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Drug-Eluting Stents for Coronary Artery Disease: A Review

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Drug-eluting stents for coronary artery disease: A review

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ABSTRACT

Over the past decade the introduction of drug-eluting stents (DESSs) has revolutionised the treatment of coronary artery disease. However, in recent years concern has arisen over the long-term safety and efficacy of DESSs due to the occurrence of late adverse clinical events such as stent thrombosis. With this concern in mind, research and development is currently centred on increasing the long-term safety and efficacy of DESSs. The aim of this paper is to provide a thorough review of currently approved and promising investigational DESSs. With dozens of companies involved in the development of new and innovative anti-restenotic agents, polymeric coatings and stent platforms, it is intended that this review paper will provide a clear indication of how DESSs are currently evolving and prove a valuable reference tool for future research in this area.

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1. Introduction

At present, coronary artery disease (CAD) is one of the leading causes of death and disability in the developed world. According to the American Heart Association CAD was responsible for approximately 445,687 deaths in the United States in 2005, representing 20% of all deaths that year [1]. CAD is caused by the development of atherosclerotic lesions within one or more of the coronary arteries which deliver oxygen and vital nutrients to the heart muscle. Several risk factors have been identified that contribute to the progression of this disease and include smoking, hypertension, diabetes and increased levels of cholesterol [1]. If the lumen becomes sufficiently narrowed, blood flow to a portion of the heart is restricted, usually resulting in angina pectoris. If untreated, vulnerable atherosclerotic lesions can become unstable and rupture. This often results in coronary occlusion and subsequent myocardial infarction.

Over the past two decades, percutaneous transluminal coronary angioplasty (PTCA) with bare-metal stent (BMS) placement has been utilised as a minimally invasive treatment for obstructive CAD. Typically, a BMS is a small, tubular, wire-mesh device which is pre-loaded in a collapsed form onto a catheter balloon, threaded to the narrowed section of the artery and expanded within the vessel. Once expanded, the BMS acts as a mechanical scaffold, reducing elastic recoil and maintaining vessel patency post-treatment. For many patients who suffer from CAD, treatment with a BMS will generally result in extremely favourable initial clinical results. However, at follow-up (6–12 months), re-narrowing of the treated artery is commonly observed in 20–30% of patients [2]. This re-narrowing of the treated artery is due to in-stent restenosis (ISR) which is defined as diameter stenosis of $\geq 50\%$ in the stented area of the vessel [3].

In recent years, DESs have been developed to address the problem of ISR. A DES typically consists of a BMS platform which has been coated in a formulation of drugs and carrier materials. The drugs commonly employed are known to interrupt the key cellular and molecular processes associated with ISR. To date, clinical evaluation has overwhelmingly proven the superiority of DESs for the reduction of ISR rates compared to BMSs, leading to the regulatory approval of a number of DESs by both the European Union (EU) Conformité Européenne (CE) and the US Food and Drug Administration (FDA). Despite the success of DESs in the treatment of CAD, concern has arisen over the long-term safety and efficacy of these devices due to cases of late adverse clinical events such as stent thrombosis. With this concern in mind, research and development in DES design is currently centred on increasing their performance and long-term safety. Though only five distinct DESs have received both CE and FDA approval for commercial sale in the EU and the US, the number of DESs currently undergoing evaluation is substantial. The aim of this paper is to provide a thorough review of both currently approved and promising investigational DESs.

In Section 2, a background on current DES technology is provided. In Section 3, the current CE and FDA approved DESs are discussed in terms of their important design features and the clinical trials which led to their approval. In Section 4, the long-term safety and efficacy of DESs is discussed. In Section 5, a selection of promising investigational DESs are presented, while in Section 6, conclusions are drawn and future prospects in the evolution of DESs are discussed. With dozens of companies involved in the innovation of DESs it is intended that this review paper will provide a clear indication of how DESs are currently evolving and prove a valuable reference tool for future research in this area.

2. Background

As mentioned in Section 1, DESs generally consist of up to three components: (1) a stent, (2) a drug-delivery mechanism and (3) an anti-restenotic drug or therapeutic agent. In this section, the types and properties of each of these components is discussed.

2.1. The stent platform

Today, most stents employed by DESs are manufactured in modular or slotted-tube configurations and are delivered by balloon-dilation. The stent is crimped to a low-profile upon a balloon-tipped catheter and introduced to the cardiovascular system via the femoral or radial arteries. The stent must therefore have a low crimped profile and must possess a high level of flexibility to enable delivery through the tortuous cardiovascular system. During expansion the stent should experience minimum shortening and upon deployment should conform to the vessel geometry without straightening the vessel unnaturally. The stent should provide optimum vessel coverage and should possess high radial strength such that it undergoes minimal radial recoil and achieves a final diameter consistent with that of the host vessel upon unloading [4]. As the stent acts as a conduit for drug-delivery it is also important that its geometrical configuration facilitates homogeneous distribution of the drug within the vessel [5].

Typically, stents are manufactured from biologically inert metals such as stainless steel. In recent years however, driven by emerging correlations between strut thickness and rates of ISR, metallic alloys such as cobalt–chromium have superseded steel as the material of choice for stent design [6]. These metallic alloys have been developed with increased levels of strength and X-ray attenuation compared to stainless steel, allowing newer stents to be designed with significantly thinner struts which do not impair the resulting strength, corrosion resistance or radiopacity of the device. Further development in stent design is currently centred on the assessment of stronger metallic alloys, compound metals and bioabsorbable materials.

2.2. The stent coating

Equally important as the actual drug or therapeutic agent that is released by a DES is the mechanism by which the drug is released. To date, the most successful method of facilitating drug adhesion and delivery from a stent has involved the use of permanent synthetic polymer coating materials such as polyethylene-co-vinyl acetate (PEVA), poly-n-butyl methacrylate (PBMA), and the tri-block copolymer poly(styrene-b-isobutylene-b-styrene) (SIBS). By carefully mixing anti-restenotic drugs with these materials, a drug-polymer matrix may be formed and applied to the surface of the stent platform. Upon deployment, drug-delivery is driven by diffusion from the matrix and the rate of this diffusion is dictated by the type, composition and number of polymers used in the drug-polymer matrix.

In recent years these permanent polymers have been superseded by advanced biocompatible permanent polymers such as phosphorylcholine (PC) and the co-polymer poly(vinylidene fluoride-co-hexafluoropropylene) (PVDF-HFP). These advanced polymers mimic the phospholipids on the outer surfaces of red blood cells resulting in a stent platform that induces minimal thrombus formation upon deployment and has minimal adverse clinical effect on late healing of the vessel wall. Further development in this area is currently centred on the assessment of biocompatible and bioabsorbable polymer coating materials and on the development of novel mechanisms of drug-release.

Fig. 1. Cell-cycle and mechanism of action of sirolimus, zotarolimus, everolimus and paclitaxel.

2.3. The anti-restenotic drug

During the deployment of a DES, any mechanical injury incurred in the vessel leads to an immediate healing response in the arterial wall. This healing response is initially characterised by the activation of platelets within the intima, leading to thrombus formation and the recruitment of blood-borne monocytes, neutrophils and lymphocytes. These cells produce mitogenic and chemotactic factors which trigger the activation of smooth muscle cells (SMCs) which undergo unrestrained proliferation and migration toward the intimal layer resulting in neointimal growth and ISR [7]. As such, the ideal anti-restenotic agent should exhibit potent anti-proliferative effects but preserve vascular healing. To date a vast number of immunosuppressive and anti-proliferative agents have been investigated for the prevention of ISR, however, only a small number have shown real effectiveness in clinical evaluation.

Sirolimus, zotarolimus and everolimus, potent immunosuppressive agents, inhibit SMC proliferation in response to cytokine and growth factor stimulation by binding to the cytosolic FK-binding protein 12 (FKBP12). This prevents the activation of the mammalian target of rapamycin (mTOR) and leads to interruption of the cell-cycle in the G1-S phase. Paclitaxel, a strong anti-proliferative agent, suppresses neointimal growth by binding with and stabilising microtubules. The stability of these microtubules inhibits their disassembly and renders them non-functional, resulting in cell-cycle arrest in the G0–G1 and G2–M phases (Fig. 1) [7]. Development in this area is currently centred on the assessment of further immunosuppressive and anti-proliferative agents as well as the evaluation of numerous migration-inhibiting, enhanced-healing and re-endothelialisation agents.

3. Current state of the art

Since 2002, five distinct DESs have received regulatory approval from the both the EU CE and the US FDA: the first-generation Cypher sirolimus-eluting stent (SES) (Cordis, Johnson & Johnson, NJ, US), the Taxus Express² paclitaxel-eluting stent (PES) (Boston Scientific, MS, US) and the Taxus Liberté PES (Boston Scientific), and the second generation Endeavor zotarolimus-eluting stent (ZES) (Medtronic Vascular, CA, US) and Xience-V everolimus-eluting stent (EES) (Abbott Vascular, CA, US).

3.1. First-generation DESs

3.1.1. The Cypher SES

The Cypher SES consists of a Bx-Velocity BMS (Johnson & Johnson) coated in a formulation of sirolimus and two permanent polymers, PEVA and PBMA. The Bx-Velocity BMS is a closed-cell,

Fig. 2. (a) Taxus Express² PES and (b) Taxus Liberté PES.

slotted-tube stent manufactured from 316L stainless steel and is comprised of a series of sinusoidal strut-segments joined by N-shaped, flexible link-segments. The drug-polymer coating is applied to the entire stent surface with a standard concentration of 140 µg of sirolimus per cm² of stent surface area and is designed to release approximately 80% of the drug within 30 days of stent deployment [8]. The Cypher SES is currently available in six lengths from 8 to 33 mm and four diameters from 2.25 to 3.5 mm. The principal safety and efficacy evidence for the Cypher SES was obtained from five clinical trials: the First In Man (FIM) trial, the RAVEL trial, and the SIRIUS trials (SIRIUS, E-SIRIUS and C-SIRIUS).

The FIM trial was a non-randomised trial involving 45 patients that demonstrated minimal in-stent neointimal proliferation with both fast- and slow-release SESs at 4 month follow-up [9]. The RAVEL trial was a randomised trial involving 238 patients with relatively low-risk lesions that demonstrated the superiority of the Cypher SES over the Bx-Velocity BMS in terms of in-segment late loss at 6 months [10]. The SIRIUS, C-SIRIUS and E-SIRIUS trials were randomised trials involving a total of 1510 patients with more complex lesions than those enrolled in the RAVEL and FIM trials. The superiority of the Cypher SES over the Bx-Velocity BMS was further demonstrated in these trials, with markedly lower rates of target-lesion revascularisation and adverse clinical events observed in patients treated with the Cypher SES [8,11,12]. The Cypher SES became the first DES to receive both CE and FDA approval in April 2002 and April 2003, respectively.

3.1.2. The Taxus PESs

The Taxus Express² PES consists of an Express BMS (Boston Scientific) coated in a formulation of paclitaxel and a permanent co-polymer, SIBS. The Express BMS is a closed-cell, slotted-tube stent manufactured from 316L stainless steel and is comprised of a series of sinusoidal strut-segments joined by straight articulations to short, narrow strut-segments (Fig. 2). The drug-polymer coating is applied to the entire stent surface in single layer with a standard concentration of 100 µg of paclitaxel per cm² of stent surface area. The release of paclitaxel is bi-phasic with an early 48 h burst followed by a low-level release over the following 10 days [13]. The Taxus Express² PES is currently available in six lengths from 8 to

33 mm and four diameters from 2.5 to 3.5 mm. The principal safety and efficacy evidence for the Taxus Express² PES was obtained from three clinical trials, the TAXUS I, II and IV trials.

The TAXUS I trial was a randomised trial involving 61 patients which demonstrated zero binary in-stent restenosis with PESs at 6 months and minimal adverse clinical events compared to BMSs at 12 months [14]. The TAXUS II trial was a randomised trial involving 536 patients that demonstrated the superiority of both slow- and fast-release PESs over BMSs in terms of stent volume obstructed by neointimal proliferation at 6 months [15]. The TAXUS IV trial was a randomised trial involving 1314 patients with more complex lesions than those enrolled in the TAXUS I and II trials that demonstrated the superiority of the Taxus Express² PES over the Express BMS in terms of in-stent late loss, binary in-stent restenosis and target-lesion revascularisation at 9 months [13]. The Taxus Express² PES became the second DES to receive both CE and FDA approval in May 2002 and March 2004, respectively.

Following FDA approval of the Taxus Express² PES, the TAXUS clinical trial program was succeeded by the TAXUS ATLAS trial, designed to assess the drug-polymer coating (paclitaxel-SIBS) employed by the Taxus Express² PES upon a new BMS platform, the Liberté stent (Boston Scientific). The Liberté stent is a closed-cell, slotted-tube stent manufactured from 316L stainless steel which has substantially thinner struts compared to the Express stent (0.097 vs. 0.132 mm) allowing for improved flexibility and deliverability. The Liberté stent platform has also been specifically designed with a dense strut configuration which ensures homogeneous distribution of paclitaxel within the vessel (Fig. 2). The Taxus Liberté PES is currently available in seven lengths from 8 to 38 mm and five diameters from 2.25 to 4 mm. The principal safety and efficacy evidence for the Taxus Liberté PES was obtained from the TAXUS ATLAS trial.

The TAXUS ATLAS trial was a randomised trial involving 871 patients that compared the safety and efficacy of the Taxus Liberté PES with an historic control arm of patients who were treated with a Taxus Express² PES in the TAXUS IV and V trials. Despite a significantly higher incidence of complex lesions in the TAXUS ATLAS patient population the Taxus Liberté PES was found to be non-inferior to the Taxus Express² PES with similar rates of adverse clinical events, in-stent late loss and target-vessel revascularisation observed at 9 months [16]. The Taxus Liberté PES received CE and FDA approval in September 2005 and October 2008, respectively.

3.2. Second-generation DESs

3.2.1. The Endeavor ZES

The Endeavor ZES consists of a Driver BMS (Medtronic Vascular) coated in a formulation of zotarolimus and a biocompatible, permanent PC co-polymer. The Driver BMS is an open-cell, modular stent manufactured from MP35N cobalt–chromium and is comprised of a series of alternating upper and lower crowns connected by axial struts in a sinusoidal pattern. The use of MP35N cobalt–chromium alloy allows for relatively thin struts (0.091 mm) to be used compared with first-generation DESs. The drug-polymer coating is applied to the entire stent surface with a standard concentration of 100 µg of zotarolimus per cm of stent length and is designed to release approximately 95% of the total dose of zotarolimus within 15 days of stent placement [17]. The Endeavor ZES is currently available in eight lengths from 8 to 30 mm and three diameters from 2.5 to 3.5 mm. The principal safety and efficacy evidence for the Endeavor ZES was obtained from four clinical trials, the ENDEAVOR I–IV trials.

The ENDEAVOR I trial was a non-randomised trial involving 100 patients that demonstrated the safety and efficacy of the Endeavor ZES with minimal binary in-stent restenosis observed at four and 12 months [17]. The ENDEAVOR II trial was a randomised trial

involving 1197 patients that demonstrated the superiority of the Endeavor ZES over the Driver BMS with significantly lower rates of binary in-stent restenosis and target-vessel revascularisation observed at 8 and 9 months, respectively [18]. The ENDEAVOR III ($n = 436$) and ENDEAVOR IV ($n = 1548$) trials were randomised trials designed to demonstrate the non-inferiority of the Endeavor ZES with the Cypher SES and Taxus Express² PES, respectively. The initial performance of the Endeavor ZES in these trials was disappointing however, with markedly higher rates of target-lesion revascularisation and significantly higher rates of in-stent late loss observed with the Endeavor ZES at short-term follow-up in both trials [19,20]. Results at longer-term follow-up have been more reassuring however, with the absolute difference in target-lesion revascularisation reduced to 1.6% at five years in the ENDEAVOR III trial and 0.5% at three years in the ENDEAVOR IV trial [21,22]. The Endeavor ZES received both CE and FDA approval in July 2005 and February 2008, respectively.

3.2.2. The Xience-V EES

The Xience-V EES consists of a Multi-Link Vision BMS (Abbott Vascular) coated in a formulation of everolimus, PBMA and a permanent biocompatible co-polymer, PVDF-HFP. The Multi-Link Vision BMS is a closed-cell, slotted-tube stent manufactured from L605 cobalt–chromium alloy and consists of a series of corrugated, zigzag strut-segments joined by single-turn link-segments. The use of L605 cobalt–chromium alloy allows for relatively thin struts (0.081 mm) to be used compared with first-generation DESs. The drug-polymer coating is applied to the entire stent surface with a standard concentration of 100 µg of everolimus per cm² of stent surface area and is designed to release approximately 80% of the total dose within 30 days of stent placement [23]. The Xience-V EES is currently available in six lengths from 8 to 28 mm and five diameters from 2.5 to 4 mm. The principal safety and efficacy evidence for the Xience-V EES was obtained from four clinical trials: the SPIRIT FIRST trial and the SPIRIT II–IV trials.

The SPIRIT FIRST trial was a randomised trial involving 60 patients that demonstrated the superiority of the Xience-V EES over the Multi-Link BMS in terms of in-stent late loss and binary in-stent restenosis at 6 months [23]. The SPIRIT II trial was a randomised trial involving 300 patients that demonstrated the superiority of the Xience-V EES over the Taxus Express² PES in terms of in-stent late loss at 6 months [24]. The SPIRIT III trial was a randomised trial involving 1002 patients that demonstrated significantly reduced in-segment late loss and non-inferior rates of target-vessel failure in patients treated with a Xience-V EES compared to the Taxus Express² PES at 12 months [25]. The SPIRIT IV trial is a randomised trial involving 3687 patients that has demonstrated the superiority of the Xience-V EES over the Taxus Express² PES in terms of target-lesion failure and target-vessel revascularisation at 12 months [26]. Interestingly, following three year follow-up of the SPIRIT II and III trials, investigators observed an increase in the absolute difference in target-vessel failure and adverse clinical events in favour of the Xience-V EES [27,28]. The Xience-V EES received CE and FDA approval in January 2006 and July 2008, respectively.

3.3. Post-approval evaluation

Since obtaining CE and FDA approval, both first- and second-generation DESs have been evaluated in dozens of clinical studies to assess their safety and efficacy when deployed in a number of patient and lesion sub-groups. These studies include evaluations of DES delivery in small vessels, long lesions, diabetics, chronic total occlusions (CTOs), bifurcated vessels, saphenous vein grafts (SVGs), patients suffering from ISR, ST-elevated myocardial ischemia, multi-vessel disease and by direct delivery [29–55]. The

Table 1

Clinical trials of current CE- and FDA-approved DESs.

Study	DES/BMS	Aims	Primary endpoint and outcome
Clinical trials of Cypher SES (Cordis, Johnson & Johnson)			
C-SIRIUS (<i>n</i> = 100) [12]	Cypher SES	To compare the efficacy of SES and BMS in long lesions	Eight month minimum lumen diameter: SES: 2.46 mm, BMS: 1.49 mm (<i>p</i> < 0.001)
DIABETES (<i>n</i> = 160) [47]	Cypher SES	To compare the efficacy of SES and BMS in diabetics	Nine month in-segment late lumen loss: SES: 0.06 mm, BMS: 0.47 mm (<i>p</i> < 0.001)
E-SIRIUS (<i>n</i> = 352) [11]	Cypher SES	To compare the efficacy of SES and BMS in long lesions	Eight month minimum lumen diameter: SES: 2.22 mm, BMS: 1.33 mm (<i>p</i> < 0.001)
FIM (<i>n</i> = 30) [9]	Bx-Velocity BMS	To assess the efficacy of slow- and fast-release (SR/FR) SESs	Four month in-stent late loss: SR SES: 0.09 mm, FR SES: –0.02 mm
MISSION (<i>n</i> = 310) [53]	Cypher SES	To compare the efficacy of SES and BMS for STEMI	Nine month in-segment late loss: SES: 0.12 mm, BMS: 0.68 mm (<i>p</i> < 0.001)
PRISON II (<i>n</i> = 200) [50]	Cypher SES	To compare the efficacy of SES and BMS in CTOs	Six month binary in-stent restenosis: SES: 7%, BMS: 36% (<i>p</i> < 0.001)
RAVEL (<i>n</i> = 238) [10]	Bx-Velocity BMS	To compare the efficacy of SES and BMS	Six month mean late loss SES: 0 mm, BMS: 0.8 mm (<i>p</i> < 0.001)
RIBS II (<i>n</i> = 150) [29]	Cypher SES	To compare the efficacy of SES and PTCA for ISR	Nine month angiographic restenosis: SES: 11%, PES: 39% (<i>p</i> < 0.001)
RRISC (<i>n</i> = 75) [54]	Cypher SES	To compare the efficacy of SES and BMS in SVG	Six month in-stent late loss: SES: 0.38 mm, BMS: 0.79 mm (<i>p</i> = 0.001)
SCANDSTENT (<i>n</i> = 322) [39]	Bx-Velocity BMS	To compare the efficacy of SES and BMS in complex lesions	Six month minimum lumen diameter: SES: 2.48 mm, BMS: 1.65 mm (<i>p</i> < 0.001)
SCORPIUS (<i>n</i> = 200) [31]	Cypher SES	To compare the efficacy of SES and BMS in diabetics	Eight month in-segment late loss: SES: 0.18 mm, BMS: 0.74 mm (<i>p</i> < 0.0001)
SESAMI (<i>n</i> = 320) [43]	Bx-Velocity BMS	To compare the efficacy of SES and BMS for STEMI	Twelve month binary in-segment restenosis: SES: 9.3%, BMS: 21.3% (<i>p</i> = 0.032)
SES-SMART (<i>n</i> = 257) [30]	Cypher SES	To compare the efficacy of SES and BMS in small arteries	Eight month binary restenosis: SES: 9.8%, BMS: 53.1% (<i>p</i> < 0.001)
SIRIUS (<i>n</i> = 1,058) [8]	Bx-Velocity BMS	To compare the efficacy of SES and BMS	Nine month target-vessel failure rate: SES: 8.6%, BMS: 21.0% (<i>p</i> < 0.001)
SIRIUS 2.25 (<i>n</i> = 100) [35]	Cypher SES	To compare the efficacy of SES PTCA and BMS in small arteries	Six month in-lesion binary restenosis: SES: 16.9%, BMS: 45.9%, PTCA: 30.6%
STRATEGY (<i>n</i> = 175) [52]	Historic Control Arm	To compare the efficacy of SES and BMS for STEMI	Eight month rate of adverse clinical events: SES: 19%, BMS: 50% (<i>p</i> < 0.001)
SVELTE (<i>n</i> = 101) [42]	Bx-Velocity BMS	To compare the efficacy of SES and BMS in small vessels	Eight month target-lesion revascularisation: SES: 0%, BMS: 13.2% (<i>p</i> < 0.001)
TOSCA (<i>n</i> = 200) [36]	Cypher SES	To assess the safety and efficacy of SES for CTOs	Six month binary in-stent restenosis: 9.5%
TYPHOON (<i>n</i> = 712) [49]	Historic Control Arm	To compare the efficacy of SES and BMS for STEMI	Twelve month target-vessel failure rate: 10.9%
	Cypher SES		Twelve month target-vessel failure rate: SES: 7.3%, BMS: 14.3% (<i>p</i> = 0.004)
	Bx-Velocity BMS		
Clinical trials of Taxus Express² PES and Taxus Liberté PES (Boston Scientific)			
SYNTAX (<i>n</i> = 1800) [48]	Taxus Express ² PES	To compare the efficacy of PES and bypass grafts	Twelve month rate of adverse clinical events: PES: 17.8%, CABG: 12.4% (<i>p</i> = 0.002)
TAXUS I (<i>n</i> = 61) [14]	Taxus NIRx PES	To compare the efficacy of PES and BMS	Twelve month rate late adverse clinical events: PES: 3%, BMS: 10% (<i>p</i> = 0.612)
TAXUS II (<i>n</i> = 536) [15]	NIR BMS	To assess the efficacy of slow- and fast-release (SR/FR) SESs and BMSs	Six month percent net volume obstruction: SR PES: 6.9%, FR PES: 7.8%, BMS: 23.2%
TAXUS IV (<i>n</i> = 1314) [13]	Taxus Express ² PES	To compare the efficacy of PES and BMS	Nine month target-vessel revascularisation: PES: 4.7%, BMS 12.0% (<i>p</i> < 0.001)
TAXUS V (<i>n</i> = 1,156) [130]	Express BMS	To compare the efficacy of PES and BMS	Nine month target-vessel revascularisation: PES: 8.6%, BMS 15.7% (<i>p</i> < 0.001)
TAXUS VI (<i>n</i> = 448) [131]	Taxus Express ² PES	To compare the efficacy of PES and BMS	Nine month target-vessel revascularisation: PES: 9.1%, BMS 19.4% (<i>p</i> < 0.0027)
TAXUS ATLAS (<i>n</i> = 871) [16]	Express BMS	To compare the efficacy of Liberté PES and Express ² PES	Nine month target-vessel revascularisation: Liberté: 7.95%, Express ² : 7.01% (<i>p</i> = 0.05)
TAXUS ATLAS DS (<i>n</i> = 247) [45]	Taxus Liberté PES	To compare direct-stenting (DS) and pre-dilation (PD) Liberté PES	Nine month percentage diameter stenosis: DS: 26.4%, PD: 29.1% (<i>p</i> = 0.06)
TAXUS ATLAS LL (<i>n</i> = 411) [51]	Historic Control Arm	To compare the efficacy of Liberté PES and Express ² PES in small vessels and long lesions	Nine month percentage diameter stenosis: Liberté: 31.7%, Express ² : 32.6% (<i>p</i> = 0.69)
Clinical trials of Endeavor ZES (Medtronic Vascular)			
ENDEAVOR I (<i>n</i> = 100) [17]	Endeavor ZES	To assess the safety and efficacy of ZES	Thirty day rate of adverse clinical events: 1%
ENDEAVOR II (<i>n</i> = 1,197) [18]	Driver BMS	To compare the efficacy of ZES and BMS	Four month late lumen loss: 0.33 mm
ENDEAVOR III (<i>n</i> = 436) [19]	Endeavor ZES	To compare the efficacy of ZES and SES	Nine month target-vessel failure rate: ZES: 7.9%, BMS: 15.1% (<i>p</i> < 0.0001)
ENDEAVOR IV (<i>n</i> = 1,548) [20]	Cypher SES	To compare the efficacy of ZES and PES	Eight month in-segment late loss: ZES: 0.34 mm, SES: 0.13 mm (<i>p</i> < 0.001)
	Endeavor ZES		Nine month target-vessel failure rate: ZES: 6.6%, PES: 7.1% (<i>p</i> _{non-inferiority} < 0.001)
	Taxus Express ² PES		

Table 1 (Continued)

Study	DES/BMS	Aims	Primary endpoint and outcome
Clinical trials of Xience-V EES (Abbott Vascular)			
SPIRIT FIRST (n = 60) [23]	Xience-V EES	To compare the efficacy of EES and BMS	Six month in-stent late loss: EES: 0.10 mm, BMS: 0.87 mm ($p < 0.001$)
SPIRIT II (n = 300) [24]	Multi-Link Vision BMS	To compare the efficacy of EES and PES	Six month in-stent late loss: EES: 0.11 mm, PES: 0.36 mm ($p < 0.0001$)
SPIRIT III (n = 1,002) [25]	Taxus Express ² PES	To compare the efficacy of EES and PES	Eight month in-stent late loss: EES: 0.14 mm, PES: 0.28 mm ($p = 0.004$)
SPIRIT IV (n = 3,687) [26]	Xience-V EES	To compare the efficacy of EES and PES	Twelve month target-lesion failure rate: EES: 4.2%, PES: 6.8% ($p = 0.001$)
Comparative trials of multiple DESs			
COMPARE (n = 1,800) [38]	Xience-V EES	To compare the efficacy of EES and PES in real world setting	Twelve month rate of adverse clinical events: EES: 6%, PES: 9% ($p = 0.02$)
ISAR-DESIRE (n = 300) [37]	Taxus Liberté PES	To compare the efficacy of SES, PES and PTCA for ISR	Six month angiographic restenosis: SES: 14.3%, PES: 21.7%, PTCA 44.6%
ISAR-DIABETES (n = 250) [32]	Cypher SES	To compare the efficacy of SES and PES in diabetics	Eight month in-segment late loss: SES: 0.43 mm, PES: 0.67 mm ($p = 0.002$)
ISAR-SMART-III (n = 360) [41]	Taxus Express ² PES	To compare the efficacy of SES and PES in small vessels	Eight month in-stent late loss: SES: 0.25 mm, PES: 0.56 mm ($p < 0.001$)
LONG-DES-II (n = 500) [40]	Cypher SES	To compare the efficacy of SES and PES in small vessels	Six month binary in-segment restenosis: SES: 3.3%, PES: 14.6% ($p < 0.001$)
REALITY (n = 1386) [44]	Taxus Express ² PES	To compare the efficacy of SES and PES	Eight month binary in-lesion restenosis: SES: 9.6%, PES: 11.1% ($p = 0.31$)
SIRTAX (n = 1012) [55]	Cypher SES	To compare the efficacy of SES and PES	Nine month rate of adverse clinical events: SES: 6.2%, PES: 10.8% ($p = 0.009$)
SORT-OUT-II (n = 2098) [33]	Taxus Express ² PES	To compare efficacy of SES and PES in a real world setting	Nine month rate of adverse clinical events: SES: 9.3%, PES: 11.2% ($p = 0.16$)
SORT-OUT-III (n = 1162) [46]	Cypher SES	To compare the efficacy of SES and ZES in a real world setting	Nine month rate of adverse clinical events: SES: 3%, ZES: 6% ($p = 0.0002$)
TAXI (n = 202) [34]	Endeavor ZES	To compare the efficacy of SES and PES in a real world setting	Six month rate of adverse clinical events: SES: 6%, PES: 4% ($p = 0.8$)

details and primary findings of these, and all previously mentioned trials are presented in Table 1. These DESs have also been subject to a number of physician-driven registries to assess their relative and real-world performance [56–64]. The details and primary findings of these registries are presented in Table 2.

4. Long-term DES safety

Following the strong performance of the first-generation DESs in clinical evaluation, these devices were widely adopted by interventional cardiologists with up to 90% of stent procedures carried

Table 2
Registries of current CE- and FDA-approved DESs.

Registry	DES	Aim	Outcome
RESEARCH (n = 958) [61]	Cypher SES Conventional BMS	To compare the efficacy of the Cypher SES and BMS in routine clinical practice	Twelve month rate of adverse clinical events: SES: 9.7%, BMS: 14.8% ($p = 0.008$), 12 month target-vessel revascularisation: SES: 3.7%, BMS: 10.9% ($p < 0.001$)
E-CYPHER (n = 15157) [64]	Cypher SES	To assess the Cypher SES in routine clinical practice and to identify predictors of adverse clinical events	Twelve month rate of adverse clinical events: 5.8%, 12 month target-vessel revascularisation: 3.07%, 12 month incidence of stent thrombosis: 0.87%
US-PMS (n = 2067) [59]	Cypher SES	To compare the efficacy of SES in on-label (ON-L) and off-label (OFF-L) patient populations	Twelve month rate of adverse clinical events: ON-L: 4.7%, OFF-L: 9.2% ($p < 0.001$) 12 month target-vessel revascularisation: ON-L: 2.5%, OFF-L: 6.2% ($p < 0.001$)
WISDOM (n = 778) [56]	Taxus Express ² PES	To assess the efficacy of the Taxus Express ² PES in routine clinical practice	Twelve month rate of adverse clinical events: 5.2%, 12 month target-vessel revascularisation: 2.0%, 12 month incidence of stent thrombosis: 0.6%
ARRIVE 1 & 2 (n = 7601) [60]	Taxus Express ² PES	To compare the efficacy of PES in simple use (SU) and expanded use (EU) patient populations	Two year target-vessel revascularisation: SU: 5.4%, EU: 9.2% ($p < 0.001$), two year rate of stent thrombosis: SU: 1.4%, EU: 3.3% ($p < 0.001$)
T-SEARCH (n = 576) [62]	Taxus Express ² PES Historic Control Arm	To compare the efficacy of the Taxus Express ² PES and the Cypher SES in routine clinical practice	Twelve month rate of adverse clinical events: SES: 10.5%, PES: 13.9% ($p = 0.4$), 12 month target-vessel revascularisation: SES: 3.7%, PES: 5.4% ($p < 0.3$)
TAXUS OLYMPIA (n = 529) [57]	Taxus Liberté	To assess the efficacy of the Taxus Liberté PES in routine clinical practice	Twelve month rate of adverse clinical events: 3.7%, 12 month target-vessel revascularisation: 2.3%, 12 month incidence of stent thrombosis: 1.7%
E-FIVE (n = 8300) [58]	Endeavor ZES	To assess the efficacy of the Endeavor ZES in routine clinical practice	Twelve month rate of adverse clinical events: 7.5%, 12 month target-vessel revascularisation: 4.5%, 12 month incidence of stent thrombosis: 1.1%
X-SEARCH (n = 649) [63]	Xience-V EES 3 Historical Control Arms	To compare the efficacy of the Xience-V EES with SES, PES and BMS in routine clinical practice	Twelve month rate of adverse clinical events: EES: 9.2%, SES: 7.3%, PES: 9.9%, BMS: 10.4%, 12 month target-vessel revascularisation: EES: 3.1%, SES: 2.2%, PES: 4.3%, BMS: 5.8%

Fig. 3. Scanning electron micrographs of 14-day endothelial coverage of Cypher SES, Taxus Liberté PES, Endeavor ZES, Xience-V EES and Multi-Link BMS in rabbit iliac arteries.

out in the US involving DES placement by late 2005 [65]. Over the following two years, however, major concerns arose over the long-term safety of DESs when a number of clinical and observational studies reported significantly increased risk of mortality in patients treated with DESs compared to BMSs beyond 12 months [66–69]. Prompted by these results, a number of large-scale, meta-analyses were undertaken to assess both the short- and long-term safety of DESs relative to BMSs [70–72]. Reassuringly, no increased risk of mortality was observed between patients treated with DESs and BMS with similar rates of death and myocardial infarction reported for DESs in each of these studies. Furthermore, in a recent meta-analysis of long-term follow-up (1–4 years) from over 22 randomised clinical trials and 34 observational studies, patients treated with DESs were associated with lower rates of death and myocardial infarction and repeat revascularisations compared to patients treated with BMSs [73].

Today, the primary concern with long-term DES safety is stent thrombosis, a potentially fatal adverse event that often leads to myocardial infarction and/or death. In the debate that followed the initial concerns over the long-term safety of DESs it emerged that restrictive and non-uniform definitions of stent thrombosis had been utilised during the initial clinical evaluation of the first-generation DESs. The Academic Research Consortium subsequently recommended standardised definitions of stent thrombosis and in 2007 these definitions were adopted in a pooled analysis of the long-term follow-up from eight clinical trials involving both the Cypher SES and the Taxus Express² PES. Though similar rates of early (less than 1 month) and late (1–12 months) stent thrombosis were observed between DESs and BMSs in this analysis, higher rates of very-late (greater than 12 months) stent thrombosis were reported with DESs [74]. Evaluation of the long-term follow-up of clinical trials and registries has since supported this observation [75–77].

Although the exact cause of stent thrombosis is not yet fully understood a number of patient, lesion, and procedural factors have been associated with an increased risk of stent thrombosis. These include, increasing age, diabetes mellitus, renal failure, increasing stent and/or lesion length, decreasing stent and/or vessel diam-

eter, treatment of bifurcation, treatment of CTO, treatment of ISR, stent under-expansion and premature discontinuation of dual anti-platelet therapy [78,79]. Of note, recent studies have identified delayed healing and incomplete endothelial strut coverage as a primary risk factor for stent thrombosis [80–83]. It has been shown that the non-erodible polymer coatings employed by DESs (particularly the first-generation Cypher SES and Taxus Express² PES) impair stent strut endothelialisation and may induce late hypersensitivity reactions and subsequent stent thrombosis (Fig. 3) [84]. As a result of these findings, research in this area is currently centred on the development and evaluation of improved DESs which maintain the impressive clinical benefits observed with currently approved devices while eradicating long-term safety concerns such as stent thrombosis.

5. Future of DESs

In this section a number of promising investigational DESs are presented and discussed. These DESs are categorised as either permanent DESs or bioabsorbable DESs and are sub-categorised by the type of polymer coating which they employ: permanent, bioabsorbable or polymer free. Each of these DESs is discussed in terms of its novel design features and its performance in clinical evaluation to date. A brief summary of these investigational DESs and the current CE and FDA approved devices discussed in previous sections is presented in Table 3.

5.1. Permanent DESs

5.1.1. Permanent polymer-coated DESs

5.1.1.1. The Taxus Element PES and Promus Element EES. The Taxus Element PES (Boston Scientific) and Promus Element EES (Boston Scientific) consist of a novel platinum–chromium stent coated in the same drug-polymer formulation as the Liberté PES (paclitaxel-SIBS) and the Xience-V EES (everolimus-PVDF-HFP), respectively. The material properties of platinum–chromium provide these DESs with increased radial strength and fracture resistance allowing for thinner stent struts (0.081 mm) compared to both stainless steel

Table 3
Current CE-/FDA-approved and promising investigational DESs.

Drug	DES	Stent material/coating material	Principal trials	Approval
Sirolimus	Cypher (Johnson & Johnson)	Stainless Steel (316L)/Permanent Polymer (PEVA-PBMA)	FIM, RAVEL, SIRIUS, E-SIRIUS, C-SIRIUS	CE/FDA
	Nevo (Johnson & Johnson)	Cobalt–Chromium (N/A)/Bioabsorbable Polymer (PLGA)	NEVO RES, NEVO RES II	–
	Yukon Choice (Translumina)	Stainless Steel (316L)/None	ISAR-TEST, ISAR-TEST 3, ISAR-TEST 4, ISAR-PEACE	CE
	Supralimus (Sahajanand Medical)	Stainless Steel (316L)/Bioabsorbable Polymer (PLLA–PVP–PLGA)	SERIES I, SERIES III RUN IN	–
	BTI (Bioabsorbable Therapeutic Inc.)	Bioabsorbable Polymer (PA & Salicylic Acid)/Bioabsorbable Polymer (Salicylic Acid)	WHISPER	–
Paclitaxel	Genous (OrbusNeich)	Stainless Steel (316L)/Combo EPC Capture Antibodies, SynBiosys Polymer and Sirolimus	REMEDEE	–
	ReZolve SES (REVA Medical)	Tyrosine-derived ReZorb Bioabsorbable Polymer	–	–
	Taxus Express ² (Boston Scientific)	Stainless Steel (316L)/Permanent Polymer (SIBS)	TAXUS I–IV	CE/FDA
	Taxus Liberté (Boston Scientific)	Stainless Steel (316L)/Permanent Polymer (SIBS)	TAXUS IV–VI	CE/FDA
	Taxus Element (Boston Scientific)	Platinum–Chromium (N/A)/Permanent Polymer (SIBS)	TAXUS ATLAS	CE
Zotarolimus	Infinnium (Sahajanand Medical)	Stainless Steel (316L)/Bioabsorbable Polymer (PLLA–PVP–PLGA)	PERSEUS	CE
	Endeavor (Medtronic Vascular)	Cobalt–Chromium (MP35N)/Permanent Polymer (PC)	SIMPLE I–II	CE
	Endeavor Resolute (Medtronic Vascular)	Cobalt–Chromium (MP35N)/Bioabsorbable Polymer (BioLinx: C19–PVP–C10)	ENDEAVOR I–IV	CE/FDA
Everolimus			RESOLUTE, RESOLUTE-AC	CE
	Xience-V (Abbott Vascular)	Cobalt–Chromium (L605)/Permanent Polymer (PVDF–HFP)	RESOLUTE-US	–
	Xience Prime (Abbott Vascular)	Cobalt–Chromium (L605)/Permanent Polymer (SIBS)	SPIRIT I–IV	CE/FDA
	Promus Element (Boston Scientific)	Platinum–Chromium (N/A)/Permanent Polymer (SIBS)	SPIRIT PRIME	CE
Biolimus	BVS (Abbott Vascular)	Bioabsorbable Polymer (PLLA)/Bioabsorbable Polymer (PDLLA)	PLATINUM	CE
	BioMatrix (Biosensors)	Stainless Steel (316L)/Bioabsorbable Polymer (PLLA)	ABSORB, ABSORB EXTEND	–
	BioFreedom (Biosensors)	Stainless Steel (316L)/None		
	Nobori (Terumo)	Stainless Steel (316L)/Bioabsorbable Polymer (PLLA)		
Tacrolimus	Janus (Sorin Biomedical)	Stainless Steel (316L)/Carbofilm (pyrolytic carbon)	STEALTH I, LEADERS	CE
Novolimus	DESyne (Elixir Biomedical)	Cobalt–Chromium (N/A)/Permanent Polymer (N/A)	BIOFREEDOM FIM	–
			NOBORI I, NOBORI II	CE
			JUPITER I, JUPITER II	CE
			EXCELLA, EXCELLA II	–

and cobalt–chromium DESs. The density of platinum–chromium is also greater than that of either 316L stainless steel or cobalt–chromium which ensures improved visibility of the thinner struts, while the continuous cell geometry also ensures homogeneous drug-delivery along the length of these DESs.

The Taxus Element PES and Promus Element PES are currently undergoing clinical evaluation in the PERSEUS and PLATINUM trials, respectively. The PLATINUM clinical trial program completed enrolment of 1532 patients in September 2009 and is designed to compare the safety and efficacy of the Promus Element EES against the Xience-V EES for the treatment of up to two de novo lesions. Two parallel sub-trials are also planned to assess the performance of the Promus Element EES in both small vessels and long lesions. The Promus Element EES received CE approval in October 2009.

The PERSEUS clinical trial program involves two parallel studies, a workhorse trial and a small vessel trial. The PERSEUS Workhorse trial is a randomised trial involving 1262 patients that has demonstrated the non-inferiority of the Taxus Element PES against the Taxus Express² PES in terms of target-lesion failure at 12 months (Element: 5.6% vs. Express²: 6.1%, $p=0.78$) and percentage diameter stenosis at 9 months (Element: 26.1 ± 17.7 mm vs. Express²: 26.3 ± 17.4 , $p=0.92$). No differences in rates of adverse clinical events, mortality, revascularisation or stent thrombosis were observed between stent groups at 12 months [85]. The PERSEUS Small Vessel trial is a single-arm trial involving 224 patients with lesion diameter 2.25–2.75 mm which has demonstrated the superiority of the Taxus Element PES against an historical control arm of Express BMSs in terms of in-stent late loss at 9 months (PES: 0.38 ± 0.51 mm vs. BMS: 0.80 ± 0.53 mm, $p<0.001$) and target-lesion failure at 12 months (PES: 6.6% vs. BMS: 20.5%, $p=0.01$). Similar rates of mortality and stent thrombosis were also observed between stent groups at 12 month follow-up [86]. The Taxus Element PES received CE approval in May 2010.

5.1.1.2. The Endeavor Resolute ZES. The Endeavor Resolute ZES (Medtronic Vascular) consists of a Driver BMS coated in a formulation of zotarolimus and a proprietary polymer referred to as Biolinx. Compared with the PC polymer coating employed by the Endeavor ZES the BioLinx polymer, which consists of a unique blend of a hydrophilic C19 polymer, polyvinyl pyrrolidone (PVP) and a hydrophobic C10 polymer, provides the Endeavor Resolute with improved biocompatibility, increased coating durability and extended drug elution. The Endeavor Resolute ZES is currently undergoing clinical evaluation in the RESOLUTE and RESOLUTE AC trials.

The RESOLUTE trial is a non-randomised trial involving 139 patients which has demonstrated the safety and efficacy of the Endeavor Resolute ZES in terms of in-stent late loss at 9 months (0.22 ± 0.27 mm) [87]. The long-term safety and efficacy of the Endeavor Resolute ZES has also been demonstrated with low rates of adverse clinical events (11.6%), target-lesion revascularisation (1.6%) and stent thrombosis (0.0%) reported at three year follow-up in the RESOLUTE trial [88]. The RESOLUTE AC trial is a randomised, all-comers trial involving approximately 2300 patients that has demonstrated the non-inferiority of the Endeavor Resolute ZES against the Xience-V EES for predominantly off-label indications in terms of target-lesion failure at 12 months (ZES: 8.2% vs. EES: 8.3%, $p=0.94$) and in-stent diameter stenosis at 13 months (ZES: 21.6 ± 14.4 mm vs. EES: 19.7 ± 14.6 , $p_{\text{non-inferiority}}=0.04$) [89]. Long-term follow-up of these trials is planned, while further evaluation of the Endeavor Resolute ZES is scheduled with enrolment of the RESOLUTE US trial currently underway. The Endeavor Resolute ZES received CE approval in October 2007.

5.1.1.3. The Xience Prime EES. The Xience Prime EES (Abbot Vascular) consists of an L605 cobalt–chromium stent coated in the same drug-polymer formulation as the Xience-V EES. This stent platform is designed to allow for high flexibility and deliverabil-

ity in more challenging lesions and is currently undergoing clinical evaluation in the SPIRIT PRIME trial, a non-randomised trial involving 500 patients that has been designed to evaluate the safety and efficacy of the Xience Prime EES in terms of adverse clinical events at 12 months. Enrolment in XIENCE PRIME began in June 2009 following the announcement that it had received CE approval.

5.1.1.4. The Elixir DESyne Novolimus-Eluting Stent (NES). The Elixir DESyne NES (Elixir Medical, CA, US) consists of a thin strut (0.081 mm) cobalt–chromium stent which is coated in a formulation of novolimus and PMBA. Novolimus, a sirolimus analogue with similar immunosuppressive properties, inhibits the activation of mTOR resulting in cell-cycle interruption in the G1–S phase. The drug-polymer coating is applied to the entire stent surface with a standard concentration of 85 µg of novolimus per cm² of stent surface area and is designed to ensure a sustained release of novolimus over a four to six week period.

The Elixir DESyne NES is currently undergoing clinical evaluation in the EXCELLA and EXCELLA II trials. The EXCELLA trial is a non-randomised trial involving 15 patients that demonstrated the safety and efficacy of the Elixir DESyne NES with low rates of in-stent late loss observed at four (0.15 ± 0.29 mm) and 8 months (0.31 ± 0.25 mm) [90]. The long-term safety and efficacy of the Elixir DESyne NES has also been demonstrated in this small patient population with only one adverse clinical event reported at two year follow-up in the EXCELLA trial [91]. The EXCELLA II trial is a randomised trial involving 210 patients that demonstrated the superiority of the Elixir DESyne NES over the Endeavor ZES in terms of in-stent late loss at 9 months (NES: 0.11 ± 0.32 mm vs. ZES: 0.63 ± 0.42 mm, $p < 0.001$). Additionally, there were no significant differences between stent groups in terms of a composite endpoint of cardiac death, target-vessel myocardial infarction and clinically indicated target-lesion revascularisation at 9 months (NES: 2.9% vs. ZES: 5.6%, $p = 0.45$) [92]. As the strut thickness and polymer employed by both devices are similar, this superiority has been attributed to the slower release kinetics of the drug-polymer coating employed by Elixir DESyne NES.

5.1.2. Bioabsorbable polymer-coated DESs

5.1.2.1. The Nevo SES. The Nevo SES (Johnson & Johnson) consists of a cobalt–chromium, open-cell stent which is dotted with multiple laser-cut holes within its struts that serve as micro-reservoirs which are loaded with a formulation of sirolimus and a bioabsorbable polymer called poly-D,L-lactide-co-glycolide (PLGA). PLGA is formed by co-polymerisation of monomers of D,L-lactic acid and glycolic acid and, in the body, is degraded by hydrolysis of ester links with by-products easily metabolised via the Krebs cycle. The Nevo SES is designed to ensure a similar drug-release profile to the Cypher SES with drug-delivery from the micro-reservoirs driven by a combination of diffusion and bulk-erosion of the drug-polymer formulation.

Reservoir-based drug-delivery was initially introduced with the Costar PES (Conor Medsystems Inc., CA, US). Though the Costar PES performed well in early clinical evaluation it was associated with significantly increased rates of target-vessel revascularisation (Costar: 8.1% vs. Express²: 4.3%, $p = 0.002$) at 8 months follow-up of the COSTAR-II trial, a randomised trial involving 1700 patients, in which the safety and efficacy of the device was compared to that of the Taxus Express² PES [93]. Although the precise cause of this failure was unclear, investigators singled out the complex patient/lesion population enrolled in the trial and the poor immediate drug-release rate of the Costar PES as possible causes. Despite the apparent failure of the Costar PES, the Nevo SES has enjoyed promising results in early clinical evaluation in the NEVO-RES-I study.

The NEVO-RES-I study is a randomised trial involving 394 patients that has demonstrated the superiority of the Nevo SES over the Taxus Liberté PES in terms of in-stent late lumen loss at 6 months (SES: 0.13 ± 0.31 mm vs. PES: 0.36 ± 0.46 mm, $p < 0.001$) with all other angiographic and clinical endpoints either statistically or numerically favouring the Nevo SES [94]. Further evaluation of the Nevo SES is currently scheduled with the NEVO-II and NEVO-III trials. The NEVO II trial is a randomised trial involving 2500 patients designed to compare the safety and efficacy of the Nevo SES with the Xience-V EES. The NEVO III trial is a non-randomised trial involving 1300 patients designed to compare the safety and efficacy of the Nevo SES with the Cypher SES.

5.1.2.2. The Supralimus SES and Infinnium PES. The Supralimus SES (Sahajanand Medical Technologies, Gujrat, India) consists of a 316L stainless steel Matrix BMS (Sahajanand Medical Technologies) coated in a formulation of sirolimus and three bioabsorbable polymers, poly L-lactide (PLLA), polyvinyl-pyrrolidone (PVP) and PLGA. The drug-polymer coating is applied to the stent platform in two layers: a base layer consisting of 140 µg sirolimus per cm² stent surface area which is incorporated in a PLLA–PLGA–PVP matrix and an outer polymer-only layer of PVP which prevents premature drug-release and is completely absorbed within two hours of stent deployment. Following absorption of this outer layer, an initial burst-phase releases 50% of the entire dose of sirolimus within the first 7 days, with the remaining drug released over approximately 41 days. The Supralimus SES is currently undergoing clinical evaluation in the SERIES I and SERIES III RUN IN trials.

The SERIES I trial is a non-randomised trial involving 126 patients which has demonstrated the safety and efficacy of the Supralimus with low rates of in-stent late loss (0.09 ± 0.37 mm) and binary in-stent restenosis (0%) reported at 6 months. Furthermore, low rates of adverse clinical events were reported at both 9 (6%) and 30 month (7%) follow-up [95]. Further evaluation of the Supralimus SES is currently underway in the SERIES III trial, a randomised trial involving 360 patients designed to compare the safety and efficacy of the Supralimus SES with the Xience-V EES.

The Infinnium PES (Sahajanand Medical Technologies) is very similar to the Supralimus SES in that it consists of the same 316L stainless steel Matrix BMS and bioabsorbable polymer matrix (PLLA–PVP–PLGA) but incorporates paclitaxel as opposed to sirolimus. The drug-release profile of the Infinnium PES is much the same as that of the Supralimus SES with complete drug-delivery taking approximately 48 days. The Infinnium PES is currently undergoing clinical evaluation in the SIMPLE II trial, a non-randomised registry involving 103 patients that has demonstrated the safety and efficacy of the Infinnium PES with low rates of adverse clinical events observed at 1 (2.9%), 6 (3.9%) and 9 months (6.8%). Furthermore, 6 month angiographic follow-up revealed low rates of in-segment late loss (0.18 ± 0.45 mm) and binary restenosis (8.3%) [96]. The drug-polymer formulations employed by both the Supralimus SES and the Infinnium PES have recently been incorporated on the L605 cobalt–chromium Corronium BMS (Sahajanand Medical Technologies) and clinical evaluation of these DESs is anticipated.

5.1.2.3. The BioMatrix and Nobori biolimus-eluting stents (BESs). The BioMatrix BES (Biosensor Interventional, Morges, Switzerland) consists of a 316L stainless steel S-Stent BMS (Biosensor Interventional) coated in a formulation of biolimus and a bioabsorbable polymer, PLLA. Biolimus is a sirolimus analogue that possesses similar anti-inflammatory properties whilst exhibiting a higher lipophilic and hydrophobic profile. As such, biolimus is more rapidly absorbed by the vessel wall where it induces cell cycle arrest in the G0 phase. The drug is mixed in a formulation with PLLA polymer and applied to the abluminal surface of the S-Stent

with a concentration of 156 μg per cm of stent length. Upon deployment, the drug-polymer formulation is designed to release the drug in a two-phase process with an initial burst release followed by the simultaneous process of sustained drug release and polymer degradation. Both the drug and polymer are fully absorbed within 6–9 months.

The principal safety and efficacy evidence for the BioMatrix BES was obtained from the STEALTH I and LEADERS trials. The STEALTH I trial was a randomised trial involving 120 patients that demonstrated the superiority of the BioMatrix BES over the S-Stent BMS in terms of in-lesion late loss at 6 months (BES: 0.14 ± 0.45 mm vs. BMS: 0.40 ± 0.41 mm, $p = 0.004$). The secondary study endpoint of event-free survival at 6 months was similar in both groups (BES: 96.3% vs. BMS: 97.5%, $p = 0.82$) and no significant differences were observed in rates of target-lesion revascularisation due to low binary in-stent restenosis rates in both stent groups (BES: 3.9% vs. BMS: 7.7%, $p = 0.4$) [97]. The LEADERS trial is a randomised trial involving 1707 patients that has demonstrated the non-inferiority of the BioMatrix BES against the Cypher SES in terms a composite endpoint of death, myocardial infarction and target-vessel revascularisation at 9 months (BES: 9% vs. SES: 11%, $p = 0.39$) [98]. The long-term safety and efficacy of the BioMatrix BES has also been demonstrated in this patient population with non-inferior rates of this composite endpoint reported at both one (BES: 10.7% vs. SES: 12.1%, $p = 0.37$) and two years (BES: 13.0% vs. SES: 15.4%, $p = 0.18$) [99]. The BioMatrix BES received CE approval in April 2008.

In May 2007, Terumo Corporation (Leuven, Belgium) agreed to license the BioMatrix BES, re-branding it as the Nobori BES, and began enrolment in the NOBORI I trials. The first phase of the NOBORI I trial was a randomised trial involving 120 patients that demonstrated the non-inferiority of the Nobori BES against the Taxus Express² PES in terms of in-stent late loss at 9 months (BES: 0.15 ± 0.27 mm vs. PES: 0.32 ± 0.33 mm, $p = 0.006$) [100]. The second phase of the NOBORI I trial was a randomised trial involving 243 patients that demonstrated the superiority of the Nobori BES over the Taxus Liberté PES in terms of in-stent late loss (BES: 0.11 ± 0.30 mm vs. PES: 0.32 ± 0.50 mm, $p = 0.001$) and binary in-stent restenosis (BES: 0.7% vs. PES: 6.2%, $p = 0.02$) at 9 months [101]. Further evaluation of the Nobori BES is currently underway in the NOBORI II trial, which began enrolment in March 2009.

5.1.3. Polymer-free DESs

5.1.3.1. The Yukon SES. The Yukon SES (Translumina, Hechingen, Germany) consists of a 316L stainless steel stent platform with a microporous surface finish that facilitates direct drug adhesion and polymer-free drug-delivery. The microporous stent is coated in a reported 2% solution of sirolimus and is designed to deliver the entire dose within three weeks of stent deployment. The principal safety and efficacy evidence for the Yukon SES is derived from the ISAR-TEST trial, a randomised trial involving 450 patients that has demonstrated the non-inferiority of a polymer-free Yukon SES against the Taxus Express² PES in terms of in-stent late lumen loss at 9 months (SES: 0.48 ± 0.61 mm vs. PES: 0.48 ± 0.58 mm, $p = 0.98$). No significant differences between stent groups were observed in rates of binary in-stent restenosis (SES: 12.6% vs. PES: 11.6%, $p = 0.78$) and target-lesion revascularisation (SES: 9.3% vs. PES: 9.3%, $p = 1.0$) at 9 months [102]. The polymer-free Yukon SES received CE approval in 2003.

Following the results of the ISAR-TEST trial, the safety and efficacy of Yukon SESs were further evaluated in the ISAR-TEST-3 and ISAR-TEST-4 trials. The ISAR-TEST-3 trial was a randomised trial that compared the safety and efficacy of a polymer-free Yukon SES, a bioabsorbable (shellac resin-based) polymer-coated Yukon SES and the Cypher SES. At 12 months, similar rates of adverse clinical events were reported for each DES. However, while the bioabsorbable polymer-coated Yukon SES was found to be non-inferior

to the Cypher SES, the polymer-free Yukon SES was found to be inferior in terms of mean late loss at 6 months (Yukon: 0.47 ± 0.56 mm vs. Cypher: 0.23 ± 0.46 , $p_{\text{non-inferiority}} = 0.94$) [103]. These observations were later supported by results from the ISAR-TEST-4 trial, a randomised trial involving 2603 patients that demonstrated the non-inferiority of a bioabsorbable polymer-coated Yukon SES against a control arm of patients treated with Cypher SESs or Xience-V EESs in terms of a composite of cardiac death, myocardial infarction and target-vessel revascularisation (Yukon: 13.8% vs. Endeavor/Xience-V: 14.4%, $p = 0.66$) at 12 months [104]. Further evaluation of the bioabsorbable polymer-coated Yukon SES is currently underway in the ISAR-TEST-5 trial.

5.1.3.2. The BioFreedom BES. The BioFreedom BES (Biosensor Interventional) is similar in its design to the Yukon SES in that it utilises microporous surface finishing to facilitate polymer-free drug adhesion and delivery. The BioFreedom BES consists of a microporous 316L stainless steel S-Stent which is coated on its abluminal surface with biolimus. The safety and efficacy of the BioFreedom BES is currently under evaluation in the BIOFREEDOM FIM trial, a randomised trial involving 180 patients which is designed to assess the safety and efficacy of low dose (78 μg of biolimus per cm stent length) and standard dose (156 μg of biolimus per cm stent length) BioFreedom BESs relative to the Taxus Liberté PES. Results from the first cohort of this trial have demonstrated the non-inferiority of the BioFreedom BES in terms of in-stent late loss (Low Dose BES: 0.08 mm vs. Standard Dose BES: 0.12 mm vs. PES: 0.37 mm, $p < 0.0001$ and $p = 0.002$, respectively) at 4 months [105]. Evaluation of a second cohort of patients enrolled in the BIOFREEDOM FIM trial is ongoing.

5.1.3.3. The Janus Tacrolimus-Eluting Stent (TES). The Janus TES (Sorin Biomedica Cardio, Italy) consists of a Carbastent BMS (Sorin Biomedica Cardio) which incorporates multiple micro-reservoirs cut into its abluminal side that are loaded with tacrolimus, a non-cytotoxic T-cell inhibitor, which inhibits smooth muscle cell proliferation in the G0 phase (Fig. 4). The drug is embedded in these reservoirs, which are designed to ensure abluminal-side drug-delivery only, with a standard concentration of 230 μg of tacrolimus per cm^2 of stent surface area. The entire stent surface is coated with a high density ultrathin film of thrombo-resistant pyrolytic carbon (Carbofilm) which is designed to improve overall biocompatibility of the device. The principal safety and efficacy evidence for the Janus TES was obtained from the JUPITER II trial, a randomised trial involving 332 patients that demonstrated the non-inferiority of the Janus TES against a carbofilm-coated Carbastent BMS in terms of in-stent late loss at 6 months (TES: 0.65 ± 0.47 mm vs. BMS: 0.66 ± 0.53 mm, $p = \text{non-significant}$) and rates of adverse clinical events at 12 months (TES: 16.1% vs. BMS: 19.5%, $p = \text{non-significant}$) [106].

5.1.3.4. The Genous Bioengineered R Stent and Combo SES. The Genous Bioengineered R stent (OrbusNeich, FL, US) consists of a 316L stainless steel R Stent BMS (OrbusNeich) which is coated on its luminal surface with monoclonal, anti-human CD34 antibodies. These antibodies attract circulating endothelial progenitor cells (EPCs) which promote the establishment of a functional endothelial layer upon the stent surface and reduce the risk of restenosis and late stent thrombosis. One possible drawback with this technology is that the CD34+ markers used to phenotype EPCs are non-specific and may also sequester unwanted cells including smooth muscle progenitor cells that can contribute to neointimal proliferation [107]. To date, the Genous stent has been evaluated in a number of prospective registries and clinical trials such as HEALING FIM, HEALING II, GENIUS-STEMI and TRIAS.

HEALING FIM is a prospective registry involving 16 patients that demonstrated the safety and feasibility of the Genous Bio-

Fig. 4. Optical microscopy images of Janus TES (Sorin Biomedica) (a) marginal section with radiopaque marker shown pre-dissolution, (b) marginal section with radiopaque marker shown post-dissolution and (c) medial section pre-dissolution and (d) medial section pre-dissolution.

engineered R stent in low-risk patients with modest rates of mean late lumen loss (0.63 ± 0.52 mm) and low rates of adverse clinical events (6.3%) observed at 6 and 9 months, respectively [108]. The HEALING II study is a second prospective registry involving 63 patients that further demonstrated the feasibility of the Genous Bioengineered R stent. Initially, at 6 months, in-stent late loss was reported as 0.78 ± 0.39 mm, however, at 18 months a significant late regression of neointimal hyperplasia was observed with in-stent late loss reported as 0.59 ± 0.31 mm (a 16.9% reduction by matched serial analysis) [109]. It was noted by investigators that a relative increase in circulating EPC titers at long-term follow-up correlated with neointimal compaction in individual patients suggesting an EPC-mediated vascular repair response.

The GENIUS-STEMI trial is a randomised trial involving 100 patients suffering from ST-elevated myocardial ischemia which was designed to compare the safety and efficacy of the Genous Bioengineered R stent with cobalt chromium BMSs (Driver BMS or Coroflex Blue BMS) in terms of adverse clinical events at 6 months. At follow-up, however, increased rates of adverse clinical events (Genous: 24% vs. BMS: 10%, $p=0.03$) and stent thrombosis (Genous: 6% vs. BMS: 0%, $p=\text{non-significant}$) were observed in patients treated with the Genous Bioengineered R stent, and larger clinical studies were recommended [110]. The TRIAS trial is a randomised trial involving 193 patients suffering from high risk de novo lesions that was designed to compare the safety and efficacy of the Genous Bioengineered R stent with the Taxus Liberté PES in terms of target-vessel failure at 12 months. At follow-up, a non-significant increase in the rate of target-vessel failure was observed in patients in the Genous group (Genous: 17.3% vs. PES: 10.5%, risk difference = 6.8%), and was attributed to a higher incidence of repeat revascularisation. Additionally, 8 month angiographic follow-up revealed significantly higher mean late loss in patients in the Genous group (Genous: 1.14 ± 0.64 mm vs. PES: 0.55 ± 0.61 mm, $p<0.0001$). In contrast, no stent thrombosis was observed in patients treated with the Genous Bioengineered R stent compared to four stent thromboses in the Taxus Liberté PES group, despite a significantly lower percentage of patients in the Genous group undergoing dual anti-platelet therapy [111].

Following the results of these trials, OrbusNeich have developed the Combo SES, a 316L stainless steel R stent which is coated on its luminal side with an EPC-capture matrix and is coated on its abluminal side in a formulation of sirolimus and a biodegradable polymer. To date, the Combos SES has shown improved endothelialisation and neointimal proliferation compared to the Cypher SES in porcine arteries. Clinical evaluation of the Combo SES is currently

underway in the REMEDEE trial, a randomised trial involving 180 patients that is designed to compare the safety and efficacy of the Combo SES with the Taxus Liberté PES in terms of late loss at 9 months [112].

5.2. Bioabsorbable DESs

5.2.1. Bioabsorbable polymer-coated DESs

5.2.1.1. The BVS EES. The BVS EES (Abbott Vascular) is manufactured from PLLA polymer and is coated with a formulation of everolimus in a poly-D,L-lactide (PDLLA) polymer matrix which contains and controls the release of everolimus from the stent. As with the bioabsorbable polymer coatings already discussed, PLLA and PDLLA polymers are slowly degraded by hydrolysis of ester links with all by-products metabolised via the Krebs cycle. The mechanical properties of the PLLA BVS EES appear favourable, with relatively high levels of radial strength and low levels of stent recoil. The drug-polymer coating is applied to the entire stent surface with a standard concentration of approximately $8.2 \mu\text{g}$ of everolimus per mm stent length and is designed to release approximately 80% of the total dose within 30 days of stent placement. Polymeric strut absorption is by bulk erosion with full absorption taking approximately two years.

The revision one BVS EES features circumferential hoops which are linked by straight bridging segments and have a strut thickness of 0.15 mm (Fig. 5). The safety and feasibility of the revision one BVS EES was evaluated in the first cohort of the ABSORB trial, a non-randomised trial involving 30 patients suffering from low-risk de novo lesions. Procedural and device success were 100% and 94%, respectively, with very low rates of adverse clinical events observed at one (3.3%), two (3.4%) and three years (3.4%) and complete freedom from stent thrombosis at three years [113–115]. In November 2009, investigators announced complete enrolment in a second cohort in the ABSORB trial that is designed to assess the safety and efficacy of a revised BVS EES.

The revision two BVS EES is constructed from the same polymer material (PLLA) as the revision one BVS EES, however, different processing techniques have been adopted to increase the duration of radial support, while maintaining the same total period of absorption (approximately two years). Although the strut thickness is unchanged (0.15 mm), the revision two BVS EES features a redesigned strut configuration, similar to that of the Multi-Link BMS, which ensures improved vessel support and uniform drug-delivery. The revision two BVS EES is currently under evaluation in the second cohort of the ABSORB trial, a randomised trial involv-

Fig. 5. (a) Revision one BVS EES geometry and (b) Magnification of revision two BVS EES with radiopaque markers shown.

ing 101 patients which has demonstrated the safety and feasibility of the revision two BVS EES in terms of mean late loss at 6 months (0.19 mm) [116]. Further clinical evaluation of the BVS EES is scheduled in the ABSORB EXTEND trial which is set to enrol 1000 patients and is designed to assess the safety and efficacy of the revision two BVS EES in more complex patients and lesions.

5.2.1.2. The BTI ideal SES. The BTI SES (Bioabsorbable Therapeutic Inc., CA, US) consists of a stent platform which is manufactured from polylactide anhydride (PA) and salicylic acid and is coated with a formulation of sirolimus in a bioabsorbable polymer matrix which is derived from salicylic and adipic acids. This novel stent is designed to release both sirolimus and salicylic acid to the arterial wall. Salicylic acid, the active ingredient in aspirin, has well-known anti-inflammatory properties as well as anti-platelet effects. As with the bioabsorbable polymers already discussed, degradation is by hydrolysis of ester bonds with all by-products metabolised via the Krebs cycle. The drug-polymer coating is applied to the abluminal stent surface with a standard concentration of approximately 8.3 µg of sirolimus per mm stent length and is designed to release the entire drug dose over 1 month. Polymeric strut absorption is by surface erosion with full absorption taking approximately 6–12 months. During absorption of the stent approximately 10 µg of salicylic acid is released to the arterial wall.

The BTI SES was first evaluated in the WHISPER trial, a first-in-man trial involving 11 patients, during which the BTI SES exhibited acceptable safety and structural integrity without incurring any acute or chronic recoil. Due to insufficient neointimal suppression which was attributed to insufficient drug dosing and rapid drug release, however, the design of the BTI SES has been revised. The revised BTI SES possesses thinner struts (0.175 vs. 0.20 mm), a higher dose of sirolimus, a slower drug-release profile, a lower crossing profile and lower percent stent-to-artery wall coverage (57% vs. 65%). Evaluation of the revised BVS SES is currently ongoing [117].

5.2.2. Polymer-free DESs

5.2.2.1. The REVA stent. The REVA stent (REVA Medical, CA, US) consists of a bioabsorbable stent platform manufactured from monomeric units of L-tyrosine which is impregnated with iodine molecules for radiopacity. This bioabsorbable stent has a period of absorption of approximately three years, can act as a drug-delivery matrix with a tuneable absorption rate and features a unique slide-and-lock design that permits expansion without material deformation. The REVA stent was first evaluated in the RESORB trial, a first-in-man trial involving 27 patients, during which the REVA stent successfully dilated lesions at implant, achieving good acute gain and reduction in diameter stenosis with no evidence of shrinkage or negative remodelling observed post-deployment [118].

At 6 and 12 month follow-up, however, higher than anticipated rates of target-lesion revascularisation (6 month: 60%, 12 month: 67%), driven by the inability of the tyrosine-derived polymer to resist clinical loading, were reported and neointimal hyperplasia at

6 months (18.0 ± 0.91 mm) was found to be similar to that observed with BMSs [119]. Following the results of the RESORB trial the REVA stent underwent a redesign which led to the development of the ReZolve SES (REVA Medical). The ReZolve SES features an improved spiral slide-and-lock design, incorporates a more robust polymer which has been modified to meet clinical demands and facilitates elution of sirolimus. Clinical evaluation of the ReZolve SES is anticipated [119].

5.2.2.2. The AMS stent. The AMS stent (Biotronik, Berlin, Germany) consists of a bioabsorbable WE43 magnesium-alloy stent that possesses both biocompatible and bio-corrosive properties while maintaining strength similar to that of 316L stainless steel (Fig. 6). The AMS stent was first evaluated in the PROGRESS-AMS trial, a non-randomised trial involving 63 patients suffering from de novo lesions that demonstrated the safety and feasibility of a drug-free AMS with zero death, stent thrombosis or myocardial infarction observed at 12 months. Disappointingly, however, high rates of overall target-lesion revascularisation were observed at four (39.7%) and 12 months (45.0%) [120]. This high rate of target-lesion revascularisation was attributed to the rate of absorption of the device with a lack of radial support allowing for excessive negative remodelling. Modification of the mechanical properties of the AMS stent for prolonged degradation and drug-delivery are currently underway.

6. Discussion

To date, a number of studies have confirmed the long-term safety and efficacy of DESs compared to BMSs. Results from long-term follow-up of the pivotal SIRIUS, TAXUS IV, ENDEAVOR II and SPIRIT FIRST trials have shown no evidence of disproportionate late clinical events with DESs compared to BMSs [22,121–123]. In a recent meta analysis involving 18023 patients DESs and BMSs were associated with similar rates of cardiac mortality at up to four years with a marked reduction in rates of target-lesion revascularisation reported in patients treated with DESs (SES vs. BMS, hazard ratio = 0.30 and PES vs. BMS, hazard ratio = 0.42) [72]. A separate meta-analysis involving a total of 192371 patients has also reported no significant differences in long-term mortality rates after DES or BMS use in both on-label (DES vs. BMS: hazard ratio = 0.97, $p = 0.72$) and off-label (DES vs. BMS: hazard ratio = 0.84, $p = 0.24$) indications. Furthermore, marked reduction in target-lesion revascularisation was observed with DES use in both randomised controlled trials (DES vs. BMS: hazard ratio = 0.45, $p < 0.001$) and observational studies (DES vs. BMS: hazard ratio = 0.54, $p < 0.001$) compared to BMSs [73].

Being the first DESs to receive both CE and FDA approval, the first-generation Cypher SES and Taxus Express² PES have been subject to a large number of investigational and comparative trials. In a randomised trial carried out to compare the safety and efficacy of the Cypher SES with the Taxus Express² PES, fewer adverse clinical events were reported in the Cypher SES group at 9 months (SES: 6.2% vs. PES: 10.8%, $p = 0.009$). This difference was attributed

Fig. 6. AMS stent (Biotronik) (A) post-expansion, (B) pre-expansion and (C) electron microscopy magnification.

to a lower incidence of target-lesion revascularisation (SES: 4.8% vs. PES: 8.3%, $p=0.03$) and angiographic in-segment restenosis (SES: 6.6% vs. PES: 11.7%, $p=0.02$) [55]. In a meta-analysis of 16 randomised trials, involving 8695 patients, the Cypher SES was identified with similar rates of cardiac death and myocardial infarction but significantly reduced rates of reintervention (hazard ratio: 0.74, $p<0.001$) and stent thrombosis (hazard ratio: 0.66, $p=0.02$) compared to the Taxus Express² PES across a number of patient and lesion subgroups at two years [124]. Although an exact cause for these findings is yet to be identified, investigators have suggested pharmacological differences between the two drugs, differences in dose response among high risk patient and lesion subgroups, and differences in release kinetics and polymer coatings employed by the two DESs as possible causes.

The Cypher SES has also compared favourably with second-generation DESs based on the findings of two recent trials, SORT-OUT-III and ZEST. The SORT-OUT-III trial is a randomised, all-comers trial involving 2773 patients that demonstrated the superiority of the Cypher SES over the Endeavor ZES in terms of adverse clinical events at nine (ZES: 6% vs. SES: 3%, $p=0.0002$) and 18 months (ZES: 10% vs. SES: 5%, $p<0.0001$) [46]. The ZEST trial is a randomised, all-comers trial involving 2640 patients which has identified the Cypher SES with improved rates of adverse clinical events compared to both the Taxus Liberté PES and Endeavor ZES at 12 months (SES: 8.3% vs. ZES: 10.1% vs. PES: 14.2%, $p=0.25$ and $p<0.001$, respectively) [125]. In the recent COMPARE trial, a randomised trial involving 1800 patients, the Xience-V EES was identified with superior rates of adverse clinical events compared to the Taxus Liberté PES at 12 months (EES: 6% vs. PES: 9%, $p=0.02$) [38]. The performance of the Xience-V EES relative to the Cypher SES is to be evaluated in the EXCELLENT trial, a randomised trial due to enrol approximately 1800 patients to assess the efficacy of the Xience-V EES against the Cypher SES in terms of lumen loss and target-vessel failure at 9 months.

It is worth noting that the results of many of the clinical trials reported thus far have been interpreted based on the assumption that endpoints such as late loss are directly indicative of the long term performance of DESs. In recent years, the significance of endpoints such as late loss and target-lesion revascularisation have been called into question, particularly following the presentation of long-term follow-up of the ENDEAVOR III and SIRTAX trials. Though the Cypher SES was associated with significantly less in-segment late loss at 8 months (ZES: 0.34 ± 0.44 mm vs. SES: 0.13 ± 0.32 mm, $p<0.001$) and lower incidence of target lesion-revascularisation at 9 months (ZES: 9.8% vs. SES: 3.5%, $p=0.04$) in the ENDEAVOR III trial, the absolute difference in rates of target-lesion revascularisation

at five years was reduced to just 1.6% [19,21]. This phenomenon, known as late catch-up, was also reported at long-term follow-up of the SIRTAX trial, a comparative study involving the Cypher SES and the Taxus Express² PES, in which angiographic in-stent late loss was significantly lower in patients treated with the Cypher SES arm at 8 months (SES: 0.12 ± 0.36 mm vs. PES: 0.25 ± 0.49 mm, $p<0.001$) but comparable between both arms at five years (SES: 0.30 ± 0.51 mm vs. PES: 0.37 ± 0.51 mm, $p<0.21$) [55]. Further comparison of the Endeavor ZES and the Cypher SES is currently underway in the PROTECT trial, a randomised trial involving 8800 patients which completed enrolment in December 2008.

Commenting on the results of these trials investigators have noted that neointimal formation may follow different timelines with different DESs. It has been speculated that late catch-up may have little to do with the different stent platforms and drugs employed by the DESs but is more likely linked to the long-term biological effect of the polymer coatings that they employ. It has also been suggested that long-term data from comparative clinical trials such as the ENDEAVOR III and SIRTAX trials, in which significant differences in DES performance emerge long after primary endpoints have been assessed, may redefine how clinical trials of DESs are designed and conducted. The long-term results of current and future comparative DES trials are eagerly anticipated.

In terms of medical engineering, DESs have benefitted considerably from numerous avenues of research over the past decade. Identification and implementation of high strength biologically inert materials has facilitated the design of DESs with significantly reduced stent struts, improving overall device safety and deliverability. The development of bioabsorbable materials should further improve the long-term safety of stent platforms and coatings with numerous devices currently showing promise in clinical trials. Innovations in micro-fabrication have led to the emergence of novel drug-delivery mechanisms such as microporous-based and reservoir-based drug-delivery, while medical imaging technologies and numerical methods such as finite element analysis and computational fluid dynamics have emerged as powerful tools in the design and optimisation of DESs [126–129].

The introduction and development of DESs over the past decade has revolutionised the treatment of CAD with reported reductions in rates of ISR of between 60–80% compared to BMSS. As with most new medical devices, however, first-generation DESs suffered from a number of defects. Many of these defects have been addressed with the second-generation of DESs and today, research is centred on further improving the overall efficacy and long-term safety of DESs. With the annual international market for DESs swelling to over €5 billion and with dozens of companies currently develop-

ing innovative stent platforms, potent anti-restenotic coatings and novel drug-delivery mechanisms it is possible that an optimum DES for the treatment of CAD will emerge in the coming years.

Conflicts of interest

No conflict of interest to declare.

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