Current Cardiology Reviews, 2017, *13*, 139-154

REVIEW ARTICLE

Current State of Bioabsorbable Polymer-Coated Drug-Eluting Stents

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ARTICLE HISTORY

Received: August 18, 2016
Revised: October 6, 2016
Accepted: October 18, 2016

DOI: 10.2174/1573403X12666161222155230

Abstract: Drug-eluting stents (DES) have been shown to significantly reduce clinical and angiographic restenosis compared to bare metal stents (BMS). The polymer coatings on DES elute antiproliferative drugs to inhibit intimal proliferation and prevent restenosis after stent implantation. Permanent polymers which do not degrade *in vivo* may increase the likelihood of stent-related delayed arterial healing or polymer hypersensitivity. In turn, these limitations may contribute to an increased risk of late clinical events. Intuitively, a polymer which degrades after completion of drug release, leaving an inert metal scaffold in place, may improve arterial healing by removing a chronic source of inflammation, neoatherosclerosis, and/or late thrombosis. In this way, a biodegradable polymer may reduce late ischemic events. Additionally, improved healing after stent implantation could reduce the requirement for long-term dual antiplatelet therapy and the associated risk of bleeding and cost. This review will focus on bioabsorbable polymer-coated DES currently being evaluated in clinical trials.

Keywords: Bioabsorbable polymer, drug-eluting stent, abluminal coating, BMS, clinical trials.

INTRODUCTION

Percutaneous coronary intervention (PCI) is a mainstay in the treatment of acute coronary syndromes and stable coronary artery disease. Since the invention of balloon angioplasty, the field of PCI has progressed significantly over the last three decades. The use of balloon-expandable metallic stents has decreased, but not eliminated, the risk of restenosis as compared to simple balloon angioplasty [1]. Permanent polymer-coated drug-eluting stents (DES) elute drugs that inhibit intimal proliferation and prevent restenosis after stent implantation. Compared to bare-metal stents (BMS), DES have similar rates of death and myocardial infarction (MI), but lower rates of clinical and angiographic restenosis [2].

DES consist of three components: a permanent metallic scaffold, the polymer, and an antiproliferative drug. First-generation stents were made of nitinol and then stainless steel; later generation metallic stent scaffolds have used cobalt chromium or platinum chromium alloys which allow thinner stent struts, whilst maintaining radial strength. Coronary scaffolds which fully degrade (for example Absorb Bioresorbable Vascular Scaffold System, Abbott Vascular, Santa Clara, USA) have been introduced in the past decade and are beyond the scope of this review [3]. Antiproliferative drugs used in current DES (for example, sirolimus, everolimus, biolimus, novolimus) generally inhibit the mammalian target of rapamycin (mTOR) pathway but have different pharmacological profiles [4].

The purpose of the polymer is to store and modulate the elution of the drug into the arterial tissue/site of the lesion. Permanent polymers used in first- and second-generation DES do not degrade; first-generation polymers included polyethylene-co-vinyl acetate (PEVA) and polybutyl methacrylate (PBMA), whereas the current best-in-class DES use polyvinylidene fluoride- hexafluoropropylene (PVDF-HFP) or phosphorylcholine [5, 6]. Animal models of arterial healing have shown that first-generation DES are associated with delayed healing, hypersensitivity, and an increased incidence of vascular inflammatory reactions compared with BMS and second-generation DES [7-11]. These observations are supported by findings in human autopsy [12, 13] and optical coherence studies [14, 15]. Second generation DES have shown improvements biocompatibility and clinical outcomes [8, 16] but may still lead to neoatherosclerosis and thrombosis [7, 17].

Delayed endothelialization and chronic inflammation associated with DES may be attributed to the drug, the permanent polymer, or both; however, persistent hypersensitivity reactions (beyond the period of drug delivery) support a role for permanent polymers in the inflammatory reaction [18, 19]. As such, efforts have been made to develop bioabsorbable polymers which, after completion of drug release, degrade leaving a bare metal scaffold in place and potentially facilitate endothelialization and reduce the risk of an in-

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flammatory reaction. The vast majority of biodegradable polymers developed are synthetic polyesters from the poly (α-hydroxy acid) family including polylactic acid and poly-glycolic acid and their co-polymer polylactic-co-glycolic acid. The potential clinical benefits of a polymer which degrades include a reduction in stent-related ischemic events and/or the potential to reduce the required duration of dual antiplatelet therapy (DAPT) after stent implantation. The recent large-scale DAPT study by Mauri *et al.* (2014) demonstrated that a long-term (30-month) DAPT regimen resulted in significantly lower rates of thrombosis compared to a shorter (12-month) DAPT regimen, but was associated with a significantly increased risk of bleeding [20]. Permanent polymer DES were used exclusively in this study; the potential for improved healing associated with bioabsorbable polymer-coated DES (BP-DES) may permit shorter DAPT duration following PCI with DES and, consequently, reduce the risk of bleeding without increasing the risk of stent thrombosis (ST).

This review will focus on permanent metallic stents releasing ‘olimus drugs from bioabsorbable polymers. A list of bioabsorbable-polymer coated DES currently being tested in clinical trials is shown in Table **1**. The time course of drug release and polymer absorption is shown in Fig. **1**.

Preclinical Trials Comparing Bioabsorbable Polymer DES to Permanent Polymer DES

Multiple animal models have demonstrated that BP-DES induce similar levels of inflammation as BMS [12-14]. Comparable vascular responses were observed after BP-DES, BMS, or a polymer-only control stent implantation in a porcine coronary artery model and endothelialization with BP-DES was complete by 28 days [21-24]. Koppara *et al.* showed that BP-DES were associated with significantly less inflammation and neointimal growth when compared to permanent polymer DES at 28 days after implantation [25]. Likewise, a reduction in the inflammatory response to stent implantation and rapid neointimal coverage was observed with BP-DES compared to a permanent polymer DES in pigs and in rabbits [26, 27].

In humans, optical coherence tomography (OCT)-based studies have demonstrated equivocal results in relation to endothelialization after implantation of BP-DES compared to permanent polymer DES, with either favorable results [18-20] or negative or neutral effects when eralier, thicker strut BP-DES were tested [21-23]. More recent BP-DES studies have found that an everolimus-eluting BP-DES displayed complete and smooth coverage over all struts by 2 months [28-34]. An evaluation of coronary lesions by OCT t five years after biolimus-eluting BP-DES implantation demonstrated fewer uncovered stent struts compared to sirolimus-eluting permanent polymer stents [35]. In a study performed by Hamilos and colleagues, endothelial dependent vasomotor function was preserved in patients with BP-DES, but not in patients who received a permanent polymer DES [36]. However, Puricel *et al.* demonstrated that endothelium dependent and independent vasomotor responses were similar between biolimus-eluting BP-DES and everolimus-eluting permanent polymer DES [37].

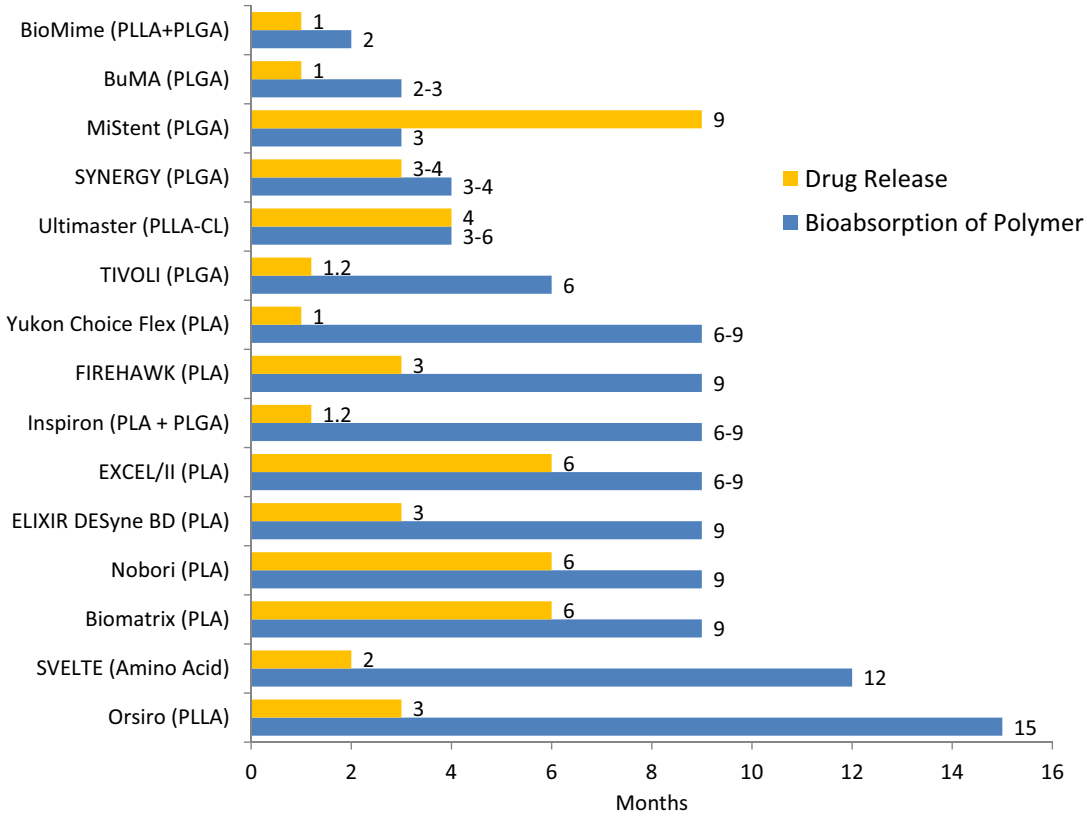

Fig. (1). Time Course For Polymer Bioabsorption.

Drug release (yellow) and polymer absorption (blue) arranged by length of polymer absorption.

Table 1. Current bioabsorbable-polymer coated drug-eluting stents tested in clinical trials.

Name	Company	Platform	Thickness (μm)	Polymer	Polymer Distribution/ Thickness	Drug	Drug Release/ Polymer Absorption
Biomatrix [49]	Biosensors	Stainless Steel	120	Polylactic acid	Abluminal/10 μm	Biolimus A9	6 mo/9 mo
Nobori [53]	Terumo	Stainless Steel	125	Polylactic acid	Abluminal/20 μm	Biolimus A9	6 mo/9 mo
Ultimaster [65]	Terumo	Cobalt Chromium	80	Poly (DL-lactide-co-caprolactone)	Abluminal/15 μm	Sirolimus	For both 3-4 mo
SYNERGY [41]	Boston Scientific	Platinum chromium	74	Polylactic co-glycolic acid	Abluminal/4 μm	Everolimus	3 mo/4 mo
Orsiro [114]	Biotronik	Cobalt chromium	61	Poly L lactic acid	Conformal/up to 7.5μm	Sirolimus	3 mo/15 mo
MiStent [75]	Micell	Cobalt Chromium	64	Polylactic co-glycolic acid	Conformal/Not reported	Crystalline sirolimus	9 mo/3 mo
DESyne BD [78]	Elixir Medical Corporation	Cobalt chromium	81	Poly L Lactide (PLLA)-based polymer	Conformal/<3 μm	Novolimus	3 mo/9 mo
TIVOLI [81]	Essen Tech	Cobalt chromium	80	Polylactic co-glycolic acid	5.5 μm	Sirolimus	80% by 1 mo/3-6 mo
EXCEL [82]	JW Medical Systems	Stainless steel	119	Polylactic acid	10-15 μm	Sirolimus	6 mo/6-9 mo
EXCEL II [85]	JW Medical Systems	Cobalt chromium	88	Polylactic acid	4 μm	Sirolimus	NR/6-9 mo
Inspiron [86]	Scitech	Cobalt chromium	75	Polylactic acid + Polylactic co-glycolic acid	Abluminal/5 μm	Sirolimus	80% by 1 mo/6-9 mo
Firehawk [95]	Microport Medical	Cobalt chromium	86	Polylactic acid	Abluminal	Sirolimus	3 mo/9 mo
Yukon Choice Flex [100]	Translumina GmbH	Stainless Steel	79	Polylactic acid	Abluminal/Not reported	Sirolimus	4 wk/ 6-9 mo
BuMA [102]	Sino Medical	Stainless Steel	100-110	Polylactic co-glycolic acid	Conformal/10 μm	Sirolimus	30 d/2-3 mo
Svelte [105]	Svelte Medical Systems	Cobalt chromium	81	Poly(ester amide)	Conformal/6 μm	Sirolimus	2 mo/12 mo
BioMime [106]	Meril Life Sciences	Cobalt chromium	65	PLLA+PLGA	Conformal/2 μm	Sirolimus	75% in 15 d/60 d

Table 2. Summary of clinical trials for the SYNERGY everolimus-eluting bioabsorbable polymer stent.

Trial	Control	# of patients/study design	Results
EVOLVE 6-months [39] 5-year [40] NCT01135225	EES	N=291; Prospective, multisite, randomized (1:1:1), single-blind, noninferiority; 29 sites (Europe, Australia, New Zealand,) Single target lesion ≤28mm, ≥2.25 to ≤3.5 mm RVD	**Clinical 1° endpoint:** 30-d TLF EES 0 (0%), SYNERGY 1(1.1%), and SYNERGY ½ Dose 3 (3.1%); SYNERGY vs EES P=0.49 and SYNERGY ½ dose vs EES P=0.25, respectively **Angiographic 1° Endpoint:** 6 m in-stent late loss in EES 0.15±0.34 mm; SYNERGY (0.10±0.25 mm) and SYNERGY ½ Dose group (0.13±0.26 mm) were both noninferior to EES; $P_{\text{noninferiority}}$<0.001) **2° endpoints:** • At 5 years, rates of cardiac death, MI, TVR, TLR, TLF, and TVF remained low and not significantly different between treatment groups; no incidence of definite/probable ST in any treatment group

(Table 2) Contd….

Trial	Control	# of patients/study design	Results
EVOLVE II 1 year [41] 2 years [42] EVOLVE II Diabetes [43, 44] NCT01665053	EES	N=1684; Prospective, multisite, single-blind, randomized (1:1) noninferiority; 125 sites (US, Canada, Europe, Australia, New Zealand, Singapore, and Japan); ≤3 target lesions ≤34mm, ≥2.25 to ≤4.0 mm RVD	**1° endpoint:** 12 m TLF was 6.5% of EES and 6.7% SYNERGY treated subjects (ITT: 97.5% upper confidence bound=2.68%; $P_{noninferiority}$=0.0005; Per Protocol: TLF EES 6.4%, 6.4% SYNERGY, 97.5% upper confidence bound=2.51%; $P_{noninferiority}$ =0.0003) **2° endpoints:** At 2 years, cardiac death (EES 1.5% vs SYNERGY 1.0%; *P*=0.35), MI (5.4% vs 5.5% based on 3x CK-MB ULN; *P*=0.89), TLR (3.1% vs 4.3%; *P*=0.17), or ST (0. 8% vs 0.4%; *P*=0.31). **Diabetes Substudy:** **1° endpoint**: 12 m TLF occurred in 7.5% of SYNERGY-treated patients with diabetes, significantly less than the performance goal (*P*<0.0001). The 2-year rate of TLF was 11.2% and definite/probable ST occurred in 1.1% of patients.
EVOLVE II QCA 12-month [45] NCT01787799	N/A	N=100; Prospective, multisite, single-arm; 12 sites (Australia, New Zealand, Singapore, and Japan) ; ≤3 target lesions ≤34mm, ≥2.25 to ≤4.0 mm RVD	**1° endpoint:** 9 m in-stent late loss 0.23 mm (1-sided 97.5% upper confidence bound 0.40 mm), and was significantly below the prespecified performance goal of 0.4 mm (*P*<0.0001). Post-procedure incomplete stent apposition was also low (2.1%), and 9-month % volume obstruction by IVUS was 5.2%. At 12 m follow-up, there were no deaths or ST. Five patients had peri-procedural non-Q wave MI (based on CK-MB>3x upper limit of normal), and 1 TLR.
EVOLVE China 12-month [115] NCT01966159	EES	N=412; Prospective, multisite, single-blind, randomized (1:1) noninferiority; 14 sites in China; ≤2 target lesions ≤34mm, ≥2.25 to ≤4.0 mm RVD	**1° endpoint**: 9 m in stent late loss (SYNERGY 0.20mm±0.33mm vs EES 0.17mm± 0.37mm). The upper 1-sided 97.3% confidence interval of the difference (0.10 mm) was significantly less than the noninferiority margin of 0.15 mm (*P*<0.0008). Clinical adverse event rates were low and not significantly different at 12 months (all *P*>0.05).

Abbreviations: CAD = coronary artery disease; EES = everolimus-eluting stents; IVUS = intravascular ultrasound; MI = myocardial infarction; RVD = reference vessel diameter; TLF = target lesion failure; TLR = target lesion revascularization; TVR = target-vessel revascularization; ST = stent thrombosis.

CLINICAL TRIALS OF BIOABSORBABLE POLYMER-COATED DES

SYNERGY Stent

The SYNERGY stent (Boston Scientific, Marlborough, USA) is the only BP-DES approved by the United States Food and Drug Administration for commercial use. SYNERGY is a thin-strut (74 µm) platinum chromium stent that delivers everolimus from a 4 µm ultrathin bioabsorbable poly (DL-lactide-co-glycolide) (PLGA) polymer applied to the abluminal surface (no drug/polymer are present on the luminal side; Table **1**). The platinum chromium platform which remains after complete degradation of the polymer has been shown to be less pro-inflammatory compared to gold, cobalt chromium, or cobalt nickel alloy platforms in cell assay, and may enhance endothelial cell stent coverage while and reducing platelet adhesion when compared with a stent coated with a PVDF permanent polymer *in vitro* [38]. Animal studies have demonstrated that PLGA absorption is complete shortly after drug release (Fig. **2**; <4 months) [24].

The EVOLVE first-human-use trial compared the safety and efficacy of SYNERGY to the permanent polymer everolimus-eluting PROMUS Element™ stent (Boston Scientific, Marlborough, USA); 2 dose formulations of everolimus were used ("SYNERGY" had an equivalent dose to PROMUS Element; "SYNERGY ½ dose" had half the dose of PROMUS Element) [39]. A total of 291 patients with *de novo* native coronary lesions were enrolled in a 1:1:1 ratio (Table **2**). The primary clinical endpoint was 30-day target lesion failure (TLF: defined as cardiac death, target-vessel related myocardial infarction [TV-MI], or target vessel revascularization [TVR]) and the primary angiographic endpoint was 6-month in-stent late loss. The 30-day TLF rates

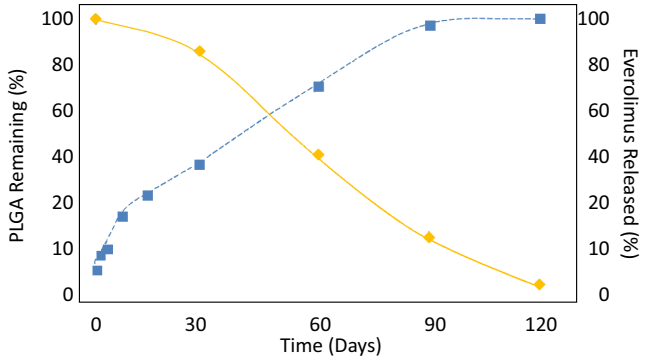

Fig. (2). Kinetics of Drug Release and Polymer Absorption in a pre-clinical porcine model with SYNERGY.

Drug release (yellow) and polymer absorption (blue). Based on Bennett and Dubois, 2013 [121].

were 0%, 1.1%, and 3.1% for patients in the PROMUS Element, SYNERGY, and SYNERGY ½ dose groups, respectively (Table **2**). The 6-month rates of in-stent late loss in both SYNERGY arms were noninferior to PROMUS Element (Table **2**) [39]. After 5 years of follow-up, subjects enrolled in the study continued to have low mortality and MI rates. There were no stent thromboses (ST) reported for any group at 5 years [40].

EVOLVE II was a global, single-blind, randomized, multicenter, noninferiority pivotal trial comparing SYNERGY to the PROMUS Element Plus everolimus-eluting stent (Boston Scientific., Marlborough, USA). A total of 1,684 'morecomer' patients with non-ST elevation MI or stable coronary artery disease were randomized 1:1 to receive SYNERGY or PROMUS Element Plus. At 12 months, the SYNERGY stent was noninferior to PROMUS Element Plus for the primary endpoint of TLF (Table **2**). There were no significant differences in clinically-indicated TVR or definite/probable ST between SYNERGY and PROMUS Element Plus at 1 year [41]. At 2 years, TLF occurred in 8.5% of PROMUS Element Plus patients compared to 9.4% of SYNERGY patients (P=0.66) [42]. Definite/probable ST was infrequent with SYNERGY and, beyond 24 hours, only 1 probable and no definite ST occurred on day 6 in the SYNERGY arm (cumulative rates at 2 years: PROMUS Element 0.8% vs SYNERGY 0.4%; P=0.31) [41, 42].

In the EVOLVE II Diabetes Substudy, patients with diabetes randomized to the SYNERGY arm in the EVOLVE II RCT (263 subjects) were pooled with diabetic subjects enrolled in a single-arm Diabetes study [43]. The primary endpoint of the EVOLVE II Diabetes Substudy, 12-month TLF, was 7.5% (34/451) in SYNERGY-treated patients with diabetes which was significantly less than the performance goal (14.5%; P<0.0001; Table **2**). At 2 years, clinical outcomes were similar to the overall population [44].

SYNERGY has also been tested in an angiographic cohort of patients in EVOLVE II QCA, a prospective, single-arm, multicenter study (N=100; Table **2**) [45]. The primary endpoint, in-stent late loss at 9 months, was 0.23±0.34 mm which was significantly less than the performance goal of 0.40 mm (P<0.0001). There were no deaths; 5 subjects had periprocedural non-Q-wave MI based on the conservative protocol definition (based on CK-MB >3x URL). No patient experienced a definite or probable ST through 12 months [45].

Finally, EVOLVE China assessed SYNERGY versus PROMUS Element Plus in a randomized controlled trial at 12 sites in China (N=412; Table **2**) [46]. The primary endpoint of 9-month in stent late loss in SYNERGY was found to be noninferior to PROMUS Element Plus. Clinical outcomes at 12 months were similar between arms [46].

Two studies are in progress to test the safety of a shorter duration of DAPT. SENIOR (NCT02099617) will compare outcomes in elderly patients receiving either SYNERGY or BMS with DAPT for 1 or 6 months depending on clinical presentation [47]. The primary endpoint is major adverse cardiac and cerebrovascular events at 12 months. EVOLVE Short DAPT study is a prospective, multicenter, single-arm post-approval study designed to assess the safety of 3-month dual antiplatelet therapy in PCI patients at high risk of bleeding (NCT02605447). The study has 2 powered co-primary endpoints assessed between 3 and 15 months post index procedure: the rate of death or MI, and definite/probable ST.

Biomatrix™ Stent

Biomatrix (Biosensors Europe SA, Morges, Switzerland) is one of the first BP-DES developed and tested clinically. The Biomatrix stent elutes biolimus A9 (a sirolimus analogue) from a tubular, laser-cut, stainless steel stent (137μm strut thickness; Table **1**). Biomatrix delivers the antiproliferative drug via a bioabsorbable polylactic acid polymer (PLA; 120 μm thick) coated on the abluminal surface of the stent (Table **1**). The PLA coating is fully absorbed within 6-9 months.

The Biomatrix stent was first tested in humans in the STEALTH trial (STent Eluting A9 BioLimus Trial in Humans), a randomized (2:1), multicenter study of 120 patients comparing Biomatrix to a BMS control. Six-month results from STEALTH demonstrated that for the primary endpoint of in-segment late lumen loss, Biomatrix had significantly less lumen loss compared to BMS (Table **3**). Event-free survival at 6 months was similar between arms (Biomatrix 96.3% vs S-Stent 97.5%; P=0.72) [48].

The STEALTH trial was followed by the larger LEADERS multicenter, noninferiority trial (Limus Eluted from A Durable Versus ERodable Stent Coating) comparing the Biomatrix stent to a sirolimus-eluting permanent polymer DES (SES: Cypher SELECT™, Cordis, Miami Lakes, USA) in 1,707 randomized patients with chronic stable coronary artery disease or acute coronary syndromes. The LEADERS trial demonstrated noninferiority of Biomatrix to SES for the composite primary endpoint of major adverse cardiac events (MACE: cardiac death, MI, or clinically-indicated TVR) at nine months (Table **3**) [49]. Five-year follow-up of the LEADERS trial demonstrated that Biomatrix remained noninferior to SES for MACE and that late ST and associated clinical events were significantly reduced with Biomatrix compared to SES (P=0.005; **Table 3**) [50].

The Biomatrix stent has also been tested in the COMFORTABLE trial (Comparison of Biolimus Eluted from an Erodible Stent Coating with Bare Metal Stents in Acute ST-Elevation Myocardial Infarction) which examined outcomes in 1,161 patients with ST-elevation myocardial infarction (STEMI) treated with either Biomatrix or the Gazelle™ BMS (Biosensors Europe SA, Morges, Switzerland). The primary endpoint for this randomized, multicenter study was MACE (cardiac death, TV-MI, and ischemia-driven TVR) at one year and was significantly lower with Biomatrix compared to BMS (**Table 3**). Biomatrix also demonstrated significantly less definite ST compared to BMS at 1 year [51]. MACE rates at 2 years were significantly lower with Biomatrix than with BMS (5.8% vs 11.9%; P<0.001) [52].

Nobori and Ultimaster™ Stents

Nobori Stent

The Nobori stent (Terumo Corporation, Tokyo, Japan) is a biolimus A9-eluting stent made of 316L stainless steel with

Table 3. Summary of clinical trials for the Biomatrix biolimus-eluting bioabsorbable polymer stent.

Trial	Control	# of patients/study design	Results
STEALTH 6-month results (2005) [116]	BMS	D*e novo* coronary lesions <24mm in length, diameter ≥2.7mm to ≤3.7mm 120 patients randomized 2:1; double-blind; multicenter	**1° endpoint:** LLL at 6 months: Biomatrix 0.14mm±0.45mm vs BMS 0.40mm±0.41mm; *P*=0.004 **2° endpoint:** Similar event free survival (Biomatix 96.3% vs BMS 97.5%; *P*=0.72) and TLR (Biomatix 3.9% vs BMS 7.7%; *P*=NS) in both groups
LEADERS 9-month results(2008) [49]; LEADERS 5-year results (2013) [50] NCT00389220	SES	Patients with chronic, stable CAD or ACS; RVD 2.25mm to 3.5mm 1,707 patients randomized 1:1; multicenter; noninferiority	**1° endpoint:** MACE at 9 months: Biomatrix 9% vs SES 11%; $P_{noninferiority}$=0.003, $P_{superiority}$=0.39) **2° endpoints:** 9-month in-stent %DS Biomatrix 20.9% vs SES 23.3%; $P_{noninferiority}$=0.001, $P_{superiority}$=0.26) 5-year MACE Biomatrix 22.3% vs SES 26.1%; $P_{noninferiority}$<0.0001, $P_{superiority}$=0.07) Very late definite ST (1 to 5 years): Biomatrix 0.7% vs SES 2.5%; RR: 0.26 [CI: 0.10 to 0.68], *P*=0.003)
COMFORTABLE 1-year results (2012) [51]; 2-year follow-up (2014) [52] NCT00962416	BMS	1,161 patients with STEMI randomized 1:1; multicenter	**1° endpoint:** 1-year MACE: Biomatrix 4.3% vs BMS 8.7%; *P*=0.004 **2° endpoints:** 1-year Definite ST with Biomatrix 0.9% vs BMS 2.1%; *P*=0 .10 13-month in-stent %DS Biomatrix 12.0mm±7.2mm vs BMS 39.6mm±25.2mm; *P*<0.001 2-year MACE Biomatrix 5.8% vs BMS 11.9%; *P*<0.001
e-Biomatrix Registry [117] NCT01289002 and NCT01254487	N/A	Consists of 2 registries: e-BioMatrix PMS N= 1,106 patients; and e-BioMatrix PMR N=4,453 patients	**1° endpoint:** 12-month MACE was 4.5% **2° endpoints:** 2-year MACE was 6.8% (cardiac death 1.5%, MI 2.4%, TVR 4.3%). ST occurred in 0.8% of patients

Abbreviations: BMS = bare metal stents; LLL = late lumen loss; TLR = target lesion revascularization; NS = non-significant; RVD = reference vessel diameter; CAD = coronary artery disease; ACS = acute coronary syndrome; SES = sirolimus-eluting stent; ST = stent thrombosis; %DS = percent diameter stenosis; MACE = major adverse coronary event; TV-MI = target-vessel myocardial infarction; TVR = target-vessel restenosis.

a strut thickness of 120 μm. The stent is coated only on the abluminal surface with a 20 μm thick bioabsorbable PLA polymer layer that fully dissolves in 6–9 months (Table **1**). The Nobori biolimus-eluting stent (Terumo Corporation, Tokyo, Japan) has been tested extensively (summarized in Table **4**).

Ostojic *et al.* performed the first feasibility study (Nobori Core) comparing Nobori to a SES (Cypher) in 107 patients. The study showed lower MACE in the Nobori group at 12 months [53]. In the NOBORI 1 trial (phases 1 and 2), Nobori was compared to a paclitaxel-eluting stent (PES; TAXUS™ Express and TAXUS Liberté™, Boston Scientific, Marlborough, MA) and was noninferior to PES for the primary endpoint of 9-month in-stent late loss [54]. Five-year follow-up data revealed no differences between the Nobori stent and PES for the death/MI or TLF (Table **4**) [55]. However, ischemia-driven and non-ischemia-driven TLR were lower in the Nobori group compared to PES. The rates of ST (ARC definite and probable) were also lower in the Nobori group (Nobori 0.0% vs PES 3.2%, *P*=0.014) [55].

Additional randomized studies with Nobori have demonstrated favorable outcomes in patients with *de novo* lesions (NOBORI Japan [56], NEXT [57]), acute or stable angina (COMPARE II [58] and BASKET-PROVE II [59]), an all-comer patient population (SORT OUT V [60]), patients with graft lesions (NEXT [57]) and in patients with long lesions (LONG-DES V [61]) (Table **4**).

A meta-analysis of randomized trials which evaluated the Nobori stent was performed and demonstrated comparable efficacy and safety of the Nobori stent to other tested DES [62]. A total of 9,114 patients randomized to receive the Nobori BP-DES (n=5,080) were compared to control DES [n=4,034: everolimus-eluting stents [EES] n=2,533; SES

Table 4. Summary of clinical trials for the Nobori and Ultimaster biolimus-eluting bioabsorbable polymer stent.

Trial	Control	# of patients/study design	Key Results
NOBORI CORE 9-month results (2008) [53]	SES	107 patients with *de novo* CAD, randomized 1:1, 5 centers	**1° endpoint:** 9-month in-stent LLL Nobori 0.10mm±0.26mm vs SES 0.13mm±0.44mm; *P*=0.660) **2° endpoints:** 12-month MACE Nobori 1.9% vs SES 4.1% 9-month in-stent % diameter stenosis for Nobori 13%±10% vs SES 20%±12%; *P*=0.002
NOBORI 1 Trial – Phase 1 9-month results (2007) [54]	PES (TAXUS Express)	120 patients with native CAD, prospective, controlled, noninferiority, randomized 2:1, 29 centers	**1° endpoint:** 9-month in-stent LLL with 0.15mm±0.27mm vs PES 0.32mm±0.33mm; *P*=0.006 0% ST for both groups
NOBORI 1 Trial - Phase 2 9-month results (2009) [118]	PES (TAXUS Liberté)	243 patients with native CAD, prospective, controlled, noninferiority, randomized 2:1, 29 centers	**1° endpoint:** 9-month in-stent LLL Nobori 0.11mm±0.30mm vs PES 0.32mm±0.50mm; $P_{noninferiority}$<0.001, $P_{superiority}$=0.001 **2° endpoints:** 9-month MACE Nobori 4.6% vs PES 5.6% ST rate Nobori 0% vs PES 4.4%
NOBORI 1 Trial – Phases 1 & 2 5-year results (2015) [55]	PES	363 patients with native CAD, prospective, controlled, noninferiority, randomized 2:1, 29 centers	**1° endpoint:** 5-year TLF Nobori 9.2% vs PES 10.4% **2° endpoints:** TLR Nobori 6.3% vs PES 16.0%) Def/prob ST Nobori 0.0% vs PES 3.2%; *P*=0.014
NOBORI Japan 9-month results (2012) [56]	SES	335 patients with *de novo* lesions in up to2 native coronary arteries, controlled, randomized 3:2, 15 centers in Japan	**1° endpoint:** Freedom from TVF Nobori 92.6% vs SES 93.8%; $P_{noninferiority}$<0.001 **2° endpoints:** 9-month in-stent LLL Nobori 0.12mm±0.30mm vs SES 0.14mm±0.34mm 9-month TLR Nobori 0.5% vs 3.9%; *P*=0.04 0% def/prob ST for both groups
SORT OUT V 9-month results (2013) [60] NCT01254981	SES	1,229, all-comers, noninferiority, randomized 1:1, 3 sites	**1° endpoint:** 9-month MACE Nobori 4.1% vs SES 3.1%; $P_{noninferiority}$=0.06 **2° endpoint:** 9-month definite ST Nobori 0.7% vs SES 0.2%; *P*=0.03
COMPARE II 1-year results (2013) [119]; 3-year results (2015) [58] NCT01233453	EES	2,707 patients with RVD between 2.0mm and 4.0mm, prospective, controlled, noninferiority, randomized 2:1, 12 sites	**1° endpoint:** 1-year MACE Nobori 5.2% vs EES 4.8%; $P_{noninferiority}$ <0.0001 **2° endpoints:** 1-year def/prob ST Nobori 0.8% vs EES 1.0%; *P*=0.58 3-year MACE Nobori 11.9% vs EES 11.1%; *P*=0.57 3-year ST Nobori 1.2% vs EES 0.8%; *P*=0.33
NEXT trial 1-year results (2013) [57] NCT01303640	EES	3,235 patients with native and graft vessel disease scheduled for PCI, prospective, noninferiority, randomized 1:1, multicenter	**1° endpoint:** 1-year TLR Nobori 4.2% vs EES 4.2%; $P_{noninferiority}$ <0.0001, $P_{superiority}$= 0.93 **2° endpoints:** 1-year def ST Nobori 0.25% vs EES 0.06%; *P*=0.18 9-month in-segment LLL Nobori 0.03mm±0.39mm vs EES 0.06mm±0.45mm; $P_{non-inferiority}$ <0.0001, $P_{superiority}$=0.52 (266±43 days after stent implantation)

(Table 4) Contd….

Trial	Control	# of patients/study design	Key Results
BASKET-PROVE II 2-year results (2015) [59] NCT01166685	EES and BMS	2,291 patients with acute or stable CAD, lesions ≥3.0mm in diameter, randomized 1:1:1	**1° endpoint:** 2-year MACE Nobori 7.6% vs EES 6.8% vs BMS 12.7%; Nobori vs EES: $P_{noninferiority}$=0.04, Nobori vs BMS: *P*=0.001 **2° endpoints:** 2-year safety end point (combination of VLST, MI, cardiac death) was similar in all three groups
LONG-DES V trial 9-month results (2014) [61] NCT01186120	EES	500 patients, long (≥25mm) coronary lesions, prospective, randomized 1:1, multicenter	**1° endpoint:** 9-month in-segment LLL Nobori 0.14mm±0.38mm vs EES 0.11mm±0.37mm; $P_{non\text{-}inferiroity}$=0.03, $P_{superiority}$=0.45 **2° endpoint:** MACE Nobori 16.7% vs EES 16.5%; *P*=0.94
INSPIRE 1 1-year results [64]	N/A	1066 patients, all-comers registry, multicenter	**1° endpoint:** Cardiac death, MI, and clinically driven TVR 4.0% patients; the rate was higher in the complex lesions (5.2% vs 2.5%, *P*=0.03)
Nobori 2 2-year results [63] ISRCTN81649913	N/A	3067 patients, all-comers registry, multicenter	**1° endpoint:** 2-year TLF 3.9% at 1 year, 5.1% at 2 years **2° endpoint:** ARC def/prob ST: 0.68% at 1 year, 0.82% at 2 years
CENTURY I 6 months [65] 4 year [66]	N/A	105 patients, Single-arm, prospective, multicenter	**1° endpoint:** late loss at 6 months was 0.04±0.35 mm **2° endpoints:** At 4 years: TLF was 6.7% and ARC definite/probable ST was 0.9%
CENTURY II 9 months [67]; 2 years [120]	EES	1101 patients, prospective, randomized 1:1, multicenter	**1° endpoint:** 9-month freedom from TLF Ultimaster 95.6% vs XIENCE 95.1% ($P_{noninferiority}$<0.0001). **2° endpoint:** 2-year TLF Ultimaster 6.5% vs XIENCE 6.6% ARC definite/probable ST 1.1% in each arm

Abbreviations: BMS = bare metal stents; CAD = coronary artery disease; EES = everolimus-eluting stents; LLL = late lumen loss; MACE = major adverse coronary event; MI = myocardial infarction; PES = paclitaxel-eluting stent; RVD = reference vessel diameter; SES = sirolimus-eluting stent; ST = stent thrombosis; TLF = target lesion failure; TLR = target lesion revascularization; TVR = target-vessel revascularization; VLST = very late stent thrombosis.

n=1,376; PES n=125]. During follow-up (median 11 months), the risk of TVR was similar for Nobori compared to control DES (odds ratio=0.91 [0.57, 1.46], *P*=0.71). There was heterogeneity in the risk estimation of TLR due to the significantly lower risk of TLR with Nobori versus PES (0.32 [0.10, 0.98], *P*=0.046; $P_{interaction}$=0.009) but with no reduction in the risk of TLR with EES or SES (3.2% versus 3.0%; 1.12 [0.74–1.69], *P*=0.59). Overall definite/probable ST (1.40 [0.66, 2.97], *P*=0.39), cardiac death/MI/TVR (1.05 [0.88, 1.25], *P*=0.59), MI (1.13 [0.87, 1.48], *P*=0.37) and death (1.09 [0.81, 1.48], *P*=0.56) were similar in Nobori and the group of control DES patients (and no heterogeneity in outcomes was observed) [62].

'Real-world' experience in the Nobori 2 [N=3,067 [63]] and INSPIRE 1 [Italian Nobori Stent Prospective Registry-1; N=1,066 [64]] registries have demonstrated low rates of TLF (3.9% and 4.0%, respectively). Patients with complex lesions had higher TLF rates (5.2% for complex lesions, 2.5% for non-complex lesions; *P*=0.032) [64].

Ultimaster Stent

The Ultimaster stent, the next generation BP-DES from Terumo, is an 80 μm cobalt chromium stent eluting sirolimus and coated with a 15 μm thick poly (DL-lactide-co-caprolactone) on the abluminal surface (without coating on hinges) (Table **1**). Both drug release and polymer degradation occur within 3-4 months.

The Ultimaster stent has been tested in the small, single-arm CENTURY I (n=105) and the larger, randomized CENTURY II studies. The primary endpoint of the CENTURY I study, angiographic late loss at 6 months, was 0.04±0.35 mm and was significantly lower than late loss in the control arm (Table **4**) [65]. Through 4 years of follow-up, the rate of TLF was 6.7% and ARC definite/probable ST was 0.9% [66]. CENTURY II was a larger-scale, prospective, multicenter, randomized noninferiority trial comparing Ultimaster (N=551) to the XIENCE™ everolimus-eluting permanent polymer stent (EES; Abbott Vascular, Santa Clara, USA; n=550) [67]. The primary endpoint, freedom from TLF at 9 months, was 95.6% with Ultimaster compared to 95.1% with EES ($P_{noninferiority}$<0.0001). At 2 years, TLF occurred in 6.5% of Ultimaster patients and 6.6% of EES patients. Other clinical event rates were similar between arms including ARC definite/probable ST (1.1% in each arm) at 2 years [67]. Additional studies of the Ultimaster Stent are in progress.

Orsiro™ Stent

The Orsiro (Biotronik, Bülach, Switzerland) Sirolimus-eluting stent is made of ultra-thin (60μm) cobalt-chromium

L605 struts covered with an 7.5 μm thick amorphous silicon carbide layer. Sirolimus is released from a biodegradable poly-L-lactic acid (PLLA) polymer, which completely degrades during a period of 12 to 24 months. Preclinical studies have shown similar suppression of neointimal proliferation for Orsiro as compared to the Cypher SES and low inflammatory scores compared to BMS [68].

The Orsiro stent was first tested in 30 patients with single *de novo* lesions [69]. The primary endpoint was 9-month in stent late loss (0.05 ± 0.22 mm). At 1 year, MACE was 10% with no MI or ST [69]. Following the initial feasibility study, the larger BIOFLOW-II trial compared the Orsiro stent with XIENCE Prime™, a permanent polymer EES [70]. A total of 452 patients were randomly assigned 2:1 to treatment with Orsiro (n=298) or EES (n=154 patients). Orsiro was noninferior to EES for the primary endpoint of in-stent late lumen loss at 9 months [70]. TLF was similar at 1 year with no cases of ST in either arm.

BIOSCIENCE was a large randomized, noninferiority trial with minimal exclusion criteria comparing Orsiro with a permanent polymer EES (XIENCE Prime/Xpedition, Abbott Vascular, Santa Clara, USA); 19% of enrolled patients had STEMI [71]. The primary endpoint, 12-month TLF, was a composite of cardiac death, TV-MI, and clinically-indicated TVR. A total of 2,119 patients were randomized to receive either the Orsiro stent (N=1,063 patients) or an EES (N=1,056). Orsiro was found to be noninferior to EES for the primary end point of TLF at 12 months. The rates of definite ST were similar between Orsiro and EES. In the subset of patients with STEMI, Orsiro-treated patients had reduced TLF compared to EES (Orsiro 3.3% vs EES 8.7%; RR=0.38 [0.16, 0,91], *P*=0.02) [71].

The BIOFLOW-III registry was designed to evaluate Orsiro in 'real-world' patients (N=1,356) [72]. The primary endpoint, 12-month TLF occurred in 5.1% of patients in the overall population and in 7.7% of patients with diabetes, 5.8% of patients with small vessels, 1.8% of patients with chronic total occlusion, and 7.2% of patients with acute MI [72].

The Orsiro stent is currently being tested in more complex patient groups.

MiStent™

MiStent (Micell Technologies, Durham, USA) is a thin-strut (64μm) cobalt-chromium stent covered with a bioabsorbable polymer and crystalline sirolimus which controls drug release through 6 months post-implantation without an initial burst (**Table 1**). The polymer is completely absorbed by the tissue within 90 days in an animal model [73]. This stent was initially evaluated in the DESSOLVE I Trial (DES with Sirolimus and a Bioabsorbable Polymer for the Treatment of Patients with De Novo Lesion in the Native Coronary Arteries; NCT01247428) which included 30 patients [73]. DESSOLVE I demonstrated low and stable in-stent lumen late loss and complete strut coverage at 18 months [73]. No ST was observed through 5 years [74].

The subsequent, larger DESSOLVE II trial (NCT01294748) compared the efficacy and safety of the MiStent with a first generation Zotarolimus-eluting stent, Endeavor™ (E-ZES; Medtronic, Santa Rosa, USA) [75]. A total of 184 patients were randomized in a 2:1 fashion with MiStent (n=123) versus E-ZES (n=61). MiStent was superior to E-ZES for the primary endpoint of 9-month in stent late lumen loss (MiStent 0.27±0.46mm vs E-ZES 0.58±0.41mm; *P*<0.001). The proportion of uncovered stent struts assessed by OCT was very low and similar in both groups. Mean neointimal thickness (*P*=0.002) and percent net volume obstruction (*P*=0.003) were significantly lower in the MiStent group at 9 months [75]. Major adverse cardiac events and ST rates were low and comparable between groups through 4 years [74].

A pooled analysis of the DESSOLVE I/II and ISAR-TEST-4 studies examined the performance of MiStent in a propensity-matched comparison (n=102 each arm) versus a permanent polymer EES [76]. In this small *post hoc* analysis, MiStent exhibited lower TLF and TLR through 3 years compared to EES (TLF: MiStent 5.0% vs EES 12.5%, *P*=0.07; TLR: 2.0% vs 8.4%, *P*=0.04) [76].

Longer-term follow-up and larger trials in 'real-world' patients with MiStent are in progress.

Elixir DESyne BD™ Stent

Elixir DESyne BD (Elixir Medical Corporation, Sunnyvale, USA) is an 81 μm thick cobalt-chromium stent eluting novolimus (an active metabolite of sirolimus) from an ultrathin (<3 μm) polylactide-based bioabsorbable polymer which degrades within 6-9 months (Table **1**).

This stent was first tested in the Excella BD trial (NCT0200956) which compared the Elixir DESyne BD Stent to the Endeavor ZES (E-ZES). A total of 146 patients were randomized in a 3:1 fashion. The study met the primary endpoint (angiographic in-stent late lumen loss at 6 months) demonstrating both noninferiority and superiority of Elixir DESyne BD as compared to E-ZES (Elixir DESyne BD 0.12±0.15 mm vs E-ZES 0.67±0.47 mm; $P_{noninferiority}$<0.001). Additionally, in-stent binary restenosis was significantly lower with Elixir DESyne BD compared to E-ZES (0% vs 7.9%; *P*=0.003). At 3 years, the device-oriented composite endpoint (DoCE: cardiac death, TV-MI, and clinically-indicated TLR) was similar in the Elixir DESyne BD and control groups [77].

This initial study was followed by the small EXCELLA II study randomizing Elixir DESyne to E-ZES in a 2:1 fashion (NCT00792753) [78]. The primary endpoint was in stent late lumen loss at 9 months and Elixir DESyne was superior to E-ZES (Elixir DESyne 0.11 ± 0.32 mm vs E-ZES 0.63 ± 0.42 mm, $P_{noninferiority}$<0.0001 and $P_{superiority}$<0.0001)(78). Neither DoCE nor its individual components were significantly different between the bioabsorbable and permanent polymer coated stents. The rate of DoCE at 5 years was significantly lower in the Elixir DESyne cohort compared to E-ZES (HR 0.38 [0.17, 0.83], *P*=0.01) [79]. No differences between groups were found for cardiac death (2.9% vs 4.2%, *P*=0.69), TV-MI (2.9% vs 7.0%, *P*=0.17), or ST (5.0% vs 7.0%, *P*=0.54). Revascularization was significantly reduced with Elixir DESyne BD compared to E-ZES at 5 years (18.7% vs 32.4%, *P*=0.04) [78].

Table 5. Summary of clinical trials for the Orsiro sirolimus-eluting bioabsorbable polymer stent.

Trial	Control	# of patients/study design	Results
BIOFLOW-I Registry [69] NCT01214148	None	First-in-human, single-arm registry of 30 patients with a single *de novo* lesion ≥22 mm, RVD 2.5 - 3.5 mm, and >50% to <90% diameter stenosis were enrolled at two sites	**1° endpoint:** In-stent late loss at 9 mos was 0.05±0.22 mm 1y clinical outcomes: MACE was 10%, no MI or ST
BIOFLOW II [70] NCT01356888	EES	N=452 prospective, multicenter, randomized (2:1), excluded AMI, LM, 3VD, LVEF<30%	**1° endpoint:** In stent late loss at 9 mos: Orsiro 0.10 ± 0.32 vs EES 0.11 ± 0.29 mm $P_{noninferiority}$<0.0001 TLF: Orsiro 6.5% vs 8.0% *P*=0.58 ST: 0 in each arm
BIOSCIENCE [71] NCT01443104	EES	N=2,119; Prospective, multisite, randomized (1:1), single-blind, noninferiority; 9 European sites, unselected patient population	Primary Endpoint: 12-mo TLF occurred in 6.5% vs 6.6% of subjects in the Orsiro and XIENCE groups ($P_{noninferiority}$<0.0004) No significant differences were noted in rates of definite ST (0.9% vs 0.4%, *P*=0.16). STEMI patients 12-mo TLF 3.3% vs 8.7%, *P*=0.024
BIOFLOW III Registry [72] NCT01553526	None	N=1356 prospective, multicenter, all-comers	**1° endpoint:** TLF at 12 months: 5.1%

Abbreviations: 3VD = 3 vessel disease; AMI = acute myocardial infarction; EES = everolimus-eluting stents; LM = left main; LVEF = left ventricular ejection fraction; MI = myocardial infarction; PES = paclitaxel-eluting stent; RVD = reference vessel diameter; SES = sirolimus-eluting stent; ST = stent thrombosis; STEMI = ST-elevation myocardial infarction; TLF = target lesion failure; TLR = target lesion revascularization; TVR = target-vessel revascularization.

TIVOLI™ Stent

TIVOLI (Essen Technology Beijing Co. Ltd., Beijing, China) is a bioabsorbable polylactic-co-glycolic acid (PLGA) polymer-coated sirolimus-eluting stent with a strut thickness of 80 μm (**Table 1**).

Xu and colleagues evaluated Tivoli in a 324 patient RCT (TIVOLI n=168 vs E-ZES n=156) [80]. The primary endpoint, in-stent late lumen loss at 8 months, was superior in Tivoli compared to E-ZES (TIVOLI 0.25 ±0.33 mm vs E-ZES 0.57 ±0.55 mm; *P*<0.0001). The 8-month rate of in-stent binary restenosis was also significantly reduced with TIVOLI (2.9% vs 8.6%; *P*=0.02). At 2 years, TLR was significantly reduced in patients receiving the TIVOLI stent compared to E-ZES (4.2% vs 9.6%; *P*=0.0495) with no significant difference in MACE (cardiac death, MI or TVR) rates between groups (6.6% vs 10.9%; *P*=0.16) [80].

The TIVOLI stent has also been evaluated in the I-LOVE-IT 2 trial; a prospective, multicenter, noninferiority study based in China (NCT01681381) which included 2,737 patients randomized 2:1 to TIVOLI (n=1,829) compared to the Firebird stent, a durable polymer SES (MicroPort, Shanghai, China; n=908) at 32 centers [81]. The primary endpoint, 12-month TLF, occurred in 6.3% of Tivoli patients vs 6.1% of SES patients ($P_{noninferiority}$=0.0002). The individual components of TLF were not significantly different between groups including cardiac death (0.7% vs 0.6%, *P*=0.62), TV-MI (3.6% vs 4.3%, *P*=0.39), and TLR (2.6% vs 2.2%, *P*=0.50). The rates of ST were also similar between cohorts (0.4% vs 0.6%, *P*=0.55).

EXCEL™ Stent

The EXCEL Stent (JW Medical System Ltd., WeiHai, Shangdong, China) is a sirolimus-eluting stent coated with a bioabsorbable polylactic acid polymer. The stent platform is a laser cut, 316L stainless steel with a strut thickness of 119 μm (**Table 1**). The 10-15 μm thick coating is absorbed completely in 6–9 months in animal models.

The RESOLVE study (NCT00713557) demonstrated noninferiority of the EXCEL stent to its comparator Firebird or Firebird II, a durable polymer coated SES (Microport Co Ltd., Shanghai, China) for the primary endpoint of MACE (all death, MI, TLR at 1 year) in STEMI patients (82). A total of 1,192 STEMI patients were randomized 1:1 to receive the EXCEL stent (n=596) or the SES (n=596). MACE at 1-year was 12.4% in the EXCEL group as compared to 13.3% in the control group ($P_{noninferiority}$=0.001). Late ST (oc-

curring >30 days) was lower in EXCEL-treated patients versus SES (0.7% vs 2.2%, *P*=0.03) [82].

The 'real-world' CREATE registry (NCT00331578) enrolled 2,077 patients treated with the EXCEL stent [83]. At 5 years, clinical outcomes were low: cardiac death 3.0%, non-fatal MI 1.5%, TLR 3.7%, and overall MACE 7.4%. The 5-year rates of definite/probable ST at and definite ST from 1 to 5 years were 1.1% and 0.3%, respectively. Patients with or without clopidogrel treatment after six months had similar clinical outcomes in a landmark analysis of a propensity score-matched cohort [83].

Additionally, the EXCEL stent was found to be superior to the polymer-free sirolimus-eluting (PF) and probucol-eluting stents (Real Dual drug-eluting stents; Dual DES) in the DKPLUS-Wave 1 randomized trial [84]. A total of 1,346 patients with *de novo* CAD were randomized to either the EXCEL or Dual DES. The rate of the primary endpoint, TVR at 12 months, was 3.5% in the EXCEL group and 13.9% in the Dual DES group (*P*=0.001). ST at 12 months was 0% in the Dual DES group and 1.2% in the EXCEL group (EXCEL vs Dual DES, *P*=0.50) [84].

The next generation of the EXCEL stent, EXCEL II, is a thinner strut (88 μm) cobalt chromium PLA-coated sirolimus-eluting stent was tested in the first-human-use CREDIT-I study [85]. A total of 45 patients were enrolled and evaluated up to 12 months post implantation. No MACE events (cardiac death, MI or TLR) occurred within the year [85].

Inspiron™ Stent

The Inspiron sirolimus-eluting stent (Scitech Medical, Aparecida de Goiânia, Goiás, Brazil) consists of a L-605 cobalt-chromium alloy platform with a 75 μm strut thickness and a Xμm thick abluminal, bioabsorbable coating which dissolves within 30 days (**Table 1**) [86]. The INSPIRON-I trial (NCT01093391) compared the Inspiron Stent with a BMS in 57 patients, randomized in a 2:1 fashion. The primary endpoint was in-segment late loss at 6 months and was reduced in the Inspiron group compared to BMS (0.19 ± 0.16 mm vs. 0.58 ± 0.4 mm, respectively; *P*<0.001) [87]. After 4 years, MACE was lower with Inspiron (7.9% vs. 23.5%, *P*=0.11), the rates of death and MI were similar between groups but the rate of TLR was lower with the Inspiron Stent as compared to BMS (0.0% vs. 23.5% respectively, *P*=0.02) [86].

The DESTINY trial (NCT01856088) is a prospective, multicenter, randomized study comparing Inspiron with Biomatrix Flex [88]. A total of 170 patients with 1 or 2 *de novo* lesions were randomized in a 2:1 fashion (Inspiron Stent:Biomatrix Stent). The Inspiron Stent demonstrated noninferiority with regards to in stent late loss at 9 months compared to the Biomatrix Stent (Inspiron 0.20 ± 0.29 mm vs Biomatrix 0.15 ± 0.20 mm; $P_{\text{noninferiority}}$ <0.001). At one year, the rates of death (0.9% vs 0.0%), MI (4.4% vs 7.4%), and TVR (2.7% vs 3.7%) were low and similar between groups [88]. An additional all-comers single-arm registry (Inspiron Registry) enrolled 470 patients who exhibited a 300 day MACE rate of 8.1%, TLR of 5.4%, and ST of 0.4% with no cases after 30 days [89]. Long-term follow-up of the DESTINY trial and enrollment in a 'real-world' registry are in progress.

FIREHAWK™ Stent

The FIREHAWK stent (Microport Medical, Shanghai, China) is an 86 μm thick, cobalt chromium, biodegradable polylactic acid polymer coated DES releasing sirolimus. Drug and polymer are poured into abluminal grooves located on the outer surface of the struts (average rapamycin dosage 3 μg/mm stent) [90]. FIREHAWK was first tested in the 21 patient FIREHAWK trial. The primary endpoint was MACE at 30 days (cardiac death, MI, TLR); there were no MACE or ST events through 13 months of follow-up.

The Target I trial compared FIREHAWK to a permanent polymer EES (XIENCE V) [91]. A total of 458 patients were randomized. Nine-month in-stent late lumen loss, the primary endpoint, was found to be noninferior in FIREHAWK stents compared to EES (0.13 ± 0.24 mm vs 0.13 ± 0.18 mm, $P_{\text{noninferiority}}$<0.0001). At 12 months, cardiac death (0.4% vs 0.0%), TV-MI (1.3% vs 1.7%), TLR (0.4% vs 0.4%), and TLF (2.2% vs 2.2%) were similar between groups; no ST were reported in either arm [91]. Three-year in-stent late lumen loss and vascular healing (as assessed by OCT) were similar between groups [92]. The long lesion subgroup of TARGET I enrolled an additional 50 patients receiving either a 33 or 38 mm stent. The primary endpoint, 9-month in stent late loss was 0.16 ± 0.16 mm with no death or ST within a year and 2 patients experiencing a MI [93]. Similar results were found in the Target II trial which was a prospective single-arm registry enrolling 730 patients. At one year, TLF was 4.4% and only 1 definite/probable ST was observed I Firehawk-treated patients [94]. Long-term follow-up of the Target II registry is in progress.

Combining the TARGET I and II trials, Gao *et al* evaluated 12-month TLF compared to a performance goal [95]. A total of 1,007 patients were included in this analysis and TLF at 1 year was 3.9% which was significantly lower than the prespecified performance goal of 9.0%. At 2 years, TLF was 4.6% which was composed of cardiac death 0.8%, TV-MI 2.9%, and clinically-indicated TLR 1.2% and definite/probable ST rate 0.1% [95].

Yukon Choice PC™ Stent

The Yukon Choice PC stent scaffold (Translumina GmbH, Hechingen, Germany) consists of a microporous stainless steel stent surface abluminally coated with sirolimus and a PLA biodegradable polymer. Mehilli *et al.* first compared this sirolimus-eluting BP-DES with a polymer-free (PF) stents and a permanent polymer sirolimus-eluting stent (SES; Cypher) in the ISAR-TEST 3 study (NCT00350454) [96]. More than 600 patients were randomized to BP-SES (n=202), SES (n=202), and PF (n=201). The primary endpoint was mean late lumen loss at 6 to 8-months and was 0.17±0.45mm in the Yukon Choice PC stent group, 0.23±0.46mm with SES, and 0.47±0.56mm in PF stent-treated patients. As such, Yukon Choice PC met the noninferiority criteria compared to SES ($P_{\text{noninferiority}}$<0.001); however, the PF stent did not ($P_{\text{noninferiority}}$<0.94)(96). At 1 year, death occurred in 2.0% of patients in each group and ST oc-

curred in 1.0%, 2.0%, and 1.5% of Yukon Choice PC, SES, and PF patients, respectively [96].

The Yukon Choice PC stent (N=1,299) was then evaluated against a permanent polymer EES (XIENCE V; n=652) or SES (Cypher; n=652) in ISAR-TEST-4 (Intracoronary Stenting and Angiographic Results: Test Efficacy of 3 Limus-Eluting Stents; NCT00598676) a prospective, randomized, open-label trial [97]. The primary endpoint was the composite of cardiac death, TV-MI, and TLR; the Yukon Choice PC Stent was noninferior to the combined permanent polymer DES group for the primary endpoint at 12 months (BP-DES 13.8 vs DES 14.4%; $P_{\text{noninferiority}}$=0.005) [97]. Cardiac death, TV-MI, TLR, and ST were similar in both groups at 12 months [97]. Between 6 and 8 months, angiographic outcomes were similar (in-stent late lumen loss BP-DES 0.24±0.6mm vs DES 0.26±0.5mm, *P*=0.49; in-segment binary restenosis (11.6% vs 11.8%, *P*=0.85) [98]. Three-year outcomes were not significantly different between the BP-DES and permanent polymer DES with regard to the primary endpoint (BP-DES 20.1% vs 20.9% DES, *P*=0.59). Rates of definite/probable ST were also similar in both groups at 3 years (1.2% vs 1.7%, *P*=0.32) [99]. While not statistically significant, the SES group displayed numerically higher rates of device-related adverse events as compared to the Yukon Choice PC arm or the EES arm at 5 years [100].

BuMA™

The BuMA stent (SINOMED, Beijing, China) is a stainless steel 100 μm thick stent coated conformally with 2 layers: an electro-grafting base layer (poly [n-butyl methacrylate] coating) and a biodegradable PLGA drug carrier [101]. The BuMA stent was compared to the EXCEL stent in the randomized (1:1) 80 patient single-center BuMA OCT noninferiority RCT study (NCT01752582) [101]. The primary endpoint was OCT-evaluated stent strut coverage at 3 months. Compared to the EXCEL stent, stent strut coverage was higher in the BuMA arm compared to EXCEL (94.2% vs 90%, $P_{\text{noninferiority}}$<0.0001). The proportion of malapposed struts and neointimal thickness were similar between stents. At 3 months, there were no cardiac deaths or STs but TV-MI was 7.5% in each group [101].

The BuMA and EXCEL stents were then compared in the larger, all-comers multicenter PANDA III trial (NCT02017275) [102]. A total of 2,348 patients were enrolled and randomized (1:1, n=1,174 in each arm); the primary endpoint of 1 year TLF (cardiac death, TV-MI, ID-TLR) with BuMA was noninferior to the EXCEL stent (6.4% in each group, $P_{\text{noninferiority}}$=0.0003). The individual components of TLF were similar between arms. The rate of 1-year definite/probable ST was significantly reduced in the BuMA arm (0.5% vs 1.3%, *P*=0.048); this difference may be influenced by the difference in polymer degradation time (EXCEL 9 months vs BuMA 3 months, Table **1**).

The second generation BuMA stent, BuMA Supreme, is currently being tested in the PIONEER global clinical program including the PIONEER, PIONEER II, and PIONEER US-Japan studies.

Svelte™

The Svelte stent (Svelte Medical Systems, New Providence, USA) is integrated with its delivery system and is made of an 81 μm cobalt chromium platform and coated with a 6 μm thick bioabsorbable amino acid drug carrier which elutes sirolimus [103]. The Svelte stent was designed to facilitate direct stenting using a transradial approach. The Svelte stent was first tested in the Direct study, a single-arm multicenter study with a primary angiographic endpoint of 6-month in stent late lumen loss and an efficacy endpoint of 6-month TVF (cardiac death, TV-MI, clinically-indicated TVR). At 6 months, in stent late lumen loss was 0.22 ± 0.27 mm; TVF (non-TLR TVR) occurred in 2 patients [103]. The SPEED registry assessed experienced compared to inexperienced operators and showed that experience demonstrably improved in device success [104].

Direct II was a small randomized study comparing Svelte (n=108) to Resolute Integrity (R-ZES; n=51) [105]. The primary endpoint of in stent late lumen loss at 6 months in the Svelte stent was noninferior to R-ZES (0.09 ± 0.31 mm vs 0.13 ± 0.27 mm, $P_{\text{noninferiority}}$=0.001) (105). TVF at 1 year was 6.5% vs 9.8% (*P*=0.52) [105].

The Svelte stent is currently being tested in the OPTIMIZE pivotal randomized clinical trial (compared to currently available DES).

BioMime™

The BioMime stent (Meril Life Science, Vapi, India) is an 65 μm thick cobalt-chromium stent eluting sirolimus from an ultrathin (2 μm) Poly L Lactide/ Polylactic co-glycolic acid -based bioabsorbable polymer of which three-quarters degrades within 2 months (Table **1**).

This stent was evaluated in the first-human-use meriT-1 study (NCT01507519) which included 30 patients [106]. The study demonstrated median 8-month in-stent late lumen loss was 0.15 mm [0.09, 0.33]. At 12 months, no cardiac deaths, MI, TLR, or ST [106].

Currently, the BioMime stent is being tested in the single-arm MeriT-II (NCT02406326) study, the larger randomized meriT-V trial (compared to an everolimus-eluting permanent polymer DES; NCT02112981) and an all-comers registry (NCT02398955).

META-ANALYSES

There have been multiple meta-analyses comparing BP-DES to permanent polymer-coated DES. The most comprehensive meta-analysis performed by Lupi *et al* included 20 studies and 20,005 patients [107]. The durable polymer DES control groups included both the first- and second-generation DES. Median clinical follow-up of the included studies was 1 year, with 7,142 coronary lesions having angiographic follow-up at 6-9 months. Compared with the DES group, the BP-DES treated patients had significantly lower in-stent and in-segment late loss (*P*<0.001). BP-DES nearly halved the rate of late ST rate in comparison to DES. When the comparators were grouped into first- and second-generation DES, late ST occurred less often with BP-DES compared to

first-generation DES (OR 0.43 [0.24, 0.79], *P*=0.006); whereas the risk of late ST was similar between BP-DES and second-generation DES (0.95 [0.30, 3.02], *P*=0.93). There were no significant differences between BP-DES and either first- or second-generation DES for overall death, MI, or acute/subacute ST. Other meta-analyses have found similar results [62, 107-112]; three meta-analyses have shown significant benefits for BP-DES in terms of late, and especially very late, ST. In all of these meta-analyses, newer BP-DES (SYNERGY, Ultimaster, Tivoli, Svelte) were not included.

Newer BP-DES with thinner struts and reduced polymer load have the potential to show even greater benefits with regards to clinical outcomes including late and very late ST [107]. This is supported by recent 'real-world' experience in the Swedish Coronary Angiography and Angioplasty Registry (SCAAR) where SYNERGY reported the lowest rate of definite ST compared to all other DES analyzed [113].

CONCLUSION

Abluminal, BP-DES appear noninferior to the first- and second-generation permanent polymer-coated DES. Studies with long-term follow up suggest that there may be less ST for BP-DES as compared to permanent polymer DES. Additional trials and longer follow-up is needed to fully elucidate the respective clinical indications of these devices in comparison to their permanent polymer counterparts. The ability to safely reduce or interrupt DAPT with BP-DES may reduce bleeding risk and cost if confirmed in adequately powered clinical studies.

ABBREVIATIONS

ACS	=	Acute coronary syndrome
BMS	=	Bare metal stents
BP	=	Bioabsorbable polymer
BP-DES	=	Bioabsorbable polymer drug-eluting stents
CAD	=	Coronary artery disease
DES	=	Drug-eluting stents
EES	=	Everolimus-eluting stent
MI	=	Myocardial infarction
PCI	=	Percutaneous coronary intervention
PES	=	Paclitaxel-eluting stent
PF	=	Polymer free
SES	=	Sirolimus-eluting stent
STEMI	=	Stent thrombosis elevation myocardial infarction
TLF	=	Target lesion failure
TLR	=	Target lesion revascularization
TVF	=	Target vessel failure
TVR	=	Target vessel revascularization

CONFLICT OF INTEREST

Dawkins K, Huibregtse B, Hou D, & Roy K are full-time employees of Boston Scientific.

ACKNOWLEDGEMENTS

Declared none.

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