Published Online March 26, 2013

Coronary stents: historical development, current status and future directions

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Introduction: Coronary angioplasty with stenting has revolutionized the treatment of coronary artery disease. This article describes the history of coronary angioplasty and stenting, reviews the contemporary stents and recommendations and highlights the on-going work and potential future directions.

Sources of data: This review examined the data on coronary stents available in PubMed.

Areas of agreement: Coronary artery stenting is the treatment of choice for patients requiring coronary angioplasty. Stents, and particularly drug-eluting stents, reduce the risk of restenosis, but may be associated with the hazard of late stent thrombosis. Dual anti-platelet treatment is recommended for patients receiving coronary stents.

Areas of controversy: The selection of stents for various lesions and patients and the duration of anti-platelet therapy remain debated areas.

Areas timely for developing research: There are on-going preclinical and clinical studies to develop better stent platforms, more biocompatible polymers, novel anti-proliferative and anti-platelet drugs, pro-healing stents and bioresorbable scaffolds.

Keywords: angioplasty/stents/bare metal stents/drug-eluting stents/ bioresorbable vascular scaffold

Accepted: February 13, 2013

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Coronary artery disease (CAD) is the leading cause of morbidity and mortality in the world. Central to the pathogenesis of CAD is the development of atherosclerotic lesions in coronary arteries. These lesions, if unstable or clinically significant, are frequently treated with percutaneous coronary intervention (PCI), which usually involves balloon angioplasty and stent implantation. PCI is one of the commonest procedures performed in contemporary clinical practice, with more than

DOI:10.1093/bmb/ldt009

1400 procedures/million carried out every year in the UK. The coronary stents have substantially evolved since their first use in 1980s and there are on-going studies to refine their design, structure and material. This article will review the development of coronary stents, their current status and the potential future directions.

History of angioplasty and stenting

Coronary angioplasty, conceptually described by Dotter and Judkins in 1964, was first performed by Andreas Gruntzig in 1977.[1] Coronary stents were developed in the mid-1980s and since then have seen major refinements in design and composition.[2] The landmark events in the history of stent development are shown in Table 1.

Plain old balloon angioplasty

The angioplasty procedures performed initially were without stent deployment, a technique that is now referred as plain old balloon angioplasty (POBA). POBA undoubtedly revolutionized the treatment of coronary artery disease. However, the outcomes were compromised by re-narrowing of coronary arteries due to acute vessel closure due to

Table 1 Historical milestones in coronary artery stenting

Time	Person(s)	Landmark events
1964	Dotter and Judkins	Conceptual description of coronary angioplasty using an implantable prosthetic device
May 1977	Gruntzig and Myler	First coronary angioplasty during coronary artery bypass graft surgery
September 1977	Andreas Gruntzig	First coronary angioplasty in an awake patient; a revolution in interventional cardiology
1979	Geoffrey Hartzler	First balloon angioplasty to treat AMI
1986	Sigwart and Puel	The first implantation of a stent in human coronary arteries; second revolution in interventional cardiology
1991	Cannon and Roubin	First coronary stenting to treat AMI
1994	Serruys *et al.* and Fischman *et al.*	Publication of first two landmark (Benestent and STRESS) trials
1994	FDA	FDA-approved use of stents to treat acute and threatened vessel closure after failed balloon angioplasty
1999	Eduardo Sousa	The first drug (sirolimus) eluting stent implanted in human coronary artery; third revolution in interventional cardiology
2002–04	EME and FDA	Approvals of Cypher and Taxus stents in Europe and USA
2011	EME	Approval of Absorb BVS (bioresorbable vascular scaffold) in Europe; fourth revolution in interventional cardiology

FDA, Food and Drug Administration USA; EME, European Medicines Agency.

dissection or elastic recoil, late vascular remodelling and neointimal proliferation.[3] Elastic recoil usually occurred in 5–10% patients immediately (minutes-hours) after the procedure leading to a rebound occlusion of the artery, which often led to severe complications, including acute myocardial infarction (AMI) and the need for emergency coronary artery bypass grafting (CABG). Angioplasty-induced endothelial cells denudation and medial tearing also exposed circulating blood cells to the sub-endothelial matrix leading to platelet aggregation and thrombosis, and hence contributing to acute closure of the artery.[4] Balloon injury also initially induced medial smooth muscle cell necrosis,[5] followed by a phase of coordinated proliferation of medial smooth muscle cells and subsequent migration of these cells into the intima in response to the release of chemo-attractants such as the platelet-derived growth factor.[4] About 80% of the migrating cells are reported to be in the G1 and S phases of the cell cycle resulting in further proliferation of these intimal smooth muscle cells.[6] This neointimal proliferation leads to post-angioplasty restenosis,[7] as shown schematically in Figure 1.

Coronary stents were, therefore, developed to overcome these issues, by scaffolding the balloon-dilated artery, sealing the dissection flaps and preventing late recoil. The vast majority of PCI procedures performed currently involve balloon angioplasty and stent deployment.

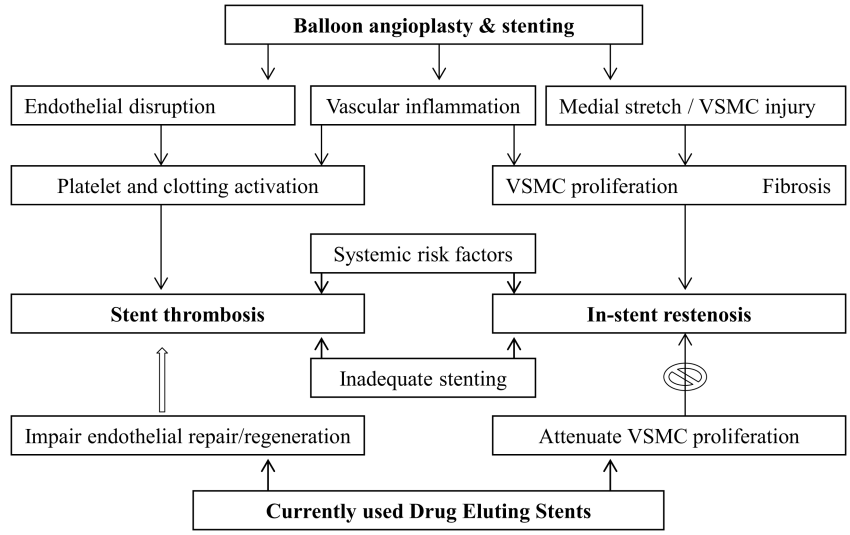


Fig. 1 Pathophysiological impact of angioplasty, stenting and drug-eluting stents. Angioplasty and stenting induces an iatrogenic injury to the vessel wall, which can activate several pathways promoting proliferation of VSMCs leading to ISR. Current DES, though attenuate restenosis, may also impair endothelial healing, making them prone to ST.

Development of coronary stents

WALLSTENT® (Schneider AG), a self-expanding, stainless steel wire-mesh structure, was the first coronary stent implanted in a human coronary artery by Sigwart *et al.* in 1986.[8] The technical challenges in using the stent delivery system (an inner shaft and outer constraining sheath) limited its clinical utility and it was withdrawn from market in 1991. Schatz and co-workers developed the Palmaz-Schatz® (Johnson & Johnson) stent in 1987, the first FDA-approved stent in the USA.[2] It was the first balloon-expandable, stainless steel, slotted tube device and remained one of the most studied and widely used stent in 1990s. Many other stents were subsequently developed in early 1990s and included: Flexstent® (Cook), Wiktor® (Medtronic), Micro® (Applied Vascular Engineering), Cordis® (Cordis) and Multi-link® (Advanced Cardiovascular Systems). The use of these stents, indeed, reduced early elastic recoil and restenosis seen with POBA.[9] However, this new technology was not without its drawbacks. These initial stents had high metallic density, resulting in a high incidence of sub-acute stent thrombosis (ST), and were bulky and technically challenging to use, resulting in frequent failure in deployment and embolization.[10] Furthermore, these initial coronary stents, although reduced the incidence of restenosis compared with POBA, were still at a significant risk of in-stent restenosis (ISR).[10] These technical challenges and potential complications kept the use of stents limited to the cases of acute or threatened closure or restenosis after POBA. In 1993, two landmark trials, the Belgium Netherlands Stent Arterial Revascularization Therapies Study (BENESTENT) and the North American Stent Restenosis Study (STRESS), demonstrated superiority of the bare metal stents (BMS) over POBA, thus establishing coronary stent implantation as an accepted standard of care for PCI.[11,12] The use of coronary stents increased exponentially over the next few years and by 1999, stents were used in nearly 85% of PCI procedures.

However, the medium and longer term follow-up of BMS revealed as high as 20–30% incidence of ISR, due to proliferation and migration of vascular smooth muscle cells (VSMCs) within the stents (Figure 1).[13] ISR may be associated with significant morbidity and mortality and the drug-eluting stents (DES) were developed to specifically address the problems of ISR encountered with BMS.[14]

Development of DES

Development of DES was another revolution in interventional cardiology. Various compounds targeting inflammation, platelet activation,

thrombosis and VSMC proliferation were tried. Coating BMS with gold (thought to be inert), carbon (like diamond), phosphorylcholine (PC) (mimicking the cell membrane) and heparin (to prevent thrombosis), amongst many others, did not confer any benefit. Activation or antagonism of various hormonal receptors, including oestrogen, glucocorticoids and mineralocorticoids, had modest effects.[15–17] However, coating BMS with anti-proliferative drugs sirolimus or paclitaxel substantially reduced ISR compared with BMS.[18–20] Sirolimus (rapamycin; an immunosuppressive compound derived from a fungus found on Easter Island, known as Rapa Nui) acts by receptor inhibition of the mammalian target of rapamycin (mTOR), resulting in the cessation of cell-cycle progression in the late G1 to S phases and, consequently, inhibits VSMC proliferation.[21] Paclitaxel (a well-known anti-cancer drug derived from Taxus brevifolia, the Pacific Yew tree) inhibits cell proliferation and migration by disturbing cellular microtubule organization.[22] These drugs were incorporated within a polymer and coated on the surface of BMS, and were released slowly over a few weeks after stent deployment. Eduardo Sousa implanted the first sirolimus-eluting stent in 1999 and it became available for clinical use as CYPHER® (Cordis) stent in 2002. CYPHER® has been tested in numerous randomized controlled trials (RCTs), including RAVEL, SIRIUS, E-SIRIUS, C-SIRIUS and ISAR-DESIRE and showed a significant reduction in ISR and target vessel revascularization compared with BMS.[18,19,23] TAXUS® (Boston Scientific), a paclitaxel-eluting stent (PES), closely followed CYPHER® and again many RCTs (TAXUS 1-IV) confirmed its efficacy against BMS.[20,24]

In 2006, a potential safety issue emerged with reports linking DES with the increased risk of ST.[25,26] Whilst the initial reports were methodologically flawed, later registries did confirm that the issue might indeed be very real,[27] possibly due to delayed endothelialization by the anti-restenotic drugs (Figure 1) or delayed hypersensitivity reaction to the polymer in DES. The concern of ST with the first generation of DES, though attracted attention of media and FDA, and transiently reduced the use of DES, also stimulated many studies furthering research into the mechanism of ST and development of novel anti-platelet agents, better polymers and newer generation DES,[28–31] discussed later in this review.

Development of adjunctive anti-platelet therapy

The presence of exposed metal struts in the coronary arteries acts as a nidus for platelet aggregation and thrombosis, and the early use of stents was associated with a high risk of ST.[10,32] This potentially

devastating complication is associated with a 50% incidence of AMI and a 20% mortality rate, and therefore, prevention of ST is of paramount importance.[32] Initially, it was tackled by the use of complex anticoagulation regimens using aspirin, heparin and warfarin, but this combination led to high rates of major bleeding, vascular complications and prolonged hospital stays. The development of new antiplatelet agents led to a breakthrough in the use of coronary stents with the adoption of a dual anti-platelet treatment (DAPT), combining aspirin with a thienopyridine.[33] Aspirin and ticlopidine were used initially; however, ticlopidine was soon replaced with clopidogrel, which is more effective and better tolerated. Clopidogrel is a pro-drug that after hepatic P450 metabolism to an active compound, irreversible inhibits the $P2Y_{12}$ receptors on platelets. PCI-CURE trial showed that in patients with acute coronary syndrome (ACS) receiving aspirin, a strategy of clopidogrel pre-treatment followed by long-term therapy is beneficial in reducing major adverse cardiac events (MACE), compared with placebo.[34]

Contemporary stents and current recommendations

Current generation of BMS

There have been significant refinements in the material and design of BMS over the last few years.[35] Initial stents were usually made up of stainless steel, because it is biologically inert. In recent years, cobalt–chromium alloys have superseded steel as the material of choice for stents, allowing newer stents to be designed with significantly thinner struts without compromising radial strength or corrosion resistance. A wide variety of currently used BMS, including Coroflex® (B-Braun), Driver® (Medtronic), Vision® (Abbott Vascular) are made up of cobalt–chromium.[2] The most recent development in the stent platform is the use of the Element Platform, which is made up of a platinum–chromium alloy, as in Omega® stent (Boston Scientific). This new platform has refined architecture with thin struts, high radiopacity, radial strength and conformability. The use of current generation of BMS, in selected (low ISR risk) patient groups could be safe and cost-effective.[36]

Current generation of DES

The newer stent platforms, described above, are now being used in the newer generation DES. The Element DES series includes everolimus-

eluting Promus Element® (Boston Scientific) and Xience-V® (Abbott Vascular), and paclitaxel-eluting Taxus® Element (Boston Scientific) stent. Furthermore, the newer generation DES also have better polymers and anti-restenotic drugs (Table 2).

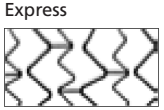
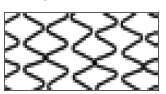
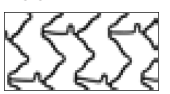
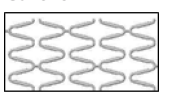
Among a variety of immunosuppressive and anti-proliferative agents tested to-date, only 'limus' type of drugs have shown real effectiveness in clinical practice. Zotarolimus is a semi-synthetic derivative of sirolimus, designed specifically for use in stents, for example Endeavor®[37] and Resolute® [38] (Medtronic), and has been shown to be non-inferior to everolimus.[38] Everolimus is a hydroxyethyl derivative of sirolimus and works similarly by inhibiting mTOR. It is a licenced product for use in oncology, transplant medicine and coronary stents. Everolimus-eluting stents have been shown to be superior, both in efficacy and in safety, to the first generation DES.[39–41] Biolimus A9, a semi-synthetic analogue of sirolimus, is similar in potency to sirolimus but is 10 times more lipophilic. Trials of biolimus-eluting BioMatrix® (Biosensors) stents have shown promising results.[42]

In the first generation DES, the drug was incorporated in permanent synthetic polymers such as polyethylene-co-vinyl acetate, poly-*n*-butyl methacrylate and the tri-block copolymer poly(styrene-b-isobutylene-b-styrene). Biocompatible polymers such as PC and co-polymer of poly-vinylidene fluoride and hexafluoropropylene superseded the previous polymers. These newer polymers held out the hope of minimal thrombus formation upon deployment and minimal adverse effect upon late healing of the vessel wall. The development of various drug coatings and polymers has been reviewed elsewhere.[43]

Given the success of DES, angioplasty balloons coated with drugs (drug-eluting balloons, DEB), have also been developed to treat small diameter coronary arteries. The BELLO study evaluated the efficacy of paclitaxel DEB compared with PES for the reduction of restenosis in vessels <2.5 mm. Whilst the late loss was less in the DEB group, angiographic restenosis, target lesion revascularization (TLR) and MACE were equal in both groups.[44] However, it is also interesting to note that in 20% cases of DEB, bailout stenting was required.

There are emerging data showing that the newer generation DES are superior to the first generation DES. Compared with PESs, newer everolimus-eluting stents have been shown to reduce composite of death or myocardial infarction (MI), ST and TLR.[45] Another recent meta-analysis of 11 randomized trials comparing everolimus- against sirolimus-eluting stents also showed a reduction in definite ST and need for repeat revascularization with everolimus-eluting stents; however, there were no significant differences in risk of MI or cardiac death.[46]

Table 2 Main drug-eluting stents

	Cypher	Taxus Express	Endeavor	Resolute	Xience-V	Promus Element	BioMatrix
Manufacturer	Cordis	Boston Scientific	Medtronic	Medtronic	Abbott Vascular	Boston Scientific	Biosensors
Platform	Bx-Velocity	Express	Driver	Driver	Vision	Omega	Gazelle
Design							
Material	SS	SS	MP35N® CoCr	MP35N® CoCr	L605® CoCr	PtCr	SS
Thickness of struts (μm)	140	132	91	91	81	81	112
Polymer	PEVA, PMBA	SIBS	PC	BioLinx	PBMA, PVDF-HFP	PBMA, PVDF-HFP	PLA
Polymer thickness (μm)	12.6	16	4.1	4.1	7.6	6	10
Drug	Sirolimus	Paclitaxel	Zotarolimus	Zotarolimus	Everolimus	Everolimus	Biolimus
Drug conc. (μg/cm^2)	140	100	100	100	100	100	156
Drug release in 4 weeks	80%	$<$10%	100%	70%	80%	80%	45%
Late lumen loss (mm)[a]	0.17[19]	0.39[20]	0.61[37]	0.27[38]	0.16[39]	0.15[70]	0.13[42]

SS, stainless steel; CoCr, cobalt–chromium; PtCr, platinum–chromium; SIBS, Poly (styrene-b-isobutylene-b-styrene); PEVA, polyethylene-co-vinyl acetate; PMBA, poly (*n*-butyl methacrylate); PC, phosphorylcholine; PVDF, poly-vinylidene fluoride; HFP, hexafluoropropylene; PLA, polylactic acid.

[a]Late lumen loss varies depending on trial population, timing of angiography and study era. The values gives are indicative only, based on pivotal trials (referenced) of these stents.

Selection of BMS vs. DES

BMS have higher incidence of ISR, whereas DES may have late ST and are generally expensive than BMS. A recent Cochrane review has shown that patients with BMS or DES have similar rate of death and AMI.[47] Both types of stents can be used in patients with stable angina as well as ACS. There are variations among different operators and regions in the use of BMS and DES.[36] The regional and international guidelines also have some differences. It would, therefore, be advisable that practitioners from various countries are aware of the guidelines applicable to them. Whilst some cardiologists argue that all patients should receive DES, it is also acceptable that shorter lesions ($\leq$15 mm) in bigger vessels ($\geq$3 mm diameter) in non-diabetic patients can be treated with BMS.[48,49] Patients with diabetes mellitus, longer lesions (>15 mm), small diameter vessels (<3 mm) should receive DES, unless DAPT is contraindicated. BMS could be a preferred choice for patients unwilling to take or unlikely to comply with DAPT. Diabetes mellitus is an independent predictor of ISR and diabetics treated with DES have significantly lower rates of death, AMI and repeat revascularization than those treated with BMS.[2,50,51] Although treatment of multi-vessel disease in diabetics is beyond the scope of this review, the recent evidence suggests that CABG may be a preferable option.[52] The ESC guidelines on myocardial revascularization provide a comprehensive review of optimal revascularization strategy for patients with stable angina and ACS.[53]

Bifurcation and covered stents

There are many stents available for specific lesion types and a detailed description of these is beyond the scope of this review.

Dedicated bifurcation stents

There are a number of specialized stents which can be implanted for lesions at coronary bifurcation.[54] The provisional strategy of stenting the main branch only has become the treatment of choice for bifurcation lesions. However, where a major branch is at risk and a two stent strategy is required, then a dedicated bifurcation stent may have a role.[54] Some of the examples of bifurcation stent include SideGuard® (Cappella), Tryton® (Vascular Perspectives), Axxess® (Biosensors), NilePax® (Minvasys); these and other bifurcation devices are reviewed elsewhere.[55]

Covered stents

The metallic platform in these stents is covered with a synthetic or biological material and can potentially be used to cover coronary perforations, aneurysms or heavy thrombus burden.[56,57] The M-Guard stent has a nylon mesh covering and can trap thrombus in the setting of

primary PCI for ST elevation myocardial infarction.[57] Pericardium-covered stent have also been used for treatment of massive thrombus burden in ACS patients, but randomized trials are warranted.[58]

Dual anti-platelet therapy

Due to the risk of ST, all patients undergoing PCI and stenting should receive DAPT, unless there is a contraindication. The duration and choice of anti-platelet agents remains somewhat controversial and may depend on patient presentation (stable angina or ACS), the choice of stent (BMS or DES) and the local/regional policies. Generally, longer duration of DAPT is recommended in patients with ACS and those receiving DES. The European Society of Cardiology (ESC) recommends 6–12 months of DAP with DES. However, it is interesting to note that 3 months of DAPT with Xience-V® (Abbot Vascular) and Xience-Prime® (Abbott Vascular) has recently been approved in Europe, based on data suggesting low incidence of ST with these stents.[40] Clopidogrel is still the most commonly used $P2Y_{12}$ inhibitor; however, it is a pro-drug which requires hepatic activation by P450 system, and consequently number of patients are clopidogrel resistant or poor responders.[59] Therefore, newer $P2Y_{12}$ inhibitors, prasugrel and ticagrelor have been developed in recent years.[59] Prasugrel therapy in ACS patients undergoing PCI has significantly reduced rates of ischemic events, including ST, but with an increased risk of bleeding and no effect on mortality.[60] Ticagrelor, a non-thienopyridine derivative $P2Y_{12}$ inhibitor, is an active drug, which following intestinal absorption can rapidly achieve adequate levels of platelet inhibition and has shown mortality benefit in patients with ACS, in comparison with clopidogrel.[61] However, no data comparing prasugrel and ticagrelor are available to-date.

Imaging-guided stent deployment

Adjunctive intra-coronary imaging during stent implantation can help to adequately deploy the stents and exclude any local complication (e.g. dissection). Intravascular ultrasound (IVUS)-guided coronary stent implantation has been shown to reduce the incidence of ST and adverse outcomes.[62] Optical coherence tomography which offers higher resolution but limited penetration is also a promising tool to optimize stent deployment.[63] However, these technologies are only used in a minority of procedures, probably due to extra cost, time and expertise involved with their use, together with parallel improvements in angiographic imaging; further data are needed to establish precise role in clinical practice.

On-going work and future developments

Despite the refinements seen in the current generation of DES leading to improved safety profile, concern persists over their long-term safety, with particular reference to the presence of durable polymers and the risk of very late ST. In an effort to address these concerns, newer stents such as DES with biodegradable polymers, polymer-free DES, DES with novel coatings and fully bioresorbable stents are being developed.

Novel anti-proliferative drugs

Zotarolimus and everolimus in current generation of DES have offered good efficacy and safety. However, the search for a better drug continues and other drugs, including novolimus and myolimus, are being tested. Novolimus, a metabolite of sirolimus, was developed specifically for use in stents. This modified mTOR inhibitor has been evaluated in EXCELLA first-in-man study (FIM) and a single-blind, prospective EXCELLA-II trial, with promising results.[64] Myolimus, a macrocyclic lactone in the same family as rapamycin, has demonstrated stability, good release kinetics and therapeutic potential in preclinical and FIM, and is now being tested in RCTs.[65]

Directional drug delivery

The concept here is to coat the anti-proliferative drug only on the outer (abluminal) surface of the stent, so that the luminal surface could be a bare metal surface or can have a different coating to enhance endothelialization or reduce platelet adhesion. This will allow drug to be where it is needed (vessel wall) and reduce the amount of the drug and polymer to be loaded on the stent platform. This technique is used in a few stents; for example, a paclitaxel-eluting system JACTAX® (Boston Scientific) that has shown promising results in FIM[55] and Combo® (OrbusNeich) stent, described later.[66]

Biodegradable polymers

DES with biodegradable polymer (BDP) may offer the benefits of a conventional DES in early phase and a BMS at later stages. These stents have controlled release of drug in parallel with biodegradation of the polymer, so that once drug elution and polymer degradation are complete, only the stent platform (BMS) is left behind.[67] The emerging data for DES with BDP appear promising: Yukon Choice PC® (Translumina),

a rapamycin-eluting stent with BDP, was non-inferior to CYPHER® for efficacy and safety at 1 year[68]; BioMatrix® (Biosensor), a biolimus-eluting stent with BDP, was non-inferior to Cypher® for MACE at 1 year[42]; Nobori® (Terumo), another biolimus-eluting stent with BDP, was non-inferior to Xience-V® at 1-year follow-up[69]; and Synergy® (Boston Scientific), an everolimus-eluting stent with BDP, was non-inferior to Promus Element® at 6 month follow-up.[70] A number of other DES with BDP including Axxess® (Biosensors), Orsiro® (Biotronik), Supralimus® (Sahajanand), DESyne® (Elixir), Infinium® (Sahajanand), Biomine® (Meril Life) are currently being tested in clinical trials.[65]

Polymer-free DES

Non-polymeric DES obviously avoid the long-term undesirable effects of polymer presence, and may improve the integrity of stents and healing of the vessel. This could be achieved by incorporating drugs into a microporous or nanoporous surface of the metallic stent. YUKON CHOICE® (Translumina) is a stainless steel stent with a micro-porous surface and sirolimus is directly applied on its surface without any polymer. Biofreedom® (Biosensors) is another non-polymeric stainless steel stent coated with biolimus. It was tested against Taxus® in FIM and showed reduction in late loss but no difference in death, AMI or ST and a double-blind randomized trial, LEADERS FREE, is planned. VESTAsync® (MIV) is also a stainless steel stent with a nanoporous surface impregnated with sirolimus. Its safety has been assessed in a small clinical trial and further randomized trials are needed. Nano^{+}® (Lepu Medical) is a stainless steel, polymer-free stent with a nanoporous surface coated with sirolimus. Bicare® (Lepu Medical) is similar to Nano^{+} but coated with probucol. Optima® (CID) is a stainless steel stent with reservoirs of tacrolimus covered with carbofilm. Amazonia-Pax® (Minvasys) is a cobalt–chromium stent with paclitaxel coating on the abluminal surface. These stents are described in detail in other reviews.[55,65]

Bioresorbable scaffolds

The rationale for a fully bioresorbable scaffold is to provide the vascular scaffold (similar to a stent) for a defined period after PCI but these scaffolds are then gradually resorbed, so that the vessel will be free of any caging and can regain its normal function. The absence of any residual foreign material and restoration of endothelial coverage would also reduce the risk of ST and the requirement for long-term DAPT.

Additionally, the bioresorbable scaffolds can overcome some of the other problems associated with the use of permanent metallic stents such as the covering of side branches, overhang at ostial lesions and inability to graft the stented segment.[65] The bioresorbable scaffolds could be either a metallic alloy or a polymer (Table 3).

Iron-based and magnesium-based alloys have been investigated as the candidates for bioresorbable scaffolds[71]; however, only magnesium alloys are currently being tested in clinical trials. AMS-1® (Biotronik) largely degraded into inorganic salts by 60 days. The PROGRESS-AMS trial was a single-arm FIM that, unfortunately, showed a significant rate of restenosis, possibly due to increased neointimal proliferation and insufficient radial strength. Further refinement of the design (AMS-2®) and paclitaxel impregnation (AMS-3®/DREAMS) has shown some improvement in BIOSOLVE-1 FIM.[72] The second generation DREAMS stent with a modified stent platform and sirolimus coating (AMS-4®) is planned to be tested in BIOSOLVE-II.

Polymeric bioresorbable scaffolds are frequently made of poly-L-lactic acid (PLLA) and poly-DL-lactic acid (PDLLA), but there are also other polymers available, each with a different chemical composition and bioresorption time. Polymeric scaffolds have less radial strength when compared with stainless steel, necessitating thicker struts leading to potentially reduced conformability. There are several bioresorbable scaffolds at various stages of development, including Igaki-Tamai® (Igaki), Absorb®BVS (Abbott Vascular), REVA® (Reva), ReZolve® (Reva), Ideal BioStent® (Xenogenics), etc., [65] and are summarized in Table 3.

Table 3 Summary of biodegradable stents used in clinical studies

Stent	Manufacturer	Material	Coating	Drug	Thickness of struts (μm)	Resorption time (months)
Metallic						
AMS 1.0	Biotronik	Mg	None	None	165	<4
AMS 3.0	Biotronik	Mg	None	Paclitaxel	125	>4
AMS 4.0	Biotronik	Mg	PLLA	Sirolimus	120	>4
Polymeric						
Igaki-Tamai	Kyto Medical	PLLA	None	None	170	24
BVS 1.0	Abbott Vascular	PLLA	PDLLA	Everolimus	150	24
BVS 1.1	Abbott Vascular	PLLA	PDLLA	Everolimus	150	24
DESolve	Elixir	PLLA	None	Myolimus	150	12–24
Ideal BioStent	Xenogenics	SA/AA	Salicylate	Sirolimus	175	>12
REVA	REVA Medical	PTD-PC	None	None	200	24
ReZolve	REVA Medical	PTD-PC	None	Sirolimus	115–230	4–6
ART 18AZ	ART	PDLLA	None	None	170	3–6
Amaranth	Amaranth	PLLA	None	None	150–200	3–6

Mg, magnesium; PLLA, poly L-lactic acid; PDLLA, poly-DL-lactic acid; BVS, bioresorbable vascular scaffold; SA/AA, salicylic acid/adipic acid; PTD-PC, poly-tyrosine-derived polycaronate.

Igaki-Tamai®, a fully bioresorbable PLLA scaffold, with no drug coating was the first device of its kind to be evaluated in humans. It has unique thermal expanding and balloon expanding properties, so that the initial self-expansion occurs following the use of a heated contrast (up to 70°C) in the delivery balloon and the final self-expansion of the stent occurs at 37°C in the 20–30 min after stent deployment. The stent has shown good safety and efficacy profile in FIM and a second larger study of 50 elective patients, and has now data available for 10-year follow-up.[73] Despite the excellent results, this device failed to become a mainstream player due the concerns about the use of heated contrast and lack of drug coating.[65]

Absorb® bioresorbable vascular scaffold (BVS) is the first drug (everolimus) eluting, fully bioresorbable scaffold, and has achieved a CE mark. It is composed of PLLA and PDLLA, which are completely resorbed *in vivo* in 12–18 months via a series of overlapping steps, including hydration, depolymerization and hydrolysis, breaking them into smaller chains, which are further metabolized by phagocytes into soluble monomers (e.g. L-lactate). These monomers are subsequently metabolized into pyruvate, which enters into Krebs cycle and eventually converted into carbon dioxide and water.[74] Absorb BVS 1.0 was tested in Absorb cohort A, a multicentre single-arm study, and was found to be safe and had a low MACE at 4-year follow-up.[75] The second generation of this device (BVS 1.1) has enhanced radial strength, mechanical integrity and release kinetics, and was evaluated in Absorb cohort B FIM and is being tested against everolimus DES in Absorb-II RCT.[76] There is still a long road ahead before BVS are routinely used in clinical practice, but the future looks bright for this technology and it has already been described as the fourth revolution in interventional cardiology.[77]

Pro-healing stents

The anti-proliferative drugs used in DES lack selectivity with respect to the targeted cell types. Therefore, they not only inhibit proliferation of VSMCs underlying neointimal formation, but also compromise endothelial repair and, hence, increase the risk for ST (Figure 1). It remains, therefore, an attractive traget to accelerate re-endothelialization. Vascular endothelial growth factor-eluting stents were tried but they not only failed to promote endothelialization but also increased neointimal proliferation.[78] The Genous® (OrbusNeich), a stainless steel stent coated with anti-CD34 antibodies to capture endothelial progenitor cells (EPCs), showed promising results in preclinical studies by promoting endothelialization without affecting neointimal proliferation.[79] However, the TRIAS trial comparing Genous® and Taxus® stents showed no

significant difference in mortality, AMI and target vessel revascularization at 2 years.[80] CD34 antibodies are not specific to EPCs and may also attract other hematopoietic stem cells (such as smooth muscle progenitor cell) which may cause an increase in neointimal proliferation. Therefore, a new generation Combo® (OrbusNeich) stent, which combines EPC capturing CD34 antibodies on the luminal surface and a sirolimus-eluting biodegradable polymer on abluminal surface has been developed. This innovative design has reduced neointimal proliferation and accelerated endothelialization in a porcine model. Combo® was shown to be safe and non-inferior to Xience-V® in the FIM study, REMEDEE (Randomized Evaluation of an Abluminal sirolimus coated Bio-Engineered Stent) and further trials to assess efficacy and safety over longer follow-up are warranted.[66] Various other potential strategies to enhance stent endothelialization are also currently being tested in preclinical studies.[81,82]

Conclusion

Coronary artery stenting is the treatment of choice for patients requiring coronary angioplasty. There have been significant developments in the design of stent platforms, leading to reduction in ISR, even with BMS. However, the newer generation DES have almost negligible ISR and, when combined with DAPT and optimal deployment, a low risk of ST. There are a number of on-going studies to evaluate newer stent platforms, anti-proliferative drugs, novel polymers, polymer-free stents and bioresorbable stents. The quest for the ideal stent continues, but perhaps there will not be one single stent suitable for all patients and lesions. Interventional cardiologists in future will have a wide variety of stents available which may enable them to practice evidence-based personalized medicine, where the choice of stent is based on genetic determinants, risk profile (for restenosis, thrombosis and bleeding) and lesion characteristics of individual patients.

Funding

JI was supported by National Institute of Health Research (NIHR), UK.

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