 eluting stent (Terumo Corporation, Tokyo, Japan),\textsuperscript{53} the Biomatrix Flex biolimus A9 eluting stent (Biosensors International),\textsuperscript{56} the Synergy everolimus eluting stent (Boston Scientific),\textsuperscript{57} and the Yukon Choice PC stenting strategy in over 700 patients, has recently completed enrolment.

The Arrow depicts the Axxess stent. Additional conventional drug eluting tomography pullback images following implantation of an Axxess stent in a bifurcation (left panel). The figure is a three dimensional reconstruction of optical coherence.

\begin{figure}[h]
\centering
\includegraphics[width=0.5\textwidth]{image.png}
\caption{The Axxess bifurcation stent (Biosensors International, Singapore). \textbf{Notes:} This is a conical, self-expanding nitinol stent eluting the drug Biolimus A9 (left panel). The figure is a three dimensional reconstruction of optical coherence tomography pullback images following implantation of an Axxess stent in a bifurcation lesion. The arrow depicts the Axxess stent. Additional conventional drug eluting stents have also been implanted in the downstream limbs of the bifurcation.}
\end{figure}
The need for a polymer coating.

International, Singapore) acts as a reservoir for an antiproliferative agent without
the abluminal surface without the use of a polymer. Preliminary data from
Figure 5

Concerns regarding polymer mediated stent thrombosis have also led to development of novel polymer-free DES. Several approaches have been examined, including microtextured stainless steel reservoirs in cobalt chromium struts and carbon coated slotted struts. The Yukon stent (Translumina, Hechingen, Germany) has a roughened stent surface to which a drug solution can be applied in the catheterization laboratory. In a clinical study of 400 patients undergoing PCI, the Yukon stent coated with a 2% rapamycin solution was shown not to be inferior, in terms of late loss at 9 months, when compared to a contemporary DES.59

The BioFreedom stent (Biosensors International, Singapore) is a stainless steel scaffold modified by microabrasion to create a highly textured abluminal surface (Figure 5). This allows drug (Biolimus A9) adhesion to the stent’s abluminal surface without the use of a polymer. Preliminary data from a first-in-man study with follow-up to 3 years are encouraging with comparable rates of in-stent late loss at 12 months when compared to a paclitaxel eluting stent (Taxus Liberte).61

**Novel stent coatings**

With an abluminal coating of the CD34 antibody on a bare metal stainless steel scaffold, the Genous stent (OrbusNeich, Fort Lauderdale, FL, USA) was developed to sequester circulating endothelial cell progenitors from the blood stream in an attempt to accelerate endothelialization and reduce stent thrombosis. While data from the e-Healing Registry of over 5000 patients undergoing PCI are encouraging with rates of target lesion revascularization and stent thrombosis of 5.7% and 1.1%, respectively, at 12 month follow-up,62 a head to head comparison with contemporary DES reported higher rates of target vessel failure with the Genous stent at 12 months,63 although this difference was no longer statistically significant at 2 years.64 A novel stent (Combo Dual Therapy stent; OrbusNeich, Fort Lauderdale, FL, USA) combining CD34 antibody technology with the antiproliferative agent, sirolimus, and a biodegradable polymer coating has recently been approved for use in Europe.

The Titan-2 BioActive stent™ (Hexacath, Paris, France) is constructed from stainless steel coated in titanium nitric oxide. Nitric oxide is an endogenous signaling molecule that induces vasodilatation and inhibits both platelet aggregation and smooth muscle cell proliferation. A deficiency in the vasodilator, nitric oxide, has been associated with in-stent restenosis and stent thrombosis.65 A number of initial small studies have demonstrated that the Titan-2 stent was superior to conventional BMS,66 and equivalent to paclitaxel (TITAX-AMI [titanium-nitric-oxide coated stents versus paclitaxel-eluting stents in acute myocardial infarction])67 and everolimus eluting stents,68 at reducing in-stent late loss. At 5 years follow-up in the TITAX-AMI titanium-nitric-oxide coated stents versus paclitaxel-eluting stents in acute myocardial infarction study, the Titan-2 stent was associated with similar rates of target lesion revascularization and a lower incidence of death or recurrent myocardial infarction when compared to paclitaxel DES.69

In addition to nitric oxide donors, stents coated with genetic information targeting nitric oxide metabolism have received attention. As an example, stent struts coated with lipopolyplexes expressing nonviral plasmid DNA encoding endothelial nitric oxide synthase, an enzyme that catalyzes the production of nitric oxide from L-arginine, have been shown to inhibit neointimal hyperplasia.70 Similarly, an in vivo study using stents coated with lipopolyplexes containing endothelial nitric oxide synthase DNA demonstrated accelerated
endothelialization, albeit without suppressing neointimal formation.71 Whether this strategy will be successful in the clinical arena remains to be determined.

**Drug eluting balloons**

Balloon angioplasty using drug eluting balloons has emerged as an alternative to stent insertion for the treatment of in-stent restenosis and in small diameter coronary vessels. Drug eluting balloons allow for local application of an antiproliferative agent at the time of barotrauma, avoiding the need for a persistent metal scaffold – a potential nidus for inflammation and restenosis. Paclitaxel is the drug most commonly applied to drug eluting balloons owing to its rapid uptake, as promoted by its highly lipophilic properties and tight binding to various cell constituents. The major differences between currently available drug eluting balloons relates largely to the loading dose, the way in which the balloon is coated (360 degrees or partial), and the excipient (an ingredient added to the drug to facilitate its uptake). A brief summary of contemporary drug eluting balloons is presented in Table 4.

A recent meta-analysis of five studies suggested that balloon angioplasty with a drug eluting balloon was superior to conventional balloon angioplasty alone, and at least equivalent to paclitaxel eluting DES use in patients with in-stent restenosis.72 In this study, drug eluting balloons reduced the risk for major adverse cardiac events (Relative Risk 0.46, 0.31-0.70; P < 0.001), mainly driven by a reduction in target lesion revascularization (RR 0.34, 0.16-0.73; P = 0.006) and also by a lower mortality risk (RR 0.48, 0.24-0.95; P = 0.034) when compared to conventional balloon angioplasty alone or DES use. In addition, late luminal loss (−0.38 mm, −0.6 to −0.15, P = 0.001) and rates of in-segment binary restenosis (28%, 14%–58%, P < 0.001) were lower with drug eluting balloon use.72

Drug eluting balloons have also demonstrated potential for the treatment of small diameter vessels where stent insertion, even if drug eluting, is associated with higher rates of restenosis. The recently published BELLO (Balloon Elution and Late Loss Optimization) study demonstrated that use of the IN.PACT FALCON drug eluting balloon (Medtronic, Santa Rosa, CA, USA) was associated with significantly less late loss when compared to paclitaxel eluting stent use in small caliber arteries (defined as <2.8 mm diameter, but 89% of arteries were <2.5 mm).73 There was no difference in secondary clinical endpoints between the two strategies at 6 months. These findings are in contrast to the smaller,

**Table 4** Contemporary drug eluting balloons

<table>
<thead>
<tr>
<th>Drug</th>
<th>Design</th>
<th>Clinical scenarios</th>
</tr>
</thead>
<tbody>
<tr>
<td>Paclitaxel</td>
<td>Coated balloon</td>
<td>Bello: Randomized comparison with TAXUS DES in small vessels. Clinical outcomes similar at 6 months.73</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Exipient, urea</td>
<td>PEPCAD I SVD (native small vessels): 12 month MACE rate of 15% and mean late loss of 0.28 mm.75</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Dose density 3 µg/mm²</td>
<td>Native vessels (any size): PEPCAD III: DEB versus Cypher DES failed to meet noninferiority criteria.74</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Exipient, iopromide (contrast media)</td>
<td>Chronically occluded vessels: PEPCAD-CTO: BMS + DEB inferior to Taxus.77</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Dose density 3 µg/mm²</td>
<td>In-stent Restenosis: PEPCAD II (versus Taxus) – MACE RR 0.42 (0.17–1.03)79</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Exipient, Dimethylsulfate/shellac</td>
<td>ISAR-DESIRE (versus Taxus) – MACE RR 0.72 (0.51–1.02)80</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Dose density 3 µg/mm²</td>
<td>PEPCAD-DES (versus POBA) – MACE RR 0.33 (0.18–0.61)81</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Exipient, iopromide (contrast media)</td>
<td>Habara et al. versus POBA – MACE RR 0.1 (0.01–0.72)82</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Dose density 2 µg/mm²</td>
<td>Native small vessels: PICCOLETO (Dior I): stopped prematurely as inferior to Taxus stent.86</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Exipient, none</td>
<td>In-stent Restenosis: PACCOCATH: lower MACE and TLR compared with POBA.87</td>
</tr>
<tr>
<td>Paclitaxel</td>
<td>Coated balloon</td>
<td>Native vessels and Restenosis: Higher restenosis rate (12.5%) versus Sequent Please (3.4%) at 6 months.88</td>
</tr>
</tbody>
</table>

**Abbreviations:** BMS, bare metal stent; DEB, drug eluting balloon; DES, drug eluting stent; MACE, major adverse cardiac events; POBA, balloon angioplasty alone; RR, relative risk; TLR, target lesion revascularization; BELLO, Balloon elution and late optimization study; PEPCAD-CTO, paclitaxel-eluting PTCA-balloon catheter to treat chronic total occlusions; PICCOLETO, paclitaxel-coated balloon versus drug-eluting stent during PCI of small coronary vessels, a prospective randomised clinical trial.
single center PICCOLETO (paclitaxel-coated balloon versus drug-eluting stent during PCI of small coronary vessels, a prospective randomised clinical trial) study which was stopped prematurely as the Dior balloon (Eurocor, Bonn, Germany) was clearly inferior to a paclitaxel DES in small vessels.\textsuperscript{73} In the PEPCAD I SVD (treatment of small coronary arteries with a paclitaxel-coated balloon catheter) trial, 118 patients with stenosis in small coronary vessels were treated with the SeQuent Please balloon catheter (B Braun, Melsungen, Germany).\textsuperscript{73} Thirty percent of patients required additional stent deployment, and mean late loss was 0.28 ± 0.53 mm, with an adverse event rate of 15% at 12 months, driven largely by recurrent target lesion revascularization.\textsuperscript{75}

It has been suggested that combining BMS implantation with drug eluting balloon use in native coronary arteries may offer an alternative strategy to DES implantation. However, clinical data do not currently support this strategy.\textsuperscript{76,77}

Drug eluting balloons afford a number of theoretical advantages over DES including a lower potential risk of stent thrombosis and a requirement for a shorter duration of dual antiplatelet therapy. One strategy for the treatment of multivessel disease might be to reserve DES use for major proximal epicardial vessels, performing balloon angioplasty alone, perhaps using a cutting or scoring balloon, followed by a drug eluting balloon to distal lesions or diseased side branches. This strategy, however, remains to be tested in clinical trials.

**Summary**

There is no doubt that the development of the coronary stent has progressed rapidly over recent years. Despite these advances, the optimal coronary scaffold remains elusive. Desirable features include ease of delivery in challenging vessels without compromising radial and longitudinal strength, adequate radio-opacity to facilitate stent positioning and visualization, and appropriate targeted delivery of an antiproliferative agent that inhibits smooth muscle proliferation without delaying endothelialization, stimulating inflammation, or promoting thrombosis. Achieving these goals is challenging but central to the future progression of coronary artery stent technology.

**Disclosure**

Dr Cruden has received sponsorship to attend scientific meetings and consultancy fees from St Jude Medical, an unrestricted Fellowship Award and sponsorship to attend scientific meetings from Boston Scientific, and research funding from Medtronic.

**References**


Research Reports in Clinical Cardiology

Publish your work in this journal

Research Reports in Clinical Cardiology is an international, peer-reviewed, open access journal publishing original research reports, editorials, reviews and commentaries on all areas of cardiology in the clinic and laboratory. The manuscript management system is completely online and includes a very quick and fair peer-review system.

Submit your manuscript here: http://www.dovepress.com/testimonials.php

Dovepress

Visit http://www.dovepress.com/testimonials.php to read real quotes from published authors.

Research Reports in Clinical Cardiology 2013:4