REVOLUTION OF DRUG-ELUTING CORONARY STENTS: AN ANALYSIS OF MARKET LEADERS

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Disclosure: Ashok S. Thakkar is an employee of Meril Life Science Pvt., Ltd. Bhargav A. Dave has declared no conflicts of interest.
Received: 27.04.16 **Accepted:** 24.08.16
Citation: EMJ. 2016;4[1]:114-125.

ABSTRACT

Percutaneous coronary intervention with drug-eluting stents (DES) is a well-established and widely-accepted treatment approach in patients with coronary artery disease. Although the underlying principle of DES remains constant for different stents available on the market, certain factors may offer variations with respect to deliverability (ease of placement), efficacy (preventing restenosis), and safety (thrombosis rates). These factors may include the type of drug (sirolimus, everolimus, biolimus, zotarolimus, novolimus, paclitaxel, docetaxel), type of stent platforms (stainless steel, platinum, cobalt-chromium, cobalt-nickel, platinum-chromium), type of polymers (permanent, biodegradable, polymer-free), thickness of stent struts (thick, thin, ultra-thin), type of coating (abluminal, conformal), and type of stent design (open-cell, closed-cell, combination of open-closed cell). In this context, we present a review on characteristic features of several of the most widely used coronary stents worldwide. Furthermore, the advancements of completely biodegradable stents are discussed. In addition, the future directions for the development of creating an ideal or perfect DES are debated.

Keywords: Biodegradable, bioresorbable vascular scaffold, coronary artery disease (CAD), drug-eluting stents (DES), percutaneous coronary intervention, polymer, strut, stent coating.

BACKGROUND

Coronary artery disease (CAD) is the most common cause of cardiovascular disability and death worldwide.[1] It is well established and widely accepted that percutaneous coronary intervention using coronary stents has revolutionised the treatment of CAD.[2] Since the first implantation of a coronary stent in 1986 and the first US Food and Drug Administration (FDA) approval for a coronary stent in 1994,[3] medical and technological advances have brought pioneering transformations. These include the establishment of newer stent designs and the development of a variety of coronary stents, including bare-metal stents, drug-eluting stents (DES), and fully bioabsorbable stents.[4]

Bare-metal coronary stents made of stainless steel, cobalt, chromium, or other metals were the first introduced to the market. Although bare-metal stents are still used in some centres, significant concerns remain regarding the high risk of restenosis and stent thrombosis. Here, restenosis occurs mainly due to proliferation of neointimal hyperplasia of smooth muscle cells after stent implantation. In order to overcome these challenges, DES containing anti-restenotic or anti-proliferative agents were developed. These DES provide local, site-specific, controlled release of an anti-restenotic drug that can inhibit neointima formation.[5] These stents have demonstrated reduced clinical and angiographic revascularisation rates when compared to bare-metal stents in various randomised controlled trials and post-marketing surveillance registries.[6-11] Subsequent developments in anti-restenotic agents, polymeric coatings, and improvised stent platforms have further reduced the risk of these complications.[5] Nevertheless, once thought to be the solution for restenosis, DES are

now faced with their own challenges of late stent thrombosis. This has renewed interest in designing a better coronary stent.[12] First-generation DES include sirolimus-eluting stents (2003) and paclitaxel-eluting stents (2004), while the second-generation DES include zotarolimus-eluting stents (2008) and everolimus-eluting stents (2008), with permanent polymer coatings.[5] Newer-generation stents, including stents with biodegradable polymers, polymer-free stents, and biodegradable stents, are the novel frontiers. While the safety and efficacy of the majority of these stents are supported by respective clinical trials and registries, larger trials and longer follow-ups are necessary to assess their long-term effectiveness.[13]

The safety and efficacy of these DES are usually evaluated in clinical trials and registries in terms of major adverse cardiac events (as a composite of cardiac death, myocardial infarction, and repeat revascularisation) and stent thrombosis.[14] Here it should be noted that the cause of these adverse outcomes could be multifactorial.[15] Although the underlying principle of DES remains constant for different stents available on the market, certain factors may offer variations with respect to deliverability (ease of placement), efficacy (preventing restenosis), and safety (thrombosis rates). Apart from patient characteristics and lesion complexity, stent design and stent composition are identified as important factors which may influence clinical outcomes.[16] In brief, these factors, shown in Figure 1, include the type of drug (sirolimus, everolimus, biolimus, zotarolimus, novolimus, paclitaxel, docetaxel), type of stent platforms (stainless steel, platinum, cobalt-chromium, cobalt-nickel, platinum-chromium), type of polymers (permanent, biodegradable, polymer-free), thickness of stent struts (thick, thin, ultra-thin), type of coating (abluminal, conformal), and type of stent design (open-cell, closed-cell, hybrid).

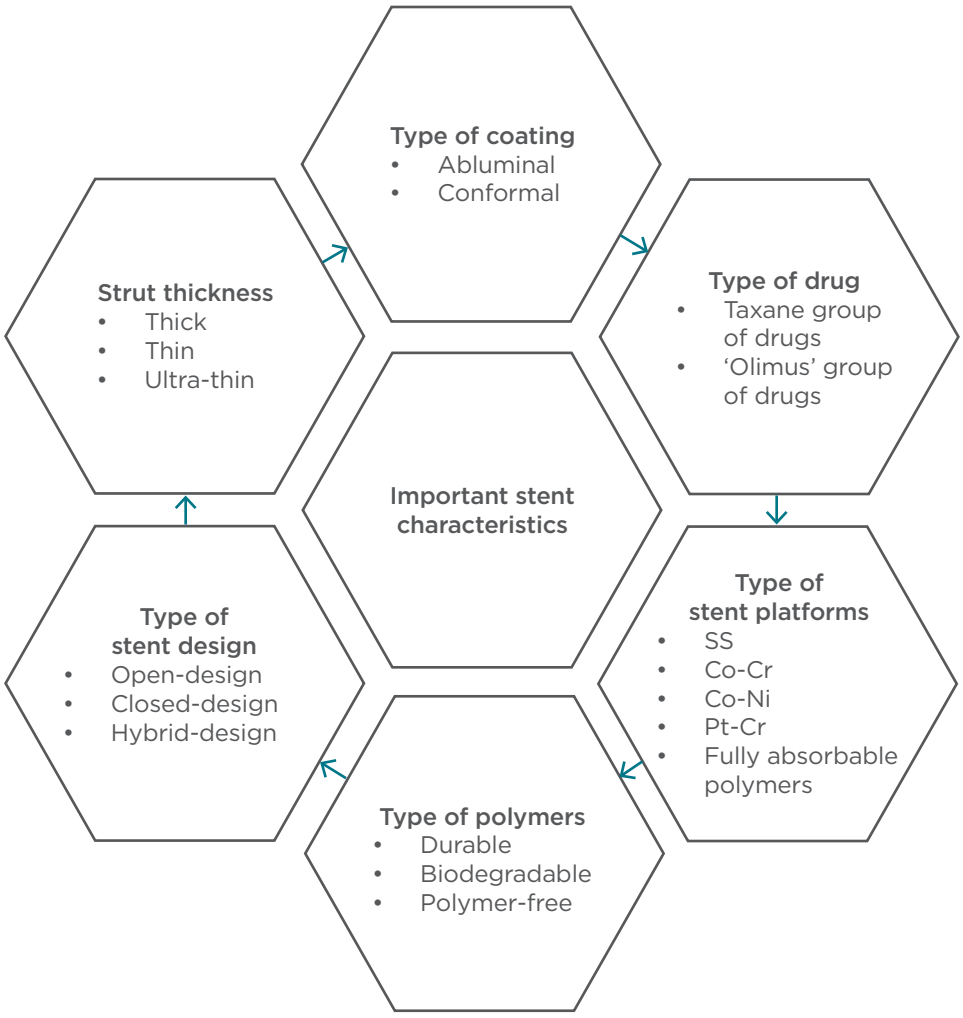

Figure 1: Important characteristics of coronary stents that can influence clinical outcomes.
SS: stainless steel; Co-Cr: cobalt-chromium; Co-Ni: cobalt-nickel; Pt-Cr: platinum-chromium.

Table 1: Appraisal of design-related characteristics of most widely-used coronary drug-eluting stents.

Stent name	Manufacturer	Drug (dose)	Polymer	Biocompatibility	Polymer thickness (μm)	Stent platform	Strut thickness (μm)
Axxion™	BioSensors International (Boon Lay, Singapore)	Paclitaxel	None	None	-	Stainless steel	119
Taxus Express²™	Boston Scientific (Marlborough, MA, USA)	Paclitaxel (1 μg/mm²)	Translute SIBS copolymer	Durable	16	Stainless steel	132
Taxus Liberté™	Boston Scientific (Marlborough, MA, USA)	Paclitaxel (1 μg/mm²)	Translute SIBS copolymer	Durable	16	Stainless steel	97
Ion™	Boston Scientific (Marlborough, MA, USA)	Paclitaxel (1 μg/mm²)	Triblock copolymer*	Durable	-	Stainless steel platinum-chromium	81–86
Promus™	Boston Scientific (Marlborough, MA, USA)	Everolimus (1 μg/mm²)	PBMA, PVDF-HFP (Fluoropolymer)	Durable	7.6	Cobalt-chromium	81
Promus™ Element™	Boston Scientific (Marlborough, MA, USA)	Everolimus (1 μg/mm²)	PBMA, PVDF-HFP (Fluoropolymer)	Durable	7.0	Platinum-chromium	81
Synergy™	Boston Scientific (Marlborough, MA, USA)	Everolimus (1 μg/mm²)	PLGA	Biodegradable	4	Platinum-chromium	74
Xience V®/ Xience Prime®/ Xience Alpine®/ Xience Xpedition®	Abbott Vascular (Green Oaks, IL, USA)	Everolimus (1 μg/mm²)	PBMA, PVDF-HFP (Fluoropolymer)	Durable	7.6	Cobalt-chromium	81
Cypher®	Cordis Corporation (Baar, Switzerland)	Sirolimus (1.4 μg/mm²)	PEVA + PBMA	Durable	12.6	Stainless steel	140
Cypher Select®	Cordis Corporation (Baar, Switzerland)	Sirolimus (1.4 μg/mm²)	PEVA + PBMA	Durable	-	Stainless steel	100
BioMime™	Meril Life Sciences (Gujarat, India)	Sirolimus (1.25 μg/mm²)	PLLA + PLGA	Biodegradable	2	Cobalt-chromium	65
Orsiro	Biotronik (Bülach, Switzerland)	Sirolimus	Dual-polymer mix†	Biodegradable	7.4	Cobalt-chromium	60–80
Coroflex® ISAR	B. Braun Melsungen (Hessen, Germany)	Sirolimus	None	None	N/A	Cobalt-chromium	60
Ultimaster®	Terumo (Tokyo, Japan)	Sirolimus	poly(dl-lactide-co-caprolactone)	Biodegradable	-	Cobalt-chromium	80
Yukon Choice® PC	Translumina Therapeutics (New Delhi, India)	GmbH Sirolimus	PLA + shellac resin	Biodegradable	-	Stainless steel	87
Yukon Choice® Flex	Translumina Therapeutics (New Delhi, India)	GmbH Sirolimus	PLA + shellac resin	Biodegradable	-	Cobalt-chromium	79

Table 1 continued.

Stent name	Manufacturer	Drug (dose)	Polymer	Biocompatibility	Polymer thickness (μm)	Stent platform	Strut thickness (μm)
Cre8™	Alvimedica (Istanbul, Turkey)	Amphilimus (Sirolimus + organic acid) (0.9 μg/mm²)	None	None	-	Cobalt-chromium	80
BioFreedom™	BioSensors International (Boon Lay, Singapore)	Biolimus A9	None	None	-	Stainless steel	
BioMatrix™	BioSensors International (Boon Lay, Singapore)	Biolimus A9	PLA	Biodegradable	10	Stainless steel	112–137
Nobori®	Terumo (Tokyo, Japan)	Biolimus A9	PLA	Biodegradable	20	Stainless steel	120
Endeavor®	Medtronic (Dublin, Ireland)	Zotarolimus (1 μg/mm²)	Phosphorylcholine	Durable	4.3	Cobalt-chromium	91
Endeavor Resolute™	Medtronic (Dublin, Ireland)	Zotarolimus (1 μg/mm²)	Biolinx‡	Biocompatible	5.6	Cobalt-chromium	81
Resolute Integrity®	Medtronic (Dublin, Ireland)	Zotarolimus (1 μg/mm²)	Biolinx‡	Biocompatible	6	Cobalt-chromium	91
Resolute Onyx™	Medtronic (Dublin, Ireland)	Zotarolimus (1 μg/mm²)	Biolinx‡	Biocompatible	-	Cobalt-chromium	81
DESolve	Elixir Medical (Sunnyvale, CA, USA)	Myolimus	Methacrylate	Durable	<3	Cobalt-chromium	81
DESyne® NOVOLIMUS™	Elixir Medical (Sunnyvale, CA, USA)	Novolimus	Methacrylate	Durable	3	Cobalt-chromium	81

*Polystyrene and polyisobutylene.
†passive coating of PROBIO (amorphous silicon carbide) and active coating of BIOlute (PLLA).
‡composed of hydrophobic C10, hydrophilic C19, and polyvinyl pyrrolidone.
PBMA: poly(methacryloyl β-alanine); PVDF-HFP: polyvinylidenefluoro-hexafluoropropylene; PEVA: polyethylene-co-vinyl acetate; PLA: poly(lactic acid); PLGA: poly(dl-lactic-co-glycolic acid); PLLA: poly(L-lactic acid); SIBS: styrene-isobutylene-styrene.

With this background, we scrutinised the available published literature on DES for the present review. The search engines included PubMed, ScienceDirect, and Google Scholar. Accordingly, the most widely described coronary stents were identified and examined for their characteristics, including stent design, strut thickness, stent platform, use of polymers, and the choice of anti-restenotic drug (Table 1). Furthermore, the advancements in completely biodegradable stents are discussed (Table 2). In addition, future directions for the development of an ideal or perfect DES are debated.

ANTI-PROLIFERATIVE DRUG

The DES system is often distinguished by the anti-proliferative drug applied to the stent. FDA-approved first-generation DES, such as the Cypher® sirolimus-eluting stent (Cordis Corporation, Baar, Switzerland) and the Taxus® Express²™ paclitaxel-eluting stent (Boston Scientific, Marlborough, Massachusetts, USA) demonstrated promising results compared to bare-metal stents.[6-9] However, these stents displayed potential for increased inflammation, delayed healing, and late stent thrombosis, which could not be ignored.

Table 2: Appraisal of design-related characteristics of fully bioabsorbable/bioresorbable coronary stents/scaffolds.

Stent name	Manufacturer	Strut material	Coating material	Eluted drug	Strut thickness (μm)	Resorption time (months)
Igaki-Tamai®	Kyoto Medical Planning (Kyoto, Japan)	PLLA	None	None	170	24–36
REVA	REVA Medical (San Diego, CA, USA)	PTD-PC	None	None	200	24
ART 18AZ	Arterial Remodeling Technologies (ART) (Paris, France)	PDLLA	None	None	170	18–24
FADES®	Zorion Medical (Zionsville, IN, USA)	Magnesium alloy + PLGA	None	None	-	6
Fortitude®	Amaranth Medical (Mountain View, CA, USA)	Semicrystalline polylactide	None	None	150–200	3–6
Amaranth BRS	Amaranth Medical (Mountain View, CA, USA)	PLLA	None	None	156	12–24
DREAMS Absorbable Magnesium Scaffold (AMS)	Biotronik (Bülach, Switzerland)	Magnesium alloy	None	None	165	<4
DREAMS-1	Biotronik (Bülach, Switzerland)	Magnesium alloy	PLGA	Paclitaxel	125	9
DREAMS-2	Biotronik (Bülach, Switzerland)	Magnesium alloy	PLLA	Sirolimus	150	9
MeRes 100™	Meril Life Sciences (Gujarat, India)	PLLA	PDLLA	Sirolimus	100	24–36
ReZolve®	REVA Medical (San Diego, CA, USA)	PTD-PC	None	Sirolimus	114–228	24
ReZolve®2	REVA Medical (San Diego, CA, USA)	PTD-PC	None	Sirolimus	100	48
Fantom®	REVA Medical (San Diego, CA, USA)	PTD-PC	None	Sirolimus	125	36
Mirage Bioresorbable Microfiber Scaffold	Mirage BRMS, Manli Cardiology Singapore	PLLA	None	Sirolimus	125–150	14
Xinsorb	HuaAn Biotechnology (Laiwu, China)	PLLA + PAL + PCL + PLGA	PDLLA	Sirolimus	160	24–36

Table 2 continued.

Stent name	Manufacturer	Strut material	Coating material	Eluted drug	Strut thickness (μm)	Resorption time (months)
BTI scaffold	Bioabsorbable Therapeutics Inc. (Menlo Park, CA, USA)	Polymer salicylate + linker	Salicylate + different linker	Sirolimus	200	12
IDEAL™ Biostent	Bioabsorbable Therapeutics Inc. (Menlo Park, CA, USA)	Polymer salicylate + linker	Salicylate + different linker	Sirolimus	175	12
Acute	OrbusNeich (Wan Chai, Hong Kong)	PCL + PDLLA + PLLA	None	Sirolimus + CD34	150	Under investigation
Absorb™ Bioresorbable Vascular Scaffold 1.1	Abbott Vascular (Green Oaks, IL, USA)	PLLA	PDLLA	Everolimus	156	24–36
DESolve	Elixir Medical (Sunnyvale, CA, USA)	PLLA	None	Myolimus	150	12–24
DESolve 100® Novolimus	Elixir Medical (Sunnyvale, CA, USA)	PLLA	PLLA	Novolimus	100	24

PTD-PC: polytyrosine derived polycarbonate; PAL: poly(aspartic acid-co-lactide), PCL: poly(ε-caprolactone); PLLA: poly(L-lactic acid); PDLLA: poly(dl-lactide acid); PLGA: poly(dl-lactic-co-glycolic acid).

This prompted the development of next-generation stents. Subsequently, many drugs have been proposed and/or tested to reduce neointimal hyperplasia and/or inflammation with DES.[17]

Overall, two major classes of anti-proliferative drugs are used in DES. The 'olimus' group of drugs (i.e. sirolimus, everolimus, biolimus, and zotarolimus) act on the mammalian target of rapamycin, a key intermediary in the phosphatidylinositol 3-kinase pathway,[18] while the taxane group of drugs (i.e. paclitaxel, docetaxel) acts downstream of these pathways by inhibiting microtubular function, which is required for cell migration and proliferation.[19] Numerous clinical studies have verified the safety and efficacy of:[20-33]

- Paclitaxel-eluting stents (Taxus Liberté™ and Ion™, Boston Scientific; Axxion™, Biosensors International, Boon Lay, Singapore)
- Sirolimus-eluting stents (BioMime™, Meril Life Sciences, Gujarat, India; Cypher, Cordis Corporation; Yukon® Choice PC, Translumina Therapeutics, New Delhi, India; Orsiro, Biotronik, Bülach, Switzerland; Coroflex® ISAR, B. Braun, Hessen, Germany; Ultimaster®, Terumo Corporation, Tokyo, Japan)

Other 'olimus'-eluting drugs are widely used in current interventional cardiology practice, including:[20-33]

- Everolimus (Xience V®, Abbott Vascular, Green Oaks, Illinois, USA; PROMUS™ and Synergy™, Boston Scientific)
- Zotarolimus (Endeavor®, and Resolute™ Integrity, Medtronic, Dublin, Ireland)
- Biolimus A9 (BioMatrix™ and BioFreedom™, Biosensors International; Nobori®, Terumo Corporation)
- Myolimus (DESolve I, Elixir® Medical, Sunnyvale, California, USA)
- Novolimus (DESyne®, Elixir Medical)
- Amphilimus (a sirolimus formulated with a polymer-free amphiphilic carrier; Cre8™, Alvimedica, Istanbul, Turkey)

Numerous trials have compared the safety and efficacy of these DES to identify an appropriate stent with better outcomes. However, sirolimus-eluting stents have shown a significantly lower risk of restenosis and target-vessel revascularisation compared with paclitaxel-eluting stents in meta-analyses of randomised trials.[34-36] Additionally, the in-stent late loss and in-stent diameter stenosis

at 1 year were lower with sirolimus-eluting stents when compared with paclitaxel-eluting stents.[36] Similarly, sirolimus-eluting stents, in comparison with zotarolimus-eluting stents, have shown better clinical outcomes in terms of restenosis, target-lesion revascularisation, and target-vessel revascularisation.[37] Furthermore, a recent meta-analysis of five randomised trials reported that everolimus-eluting stents and sirolimus-eluting stents have comparable outcomes.[38] Amphilimus-eluting coronary stents have also shown promising preliminary results in diabetic patients.[28] It should be noted that the selection of appropriate anti-proliferative agents among various DES could be a key determinant factor in percutaneous coronary intervention outcomes.

STENT PLATFORM

DES platforms must have:

- A low crimped profile
- High flexibility
- Excellent trackability
- High deliverability
- Minimum shortening during expansion
- Good conformability upon deployment
- High radial strength
- Minimal radial recoiling[26]

In the majority of conventional DES, either stainless steel or cobalt-chromium alloys are used as the metal platform. These metals exhibit reasonably good behavioural profiles in terms of biocompatibility, fatigue testing, and fracture.[27] While stainless steel alloys offer favourable vascular biocompatibility, visualisation under x-ray fluoroscopy is challenging, especially with thin-strut design stents.[39] In this regard, cobalt-chromium alloys offer superior benefits by providing denser metal and by allowing thinner struts, which may enhance acute stent performance while retaining adequate radiopacity.[22,27] Several other radiopaque materials such as tantalum or gold were initially explored; however, the clinical data indicated increased restenosis and mortality risk with gold-coated stents.[39] Recently, platinum-chromium metal based stent platforms have been developed, which seems to be an attractive metal compound for stent alloys owing to its superior strength, fracture resistance, chemical stability, and biocompatibility.[40] Furthermore, the radiopacity of platinum-chromium is higher, allowing the use of thinner struts without sacrificing visibility.[39] Another revolution in stent platform comprises the development of nickel-titanium (nitinol)-based self-expanding coronary stents.[22] Since radiographic visibility of the stent is an important feature associated with procedural outcomes, the majority of stents offer two radiopaque markers at the two stent edges to help make the stent implantation more predictable and controllable.[29,33]

The stainless steel platform based DES include Axxion (Biosensors International), Taxus Liberté (Boston Scientific), Cypher (Cordis Corporation), Yukon Choice PC (Translumina), BioMatrix (Biosensors International), BioFreedom (Biosensors International), and Nobori (Terumo). The cobalt-chromium based DES include BioMime (Meril Life Sciences), Promus (Boston Scientific), Xience V, Endeavor (Medtronic), Orsiro (Biotronik), Elixir (Elixir Medical), Cre8 (Alvimedica), Coroflex ISAR (B. Braun), and Ultimaster (Terumo). The platinum-chromium based DES include PROMUS™ Element™ and Synergy (Boston Scientific).[20,22,27-32]

STENT DESIGN

Stent design plays an important role in providing flexibility, deliverability, adequate scaffolding, and radial hoop strength. In recent years, the stent designs have evolved significantly. In the majority of currently used stents, the stent design comprises either an open-cell structure (e.g Xience V and MULTI-LINK VISION®, Abbott Vascular; Endeavor and Driver®, Medtronic; Taxus Liberté and Express™, Boston Scientific; Cre8, Alvimedica) or undulating longitudinal connectors with a closed-cell structure (e.g. Cypher and Bx Velocity®, Cordis Corporation) to connect the expandable circumferential slotted structures.[27,28] In closed-cell design, all internal inflection points of the structural members are connected by bridging elements. This offers advantages of optimal scaffolding and a uniform surface, regardless of the degree of bending. However, stents with closed-cell designs are reported to be less flexible than a similar stent with an open-cell design.[41] On the other hand, closed-cell stent designs are reported to have less plaque prolapse and have improved drug-delivery distribution.[27] While the open-cell design facilitates access to side branches and the possibility to pen the side-stent struts of the stent, the closed-cell design does not allow significant expansion of the opening toward the side branch even after crossing and inflating a balloon.[33] Considering these

factors, a hybrid-cell structure comprising a mix of open-cell stent design in the mid segments and closed-cell design at the edges has been developed in recent years. These stents (e.g. BioMime) may offer the advantages of high radial strength (due to closed-cell design at the edges) and the benefits of improved conformability and side branch access (due to open-cell design in the mid segments).[41] The stent design may play a vital role in treating bifurcation lesions.

STRUT THICKNESS

In addition to the stent design and type of metal used, the strut thickness may significantly affect vascular response.[42] It has been postulated that a wide strut can contribute to increased rates of periprocedural myocardial infarction, either by distal embolisation or by completely covering a side branch that is no longer accessible with a wire.[43] On the other hand, thinner struts may offer lower restenosis rates and improved healing, possibly due to less stent-induced arterial injury, lessened inflammation, and lessened neointimal hyperplasia.[42,43] Clinical studies have also demonstrated that reduced strut thickness results in lower restenosis rates after stent placement.[44,45] Thinner struts also result in improved stent deliverability, increased flexibility, and allow lower-pressure deployment.[15]

The majority of currently available commercial coronary stents have a strut thickness <100 μm. However, the first-generation stainless steel based coronary stents have a strut thickness of 132 μm (Taxus Express^2) to 140 μm (Cypher, BX Velocity). Subsequent medical advances with the use of stronger and more radiopaque metals such as cobalt-chromium and platinum-chromium, have allowed the incorporation of thinner struts without sacrificing strength or visibility. Currently available stents with thinner strut thickness (60–97 μm) are shown in Table 3. Overall, it should be noted that thinner struts may provide significant advantages with regard to acute stent performance characteristics.[27,42]

POLYMER

There is strong evidence to suggest that the use of polymers in stents may influence the incidence of late and very late stent thrombosis and, subsequently, this has become a fundamental area for new research and stent development.[15] The initially developed major DES systems used biostable or non-biodegradable polymers.

Table 3: Currently available drug-eluting coronary stents with thinner strut thickness.[23,27-31,39]

Manufacturer	Product	Strut thickness (μm)
Boston Scientific (Marlborough, MA, USA)	Taxus™ Liberté™	97
Medtronic (Dublin, Ireland)	Endeavor®	91
Translumina Therapeutics (New Delhi, India)	Yukon® Choice PC	87
Boston Scientific (Marlborough, MA, USA)	Ion™	81–86
Boston Scientific (Marlborough, MA, USA)	Promus™	81
Boston Scientific (Marlborough, MA, USA)	Promus Element™	81
Abbott Vascular (Green Oaks, IL, USA)	Xience V®	81
Abbott Vascular (Green Oaks, IL, USA)	Xience Alpine®	81
Medtronic (Dublin, Ireland)	Resolute	81
Medtronic (Dublin, Ireland)	Resolute Onyx™	81
Elixir Medical (Sunnyvale, CA, USA)	DESyne®	81
Alvimedica (Istanbul, Turkey)	Cre8™	80
Terumo EMEA (Leuven, Belgium)	Ultimaster®	80
Translumina Therapeutics (New Delhi, India)	Yukon® Choice Flex	79
Boston Scientific (Marlborough, MA, USA)	Synergy™	74
Meril Life Sciences (Gujarat, India)	BioMime™	65
Biotronik (Bülach, Switzerland)	Orsiro	60–80
B. Braun Melsungen (Hessen, Germany)	Coroflex® ISAR	60

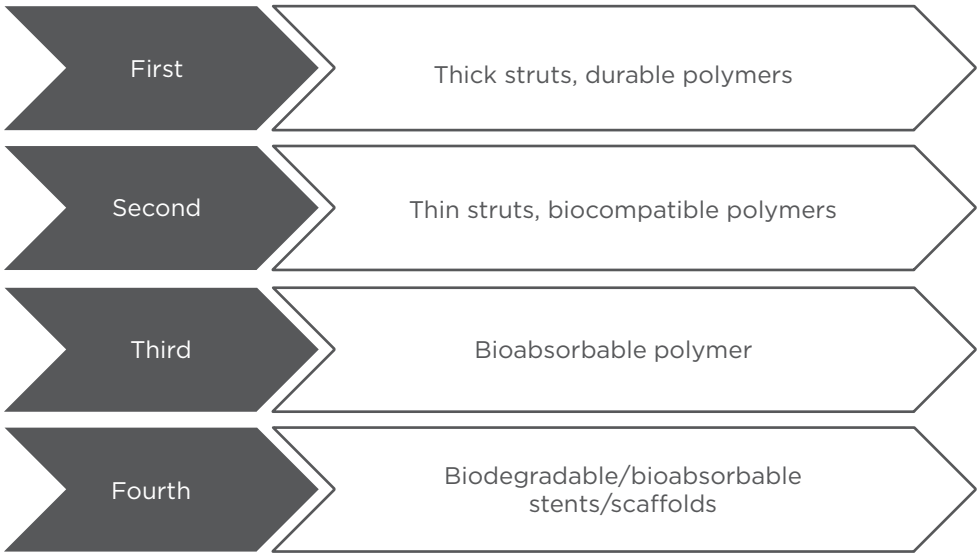

Figure 2: Differences between the first, second, third, and fourth-generation of drug-eluting stents.

The Cypher DES elutes sirolimus from a polyethylene-co-vinyl acetate/poly N-butyl methacrylate polymer, while the Taxus Express[2] elutes paclitaxel from a styrene-isobutylene-styrene polymer.[27] Subsequently developed stents with biostable polymers include the Endeavor DES system that elutes zotarolimus from phosphrylcholine polymer and the Xience V DES system that elutes everolimus from flouropolymer.[46] The advantages of using biostable polymers include the controlled release of the drug, uniform drug delivery, and a longer shelf-life. However, the utility of biostable polymers in the stent system negatively affects the long-term clinical outcomes as presence of the polymer, even after the drug has been eluted, stimulates local inflammatory reaction and delays healing of affected arteries.[47] Accordingly, stents with these biostable polymers possess high risk of late restenosis and very late stent thrombosis.[27] This has led to the development of DES coated with biodegradable polymers, offering the clinical advantages of controlled-drug release along with biodegradation of the polymers.[15]

Using biodegradable polymers such as polylactic-co-glycolic acid (or others) in the stent system is appealing because the drug-elution is completed along with the bioabsorption of the polymer drug carrier. This would reduce local inflammatory reaction and irritation, leaving only the metal stent in adhesion with neointima and endothelium, thereby reducing the long-term risks associated with the presence of a permanent polymer. Thus, the coronary stent systems with biodegradable polymers may offer the benefits of anti-restenotic efficacy of standard DES in the initial period, when the risk of restenosis and stent thrombosis is high, whereas once the polymer has biodegraded, it may offer the safety benefits of a bare-metal stent.[15,48] Currently, DES such as BioMime, BioMatrix, Nobori, Yukon® Choice Flex, Synergy, and Orsiro have anti-proliferative drugs coated along with biodegradable polymers. These stents have shown encouraging results in various clinical studies.[49-51]

The recent revolution in the field of interventional cardiology includes the use of metallic stent structures with porous surfaces, allowing appropriate drug-elution kinetics without the use of a polymer.[52] This approach could be clinically beneficial if the optimal dosing and pharmacokinetics of the anti-proliferative drug can be achieved with it. Currently, the DES that use a non-polymer approach include Biolimus A9® DES system (Biosensors International) with biolimus drug, VESTAsync™ DES system (MIV Therapeutics, Surat, Gujarat, India), Coroflex ISAR DES system (B. Braun), and BioFreedom DES system (Biosensors International) with hydroxyapatite releasing sirolimus, and Cre8 DES system (Alvimedica) with amphilimus drug.[27-32]

TYPE OF COATING

The type of coating on each DES may also play a key role.[5] Between the two types, conformal

coating inhibits smooth cell proliferation all over the stent surface, while abluminal coating will only have an effect on the outer surface of the stent (i.e. opposite to luminal side), which may contribute to the risk of increased neointimal thickness over the luminal surface. Hence, theoretically, conformal coating scores over abluminal coating. Currently available DES systems with abluminal coating include Biomatrix, Nobori, Elixir, Cre8, and Orsiro, while the DES systems with conformal coating include Xience V, Endeavor, and BioMime. In addition, the thickness of the coating is also considered to play an important role in clinical outcomes. It is desirable to have a thinner homogenous coating on the surface of DES.[15,29]

FULLY BIOABSORBABLE DRUG-ELUTING STENTS

Fully biodegradable or bioabsorbable stents/scaffolds, made of polymers or metal alloys with or without a drug coating, have been developed with an aim to provide immediate scaffolding to the stenosed artery, followed by complete biodegradation of the stent/scaffold within 6 months to 2 years, leaving behind a naturally healed similar vessel.[26,27] The concept of a fully bioabsorbable stent/scaffold was established with the fact that the long-term placement of a bare-metal stent in the vessel wall would be inflammatory and leads to inevitable restenosis. Thus, fully bioabsorbable stents/scaffolds may reduce the chronic inflammation associated with a metallic platform.[27] Such stents/scaffolds would also prevent the need for long-term antiplatelet therapy. Future surgical options will not be restricted as no foreign material would be left behind.[26] However, fully bioabsorbable stents/scaffolds are associated with certain challenges. The major problems associated with fully bioabsorbable stents/scaffolds include early stent absorption, leading to the loss of scaffolding and allowing late loss, and a greater degradation rate of polymer as compared with a metallic structure, potentially leading to long-term adverse effects due to inflammation. Other concerns include flexibility, deliverability, vascular compatibility, and radial hoop strength.[39]

In general, there are two types of fully bioabsorbable stents/scaffolds: those made from organic biopolymers and those made from corrodible metals.[26] The currently available fully bioabsorbable stents/scaffolds include:

- Everolimus-eluting bioresorbable vascular scaffold Absorb™ (Abbott Vascular)
- Sirolimus-eluting bioresorbable vascular scaffold MeRes 100™ (Meril Life Sciences)
- Sirolimus salicylate-eluting The IDEAL™ stent (Bioabsorbable Therapeutics Inc, Menlo Park, California, USA)
- Novolimus-eluting bioresorbable coronary scaffold DESolve® 100 Novolimus (Elixir Medical)
- High molecular weight poly-L-lactic acid (PLLA)-based Igaki-Tamai® stent (Kyoto Medical Planning, Kyoto, Japan)
- DRug Eluting Absorbable Metal Scaffold (DREAMS) absorbable magnesium scaffold (Biotronik)
- Tyrosine polycarbonate polymer-based REVA stent (REVA Medical, San Diego, California, USA)

Clinical studies have shown favourable efficacy and safety with fully bioabsorbable stents/scaffolds in CAD patients.[53-60]

THE PURSUIT FOR AN IDEAL DRUG-ELUTING STENT

The major differences between the first, second, third, and fourth-generations of DES are depicted in Figure 2.[61] Although considerable advances have been made in platform, drug, and polymer technology since the introduction of the first-generation DES, the pursuit for an ideal DES is still ongoing. Extensive worldwide research is focussing on further optimisation of stent design to incorporate thinner struts, reduced use of durable polymers, and combination therapies to inhibit restenosis, while promoting endothelialisation and reducing dependence on dual antiplatelet therapy.[39] In addition, there is a need to develop DES that are customised to treat specific patient profiles such as those with diabetes, small vessels, bifurcation lesions, long lesions, or tapered lesions. One such revolution in this regard is the development of BioMime™ Morph sirolimus-eluting stent (Meril Life Sciences) for the management of patients with long tapered lesions.

Overall, it can be postulated that the ideal DES should most likely incorporate a number of newer and improved materials and delivery systems to further enhance safety, efficacy, and cost-efficiency. The characteristic features of the ideal DES system may include:[27]

- Eluting an 'olimus' drug (e.g. sirolimus, everolimus, biolimus A9, myolimus, novolimus)
- High flexibility and high conformability (hybrid open-cell design)
- Adequate radiopacity and radial strength (metallic platform)
- A very thin (homogeneous) surface of bioabsorbable (non-inflammatory) polymer
- Thinner struts
- Stimulation of early re-endothelialisation
- A thrombus-resistant luminal surface
- A very low-profile stent delivery system
- A high-pressure balloon (suitable for direct stenting)
- Drug-elution for about 60–90 days, followed by complete absence of drug release
- Minimising the need for antiplatelet treatment for ≤3 months
- Minimal late loss (≤0.2 mm)

SUMMARY

The present review reports development and revolution in coronary DES technology, with major emphasis on advancements in the type of drug used (sirolimus, everolimus, biolimus, zotarolimus, novolimus, paclitaxel, docetaxel); type of stent platforms (stainless steel, platinum, cobalt-chromium, cobalt-nickel, platinum-chromium); type of polymers (permanent, biodegradable, polymer-free); thickness of stent struts (thick, thin, ultra-thin); type of coating (abluminal, conformal); and type of stent design (open-cell, closed-cell, combination of open-closed cell). Although considerable advances have been made, the pursuit for an ideal DES system is still ongoing. While the safety and efficacy of a majority of the contemporary stents on the market are supported by respective clinical trials and registries, larger trials and longer follow-ups are necessary to assess the effectiveness of certain novel devices. Overall, it can be concluded that DES will continue to play a prominent role in the management of patients with CAD.

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