

NEW STENT TECHNOLOGIES

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), reducing rates of acute vessel closure associated with balloon angioplasty from >5% to <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. 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).

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 polymer coating the stent, stent malapposition and significant disruption to the architecture and integrity of the stent scaffold. In contrast, clinically significant in-stent restenosis usually presents within 6-12 months of stent implantation, manifesting as recurrent angina. Early studies with first generation BMS reported angiographic restenosis rates of 22-32%. Factors associated with in-stent restenosis include, longer lesion and stent length, smaller vessel diameter, ostial lesion location, target vessel bifurcation, significant disruption to the architecture or integrity of the stent scaffold, and the presence of diabetes.

Evolution of stent scaffold design combined with the local delivery of anti-proliferative agents, such as sirolimus, and the concomitant use of dual antiplatelet therapy have reduced but not abolished rates of stent thrombosis and clinical restenosis. In a recent large scale, randomized trial comparing clinical outcomes at two 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. Clearly, these two important complications remain of concern for the interventional cardiologist and continue to drive advances in coronary stent design and technology. This review will focus on recent developments in coronary stent technology designed to address the issues of stent thrombosis and in-stent restenosis.

STRUCTURE

The key concerns in early coronary stent development were restenosis and deliverability. Reduction of stent strut thickness was associated with a lower incidence of restenosis, possibly related to less vascular trauma. 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 μ m) and Driver (Medtronic Inc, Minneapolis, MN, USA: strut thickness 81 μ m) coronary stents, which have been demonstrated to be comparable platforms). Thinner stent struts can be less radio-opaque which compromises angiographic visibility but previous attempts to improve radio-opacity using gold markers were associated with higher rates of restenosis. More recently, a novel alloy comprising stainless steel and platinum has been developed (Element stent (Boston Scientific, Natick, MA, USA), strut thickness 81 μ m); 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 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, 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. The recently released Promus PREMIER DES (Boston Scientific, Natick, MA, USA) 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 .

BIOABSORBABLE DEVICES

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. Moreover, the duration and process of stent resorption requires careful attention. If resorption is too rapid, recoil may occur compromising 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 anti-proliferative drug coating, the Igaki-Tamai stent (Kyoto Medical Planning Co., Kyoto, Japan) was the first biodegradable stent to undergo clinical evaluation in humans, demonstrating 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, Santa Clara, CA, USA) is the first bioabsorbable stent to become commercially available. 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 anti-proliferative 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 bioresorbable stent (Biotronik, Berlin, Germany) is the only fully bioresorbable metallic stent to undergo clinical evaluation in man. Coated with a bioabsorbable polymer and the anti-proliferative drug, paclitaxel, this magnesium based stent exhibits mechanical properties similar to conventional metallic stents, permitting thinner strut size to facilitate delivery. Modification of the magnesium alloy addressed the issue of early recoil 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.

The IDEAL BDS stent (Bioabsorbable Therapeutics, San Jose, CA, USA) is a fully absorbable sirolimus eluting stent that releases salicylic acid and has been promoted as possessing both anti-proliferative and anti-inflammatory properties.

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 radiopaque 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.

Whilst 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, 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 STENTS

The self-expanding coronary nitinol Wallstent (Boston Scientific, Natick, MA, USA) was the first stent used in the coronary circulation, but had issues with deliverability and high restenosis rates. This concept was soon abandoned with the arrival of balloon expandable stents. More recently, however, the use of self-expanding scaffolds have 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 biostable polysulphone polymer eluting paclitaxel, is approved for use in Europe. Whilst its use has been promoted in the setting of bifurcation lesions, its real strength probably lies in the treatment of acute myocardial infarction where vessel sizing due to thrombus and vasoconstriction may be ambiguous. In the recently published APPOSITION II study, the STENTYS stent was associated with significantly less early strut malapposition (0.58% vs. 5.46%, $p < 0.001$) when compared to a conventional bare metal stent. It remains to be determined whether these benefits will translate into improved longer-term clinical outcomes.

Delivered via a 0.014-inch guidewire 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, the Cardiomind Sparrow 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 anti-proliferative agent sirolimus. With a strut thickness that is approximately 50% of conventional DES, radial strength remains a concern but early reports are promising.

BIFURCATED 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 re-wire 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 anti-proliferative drug coating and the principles behind the design. Although a number of smaller studies have highlighted the potential of dedicated bifurcation

stents, 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 whilst maintaining direct access to the side branch after main vessel stenting (eg Xience SBA (Abbott Vascular, Santa Clara, CA, USA)); and conical stents (eg Axxess stent (Biosensors International, Singapore)).

The Tryton Side Branch stent system is a cobalt chromium BMS (strut thickness 83µm), 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/vessel ratio, full strut coverage at the side branch ostium and the ability to adapt to a wide spectrum of bifurcation angles and sizes. The bare struts in the side branch do not seem to predispose to side branch in-stent restenosis. The Tryton IDE study, a randomized comparison of a dedicated two stent strategy using the Tryton stent with conventional provisional bifurcation stenting strategy in over 700 patients, has recently completed enrolment.

The Sideguard stent is a novel nitinol self expanding BMS (64 µm 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 11 patients (no significant restenosis was seen at 6 month follow up) and in a small single centre UK study (successful deployment in 20 patients; major adverse cardiac events in 5% 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 (Side Branch Access) 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 (Biolimus A9), conical shaped nitinol stent, which is deployed by withdrawal of a covering sheath. It should be deployed at the level of the carina, thus providing scaffolding to the bifurcation and ostia of both side branches whilst 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, in which 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, whilst rates of major adverse events, target lesion revascularization and stent thrombosis were 7.7%, 6.4% and 1% respectively at 9 month follow-up.

DRUG DELIVERY SYSTEMS

The realization that stent scaffolds could be used as vehicles to target local drug delivery direct to the vessel wall revolutionized PCI. Following the emergence of DES in 2002, the anti-proliferative agents sirolimus (and its metabolites) and paclitaxel have been the predominant drugs eluted by DES. Polymer coatings were developed to deliver these anti-proliferative 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 anti-proliferative drugs (on Cypher (Cordis, Bridgewater, NJ, USA) and Taxus (Boston Scientific, Natick, MA, USA) stents) were not designed for vascular compatibility and were linked to inflammation and stent thrombosis. This led to efforts to develop biologically inert

(but non-erodable) polymers. Several trials have demonstrated a very low incidence of stent thrombosis with these newer agents compared to the first generation DES.

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 post-stent 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, which have demonstrated non-inferiority against permanent polymer stents. These include the Nobori biolimus A9 eluting stent (Terumo Corporation, Tokyo, Japan), the Biomatrix Flex biolimus A9 eluting stent (Biosensors International, Singapore), the Synergy everolimus eluting stent (Abbott Vascular, Santa Clara, CA, USA) and the Yukon Choice PC rapamycin eluting stent (Translumina Therapeutics, Hechingen, Germany). A meta-analysis of pooled individual data from the ISAR-TEST and LEADERS trials revealed the risk of target lesion revascularization and stent thrombosis to be lower at 4 years in patients treated with bioresorbable polymer compared to durable polymer drug eluting stents (HR 0.82, 95% CI 0.68-0.98 and 0.56, 95% CI 0.35-0.90).

Concerns regarding polymer-mediated stent thrombosis have also led to development of novel polymer-free DES. Several approaches have been examined, including micro-textured 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 using a 2% rapamycin solution, was shown to be non-inferior in terms of late loss at 9 months when to a contemporary DES.

The BioFreedom stent (Biosensors International, Singapore) is a stainless steel scaffold modified by micro-abrasion to create a highly textured abluminal surface. 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 three years are encouraging with comparable rates of in-stent late loss at 12 months to a paclitaxel eluting stent (Taxus Liberte).