Review Article

Title: Are Biodegradable Third Generation Drug Eluting Stents the Answer to Instent Restenosis

Abstract: The third generation biodegradable Drug Eluting Stent (DES) are being evaluated and being introduced in clinical practice. They have been designed to overcome limitations associated with durable polymer and a persistent metallic stent scaffold which could be related to late target lesion revascularization (TLR) and very late stent thrombosis (VLST). Although a recent pooled data analysis found that biodegradable polymer stents were superior for TLR and VLST compared with first generation Sirolimus Eluting Stent (SES), superiority has not been demonstrated against second generation Everolimus eluting stents (EES) and is yet to be conclusively proven randomized trials. This paper reviews the key features, recent trial data, and future directions of the third generation of DES technology including stents with fully biodegradable scaffolds, stents with biodegradable polymer, and polymer free stents.

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Key Words: Biodegradable; Coronary; Stents.

ABBREVIATIONS:

PLLA, poly-L-lactic acid;
PDLLA, poly-D,L-lactide;
PLGA, polylactic-co-glycolic acid;
PLA, polylactide derivative.
BR, binary restenosis;
DD, non-polymeric dual DES;
FIM, first-in-man;
LLL, in-stent late lumen loss (mm);
MACE, major adverse cardiovascular events;
NP, non-polymeric DES;
ST, definite/probable stent thrombosis;
TLF, target lesion failure;
PP, permanent polymer;
BP, biodegradable polymer;
SD, standard dose;
NS, not significant.

PLA,poly-L-lactide;
PLC, 75:25 poly-L-lactide-co-caprolactone;
PLGA, 50:50 poly-D,L-lactide-co-glycolide;
PLLA, poly-L-lactic acid;
PVP, polyvinyl pyrrolidone;
USS, uncovered stent struts;
NS, not significant.
RCT, Randomized control trial

INTRODUCTION

Interventional cardiology is currently in the process of refining the third generation of DES technology. It incorporates a broad mix of technologies ranging from incremental improvements in existing stent scaffolds, antiproliferative coats, polymer free, biodegradable polymer coated scaffolds, fully biodegradable scaffolds, newer nano-material coatings and stem cell therapy.

Compared with first generation DES, the second generation stents have advantages like having thinner struts and increased flexibility, more biocompatible polymers and new generation antiproliferative agents [1,2]. Even the second generation DES are not free from disadvantages as the persistent presence of a stent scaffold or polymer beyond its short-term function is related to late target lesion revascularisation (TLR) and very late stent thrombosis (ST). The two year pooled results from the SPIRIT II, III, IV and COMPARE trials prove that Everolimus eluting stents (EES) have a superior safety and efficacy profile compared with first generation paclitaxel eluting stents (PES) because of lower rates of myocardial infarction (MI) (RR, 0.57; 95% CI, 0.45–0.73), ST (RR, 0.35; 95% CI, 0.21–0.60) and ischemia driven TLR(RR, 0.59;95%CI, 0.47–0.73) [3-5]. Neither EES nor zotarolimus eluting stents (ZES) have demonstrated superior clinical outcomes to first generation sirolimus eluting stents (SES) [6-9].

Major concern with second generation DES is very late stent thrombosis (VLST) rates beyond one year. The pathogenesis of late restenosis and stent thrombosis in second generation DES include neointimal hyperplasia, persistent inflammation of the vessel wall, in-stent neoatherosclerosis, uncovered struts and/or polymers with secondary stent malapposition and stent fracture [10-13].

The Bern-Rotterdam cohort followed 4212 patients treated with EES for four years and reported a definite or probable ST rate of 6.3% and a VLST rate of 2.0%. Although the 2% VLST rate is stastically significant and lower than the corresponding VLST rate for first generation PES (4.0%, $p < 0.0001$) and SES (2.8%, $p = 0.02$), it represents an ongoing 0.67% annual risk of ST after one year [14]. The HORIZONS-AMI [15] trial at three years, LEADERS [16] and SYNTAX [17, 18] trials at four years and the SIRTAX LATE [80] trial at five years demonstrated similar annual VLST rates of 0.6–0.85% for PES and SES.

Long term efficacy in terms of repeat revascularization rates, TLR incidence rate and late lumen loss (LLL) are other major limitations of second generation DES. Four year repeat revascularization rates of up to 28.8% have been reported for first generation PES in high risk patients undergoing PCI for left main stem and triple vessel disease [17]. Five year SPIRIT III data of 669 low risk patients treated with EES revealed an annual TLR incidence rate of 1.3% beyond one year with TLR increasing from 3.5% at one year to 8.6% at five years [19]. Second generation DES are also associated with a persistent increase in late lumen loss (LLL). In SPIRIT II EES cohort the mean in-stent LLL increased from 0.17±0.32mmto 0.33±0.37mm [20] while in the ISAR-4 EES cohort [21,22] it increased from 0.14±0.41mm to 0.29±0.51mm between six and 24 months interval. Additional limitations with current generation DES include restrictions to non-invasive imaging with CT and MRI, difficulties with future surgical and transcatheter revascularization, long term disruption of native vascular fluid dynamics and vasoreactivity, chronic inflammation, delayed endothelialization and the need for six or more months of dual antiplatelet therapy (DAPT) [23-28].

The ultimate dream would be to develop a stent system which has best combination of metallic alloys and/or polymers with all desirable properties favourable combination-drug eluting capabilities. This paper reviews the key features, recent trial data, and future directions of the third generation of DES technology including stents with fully biodegradable scaffolds, stents with biodegradable polymer, and polymer free stents.

Fully Biodegradable Scaffolds

Fully biodegradable scaffolds aim to combine the advantages of the first and second generation of DES while additionally targeting their disadvantages and limitations. They provide a stable vascular scaffold in the short term, thereby minimizing constrictive remodeling , preventing restenosis due to vascular recoil, and loose intimal dissection flaps [29-31]. The fully biodegradable scaffolds score over the older generation stents by reducing the limitations including but not limited to long-term in-stent restenosis and stent thrombosis associated with a permanent metallic scaffold.

They have been associated with the development of a homogenously thickened neointima, suggestive of a thicker, more stable fibrous cap [12], potential for expansive arterial remodeling and a return of normal vasomotion [32], theoretical decrease in paradoxical peri-stent vasoconstriction[33], facilitating improved non-invasive CT and MRI imaging, wider future transcatheter and/or surgical revascularization options, freedom from jail branch obstruction, less impediment to vascular growth in the pediatric population and limit the need for prolonged DAPT [32,34,45].

Metallic biodegradable scaffolds can be magnesium or iron based. Magnesium has a shorter degradation period of four to 12 months compared with four or more years for iron [37,38]. A polymer coat is used to contain and control the release of an antiproliferative agent. These are designed to biodegrade by Krebs cycle into carbon dioxide and water over six to 24 months, after the antiproliferative agent has been fully released [33,36].

ABSORB BVS

ABSORB A and ABSORB B : The bioabsorbable everolimus-eluting stent system ABSORB BVS (Abbot Vascular, Santa Clara, CA, USA). The ABSORB BVS stent is based on a poly-L-lactic acid (PLLA) scaffold with a poly-D,L-lactide (PDLLA), everolimus impregnated polymer coat. The device has been assessed in two small single arm industry sponsored non-randomized trials, ABSORB A and ABSORB B. Both studies were restricted to lesions with a RVD of 2.5–3mm and length less than 14mm. Patients received a minimum of six months DAPT post stent insertion.

Five year data from the ABSORB A trial, a 30 patient study using the first iteration BVS 1.0 [34,39,40], revealed a MACE rate of 3.4%, representing a single non-q wave MI at 46 days, and TLR and ST rates of 0%. LLL increased to 0.48±0.28mm at 24 months. Mean in-stent LLL was 0.43±0.37mm at six months which was largely attributed to scaffold recoil.
Optical coherence tomography (OCT) at 24 months showed a smooth endoluminal lining appearance with virtually indiscernible struts suggested almost complete stent biodegradation.
Intravascular ultrasound (IVUS) results suggested expansile arterial remodeling with the minimum lumen area (MLA) increasing from 3.92±0.98mm2 to 4.34±1.74mm2 from six to 24 months. There was evidence of a return of normal arterial vasomotion at two years with five of nine patients demonstrating arterial vasodilatation on acetylcholine administration [41].

ABSORB B trial assessed the BVS 1.1 stent, a revision of the BVS 1.0 designed to improve radial support beyond six months and allow stent storage at room temperature in 100 patients [36]. The 24 month MACE rate was 9%, comprising a TLR rate of 6% and non-q-wave MI rate of 3%. There were no ST events [40]. LLL increased from 0.19±0.18mm at six months to 0.27±0.25mm at 12 months and was stable at 0.27±0.20mm out to 24 months [42]. Between six and 24 months, mean lumen area by IVUS increased from 6.36mm2 to 6.85mm2 with a small increase in MLA from 5.12mm2 to 5.13mm2. Vasoreactivity was demonstrated at 12 months on administration of methylergonovine and acetylcholine [40].

ABSORB EXTEND & ABSORB II : Two larger trials with less restrictive inclusion criteria are currently enrolling patients. ABSORB EXTEND is a 1000 patient multinational single arm trial and ABSORB II is a 500 patient RCT comparing the ABSORB BVS against the second generation DES, Xience PRIME (Abbot Vascular, Santa Clara, CA, USA) [43,44]. Six month data from the first 200 patients enrolled in the ABSORB EXTEND trial revealed a MACE rate of 2.5% comprising an MI rate of 2% and TLR rate of 0.5% [45].

Despite significant recent interest in biodegradable scaffolds, clinical and trial experience is limited. Only two devices, the bioabsorbable everolimus-eluting stent system ABSORB BVS (Abbot Vascular, Santa Clara, CA, USA) and the Igaki-

Tamai stent (Kyoto Medical Planning Co., Kyoto, Japan) have had trial results published in peer reviewed journals. Both of these stents have the European C.E. mark although the Igaki-Tamai is currently only used in peripheral arteries. There is no randomized data and trials have less restrictive inclusion criteria with respect to reference vessel diameter (RVD) and lesion length. Complex lesions including left main coronary artery (LMCA), left main stem, ostial lesions, saphenous vein graft disease and bifurcations have been excluded [32,34,46-49].

Igaki-Tamai stent: The Igaki-Tamai stent was the first ever fully biodegradable stent. The device was also based on a PLLA polymer scaffold but required contrast heated to 80 ◦C to self expand. It was first implanted in 1999 and 10 year data for 50 patients was reported in 2012 [1, 46]. The study was non-randomised and industry sponsored. At 10 years, rates of TLR, ST and MI were 28%, 4% and 8% respectively. Mean in-stent LLL reduced from 0.91±0.69mm at six months to 0.59±0.50mm at three years while MLA increased from 3.64±1.68mm2 to 5.18±2.09mm2 over the same period, suggestive of expansile arterial remodeling. At three years, IVUS echogenicity had returned to pre-stent levels, indicating complete stent degradation [46].

ReZolve stent (Reva Medical, San Diego, CA, USA): The ReZolve device is based on a tyrosine polycarbonate rather than PLLA scaffold and has the advantage of being radio-opaque [33]. It elutes sirolimus and is being assessed in the RESTORE single arm clinical trial which is currently enrolling a target cohort of 50 patients [49]. An earlier iteration of the stent was assessed in 27 patients in the 2008 RESORB trial which reported a six month TLR rate of 67% and 30 day q-wave-MI rate of 7% [1,35].

DESolve stent (Elixir Medical Corporation, Sunnyvale, CA, USA): DESolve has a PLLA scaffold with a myolimus eluting PLA coat. Six month clinical data of a 16 patient FIM trial revealed a TLR rate of 7%, MI and cardiac death rate of 0% and LLL of 0.19±0.19mm [47]. A larger trial with the DESolve Nx novolimus eluting stent is underway with a target enrolment of 120 patients [50].

ART bioresorbable stent (Arterial Remodelling Technologies, Paris, France): The ART non-drug eluting bioresorbable stent is based on a PLA scaffold and has recently started enrolling patients in the ARTDIVA FIM trial [51].

DREAMS drug eluting absorbable metal stent (Biotronik, Berlin, Germany) is the only metal biodegradable stent currently undergoing trial assessment. It comprises a magnesium alloy scaffold with a paclitaxel impregnated PLGA coat. It was evaluated in the BIOSOLVE-1 46 patient FIM trial which reported a 12 month TLR rate of 4.7%, MI rate of 2.3% and no ST events. Mean LLL was 0.64±0.50mmat six months and 0.52±0.39 at 12 months [48].

Biodegradable polymeric scaffolds have a number of limitations including but not limited to thicker struts with an increased crossing profile, limited post-dilatation options which mandates quantitative vessel sizing, radio-lucency with more challenging angiographic visualization.

There is also a scarcity of trials testing complex anatomy and challenging lesion subsets including ostial, bifurcation and heavy calcified disease [24]. Potential risk like strut fracture secondary to post-dilatation was observed in one patient at 46 days post stent insertion in the ABSORB A trial. It was hypothesized that fracture resulted from the 3.0mm×12mm stent being over expanded post dilation with a 3.5mm×9mmballoon [52].

Biodegradable polymer DES have demonstrated non-inferiority to both first and second generation DES for safety and efficacy. Although a recent pooled analysis of the ISAR-TEST 3, ISAR-TEST 4 and LEADERS trial data found that biodegradable polymer stents were superior for TLR and VLST compared with first generation SES, superiority has not been demonstrated against second generation EES and is yet to be proven in any single substantial randomized trial [53].

Non-polymeric Drug Eluting Metallic Stents

Non-polymeric DES comprises of a metal alloy scaffold directly impregnated with an anti-proliferative agent. The absence of a polymer coat offers a theoretical basis to minimize the duration of DAPT in patients with a high bleeding risk to one month or less based on the BMS guidelines [27] while still providing the established late safety of a BMS and the antiproliferative effects comparable to polymer based DES. Table 1 gives a brief outline of non-polymeric Drug eluting metallic stents.

LEADERS-FREE trial is comparing the BioFreedom with the Gazelle BMS in 2500 randomized patients at high risk of bleeding with the primary endpoints of non-inferiority for MACE and superiority for clinically driven TLR. Importantly, patients will be treated with only one month of DAPT [54].

Yukon SES (Translumina, Hechingen, Germany) has been examined in two independently funded, assessor blinded, randomized trials, the ISAR-TEST and ISAR-TEST 3. The ISAR-TEST trial included 450 patients across two centers and reported non-inferiority of the Yukon SES compared with the durable polymer-based TAXUS PES [55] for six month in-stent LLL (0.48±0.61mm vs 0.48±0.58mm, *p* = 0.98) and death & MI (4.4% vs 4.0% , *p* = 0.81). Despite the encouraging early results, it performed poorly in the subsequent three-arm ISAR-TEST 3 study, failing to demonstrate non-inferiority with the first generation Cypher stent in 650 patients for the primary endpoint of in-stent LLL at six to eight months (0.47±0.56mm vs 0.17±0.45mm vs 0.23±0.46mm, *p* = 0.94) [56]. At two years, however, there was no difference for a composite endpoint of death or MI (7.0% vs 6.9% vs 6.4% *p* = 0.97); for TLR (13.9% vs 8.4%vs 10.4 *p* = 0.19); or for ST (1.0% vs 0.5% vs 1.0%, *p* = 0.82) [57].

A non-polymeric dual-DES utilises the Yukon stent platform, but incorporates a second antiproliferative agent – probucol, a potent liposoluble antioxidant which reduces neointimal hyperplasia. The stent has been examined in the independently funded, assessor blinded, multicentre randomized ISAR-TEST 2 and ISAR-TEST 5 trials.

ISAR-TEST 2 trial compared this dual-DES (n=333) with the first generation Cypher SES (n=335) and the second generation Endeavour zotarolimus eluting stent (ZES) (n=339)(Medtronic Inc., Santa Rosa, CA, USA) [58] with promising results. The dual-DES was superior to the Endeavour stent at six months for binary angiographic restenosis (dual-DES 11.0% vs ZES 12.0%, p=0.68 vs SES 19.3%, *p* = 0.002), in-stent LLL 0.23±0.50mm vs 0.24±0.51 (*p* = 0.78) vs 0.58±0.55mm, (*p* < 0.001), and TLR (6.8% vs 7.2% (*p* = 0.83) vs 13.6%, *p* = 0.001)); its results were comparable with the Cypher stent. At two years, there was no significant difference in clinical outcomes including cardiovascular death or MI (dual-DES 7.8% vs ZES 9.2% vs SES 10.2%, *p* = 0.88); TLR 7.7% vs 10.7% vs 14.3% (*p* = 0.009); BR 13.9% vs 18.6% vs 20.9% (*p* = 0.047) and LLL 0.30±0.54 vs 0.35±0.60 vs 0.57±0.57 (*p* < 0.001) [59].

ISAR-TEST 5 trial compared the dual-DES (n=2002)with the Resolute ZES (n=1000)(Medtronic Inc., Santa Rosa, CA, USA) and demonstrated the dual-DES to be non-inferior with regards to the BR 13.3% vs 13.4% (*p* = 0.95); LLL 0.31±0.58 vs 0.30±0.56 (*p* = 0.50) and primary endpoint of MACE at 12 months (13.1% vs 13.5%, *p* = 0.74) and ST 1.1% vs 1.2% (*p* = 0.80) [60].

BioFreedom BES (Biosensors Europe SA, Morges, Switzerland) The Biolimus-A9 eluting BioFreedom stent is currently being assessed in a first in man (FIM) randomized, three arm trial of 182 patients [61]. It was shown to be non-inferior to the TAXUS Liberte for mean in-stent LLL at 12 months (0.17±0.22mm vs 0.35±0.22mm, *p* = 0.001) and for MACE at two years (6.8% vs 10.0%, *p* = not significant).

VESTASync SES (MIV Therapeutics, Atlanta, GA, USA): This SES is currently being assessed in the small, industry funded, double blinded, multicentre VESTASync II study (*n* = 75; NP *n*=50 vs BMS *n* = 25). It has been shown to be non-inferior to the GenX durable polymer stent (MIV Therapeutics, Atlanta, GA, USA) with regards to in-stent late lumen loss at nine months (0.39±0.20mm vs 0.74±0.52mm, *p* = 0.03) [62].

Biodegradable Polymer Drug Eluting Stents

Durable polymers of first and second generation DES remain within the coronary artery environment long after their purpose is fulfilled, and have deleterious effects by causing inflammation, delayed vascular healing, as well as

providing a platform for accelerated neoatherosclerosis [1,63]. They are also considered to play a pivotal role in late stent thrombosis (ST) [10-13]

Biodegradable polymers have been the focus of active research and development. The scientists continue to be challenged by issues like composition, degradation time of the polymer, biocompatibility, interaction and pharmacokinetic profile of the antiproliferative agents. Table 2 gives a brief outline of biodegradable Polymer DES.

BioMatrix (Biosensors Inc., Newport Beach, CA, USA)

Biolimus-A9 is a sirolimus analogue with extreme lipophilicity that enables targeted tissue uptake and minimizes systemic exposure. It has been combined with an abluminal polylactic acid (PLA) polymer that biodegrades within six to nine months, eluting 45% of the antiproliferative agent within the first 30 days.

LEADERS study was an industry funded, multicentre, non-inferiority powered randomized controlled trial (RCT) that examined the use of Biomatrix-Flex BES against the durable polymer first generation Cypher SES (Cordis, Miami Lakes, FL, USA) [16, 64, 65]. 1707 patients (BES n = 857 vs SES n = 850) were enrolled and 96.5% were followed to five years. Patients as well as assessors of angiographic films and staff involved with clinical follow-up were blinded to the assigned stent. Operators involved with stent insertion were not blinded. Non-inferiority was demonstrated for the primary endpoint of major adverse cardiovascular events (MACE) at nine months (9.2% vs 10.5%, p = 0.39) and at five years (22.3% vs 26.1%, p = 0.071). The definite VLST at five years was also found to be significantly low (0.66% vs 2.5% p = 0.003).

COMFORTABLE AMI trial was an industry funded, assessor blinded, multicentre study of 1161 patients randomized to either the BioMatrix- Flex or the Gazelle BMS Biosensors Europe SA, Morges, Switzerland) (BES n = 575 vs BMS n = 582). It showed that Biomatrix- Flex BES had lower rates of definite VLST from one to five years compared with the Cypher SES (0.66% vs 2.5%, p = 0.003) [65]. Its efficacy and safety has also been validated in primary PCI for acute ST elevation myocardial infarction (STEMI) [66]. This showed superiority for MACE at 12 months in favor of the BES (4.3% vs 8.7%, p = 0.004). There was no significant difference in the rate of definite or probable late ST (2.5% vs 3.7%, p = 0.25) at 12 months.

Nobori (Terumo, Somerset, NJ, USA) stents

The Nobori BES has also reported encouraging results in both the NOBORI 1 and NOBORI CORE trials [67,68] and more recently in the ongoing, large, industry funded, randomized, all-comers COMPARE II trial (BES *n* = 1795 vs EES *n* = 912) [69]. At 12 months, the stent was non-inferior for MACE compared with a durable polymer EES (5.2% vs 4.8%, p = 0.69) and had very low but similar rates of definite or probable late ST (0.8% vs 1.0%, p = 0.58). BASKET-PROVE II completed

recruitment of 2400 all-comer patients randomized to either the Nobori BES, the Xience Prime EES, or the PRO-Kinetic BMS in 2012[70]. They will be followed over five years for MACE and other clinical end points.

NOBORI 2 and eNOBORI are two large, prospective, single-arm, multicenter, registries that enrolled 3067 and 7750 patients respectively, out of which 248 and 703 were STEMI patients. All adverse events were adjudicated by an independent clinical event committee in NOBORI 2, while adjudication in eNOBORI (including stent thrombosis) is ongoing. At 1-month, there were no MIs observed. Total of 5 patients died because of cardiac reasons (0.9%) and one TLR (0.17%) and one TVR (0.4%) were found. The TLF rate was 1.0%. In the cohort of patients followed at 3-year, 2 patients suffered a cardiac death (0.8%), 10 had an MI (4.0%) and TLF rate was 6.1%. A total of 96% of the patients were angina free. Regarding stent thrombosis (ST), occurring up to 3 years, total of 4 cases have been detected (1.6%), out of which 3 cases were subacute (1.2%) and one case of late ST (0.4%). There was no very late ST detected at 3 years follow up. [71]

Supralimus (Sahajanand Medical)

PAINT trial, an industry funded, multicentre, unblinded trial with 274 randomised patients to the Supralimus stent, the Infinnium bioabsorbable polymer PES (Sahajanand Medical Technologies Pt. Ltd., India), or the Millennium Matrix BMS (Sahajanand Medical Technologies Pt. Ltd., India) groups (SES n = 106 vs PES n = 111 vs BMS n = 57) examined the Supralimus stent [72,73]. The polymers included PLLA, PLGA, PLC and PVP. Clinical events were adjudicated by an independent committee. At nine months angiographic follow-up, the Supralimus stent had significantly less instent LLL than the BMS (0.32±0.43mm vs 0.90±0.45mm, $p < 0.001$) and the Infinnium stent (0.32±0.43mm vs 0.54±0.44mm, $p = 0.001$). The Supralimus stent also had superior rates of MACE compared with the BMS at 12 months (8.6% vs 21.1%, $p = 0.01$) and three years (12.5% vs 33.3%, $p < 0.01$).

Excel (JW Medical System, Weihai, China)

The industry funded CREATE study was a large single-arm, multicentre, prospective registry of 2077 patients implanted with the Excel stent. It reported a MACE rate of 4.5% and definite or probable ST in 1.0% of patients at three year follow- up, half of which occurred beyond one year [74,75].

SYNERGY (Boston Scientific)

Everolimus Eluting Stents As durable polymer EES have become the most widely used DES worldwide, it is not surprising that advancement continues in this direction through clinical investigation of the Synergy stent (Boston Scientific Corp., Natick, MA, USA). Clinical experience with the stent is limited but the industry funded, assessor blinded EVOLVE randomized trial recently demonstrated non-inferiority for its primary endpoint of in-stent late loss at six

months when compared with the PROMUS Element durable polymer EES (Boston Scientific Corp., Natick, MA, USA)(0.10±0.25mm vs 0.15±0.34mm, p = 0.19) [76]. MACE was also comparable between the stents.

The JACTAX Liberte Paclitaxel Eluting Stents *(*PES) (Boston Scientific, Natick, MA, USA) is the effort to advance the initial success of the first generation TAXUS PES into a third generation bioabsorbable polymer DES. The industry funded, single centre OCTDESI pilot study examined 60 patients randomized to either a JACTAX high dose stent (n=20), a JACTAX low dose stent (n=21), or a TAXUS Liberte stent (n=19), with percentage of strut coverage as the primary endpoint. Angiographic endpoints were assessed by an independent core laboratory. At six months, the results were comparable across the three stents for both percentage of uncovered struts (7.0±12.2% vs 4.6±7.3% vs 5.3±14.7%, *p* = 0.81) and for in-stent late loss (0.25±0.32mm vs 0.39±0.43mm vs 0.24±0.44mm, *p* = 0.39) [77].

Combo stent (OrbusNeich, Fort Lauderdale, FL, USA)

The Combo stent is a novel biodegradable polymer SES that utilizes endothelial progenitor cell (EPC) capture technology in addition to low-dose abluminal sirolimus. This EPC capture technology is a luminal coating of immobile CD34 antibodies and aims to capture EPCs that differentiate into endothelial cells to form mature endothelial coverage of stent struts. Early data from the small, industry funded, non-randomized REMEDEE trial showed non-inferiority for its primary angiographic endpoint of in-stent late loss at nine months when compared with the TAXUS Liberte durable polymer PES (0.39±0.45mm vs 0.44±0.56mm, *p* = 0.55) [78]

ISAR-TEST 4 was an independently funded, assessor blinded trial that randomized 2603 patients from two centers to a novel, non-commercially available biodegradable polymer SES or a durable polymer DES, either the first generation Cypher SES or the second generation Xience EES [79]. Non-inferiority of the biodegradable polymer SES was demonstrated for the primary endpoint of MACE at 30 days (4.4% vs 4.5%, *p* = 0.87) and at one year (13.8% vs 14.4%, *p* = 0.66), as well as for definite or probable late ST at one year (1.0% vs 1.5%, *p* = 0.29).

Ongoing Clinical trials

The database of the clinicaltrials.gov was searched for biodegradable coronary stents and 18 open trials were identified. Table 3 gives the brief outline of identifier number, design types, primary outcomes and current recruitment status of the “open studies”.

Discussion:

The field of interventional cardiology is experiencing a great deal of cutting edge research especially in order to reduce the disadvantages of second generation stents. Although the second generation stents have come a long way and offer significant benefits including a large evidence base, good deliverability and operator

familiarity, long term definite or probable ST rates of up to 0.67% per annum and TLR rates of 1.3% per annum suggest a scope for improvement.

Although a recent pooled analysis of the ISAR-TEST 3, ISAR-TEST 4 and LEADERS trial data found that biodegradable polymer stents were superior for TLR and VLST compared with first generation SES, superiority has not been demonstrated against second generation EES and is yet to be proven in any single substantial randomized trial [53]. Trials to date have been small, non- randomized and exclusively industry funded. Early trial data has shown the promise of longer term expansile remodeling and restoration of vasoreactivity but the clinical implication of this is uncertain and there is no large study to backup this hypothesis. Moreover, deliverability, expansion constraints together with an absence of data in complex lesions suggests the need for further research.

Two larger trials with broader inclusion criteria are currently underway and should provide a greater indication of performance of third generation stents. There is a need for developing a technology which can provide excellent efficacy and safety, deliverability in broad range of clinical settings, minimal limitations on non-invasive imaging and future revascularization procedures, and limit the need for prolonged DAPT.

Table 1: Non-polymeric drug eluting stents.

Study (*n*) **Current status**	**Stent (Manufacturer)**	**Drug**	**Results/endpoints**
ISAR-TEST [52] (NP *n* = 225 vs PES *n* = 225) Completed	Yukon (Translumina)	Sirolimus	9 months LLL 0.48±0.61 vs 0.48±0.58 (*p* = 0.98) Death and MI 4.4% vs 4.0% (*p* = 0.81)
ISAR-TEST 2 [55] (DD *n* = 333 vs SES *n* = 335 vs ZES *n* = 339) Completed	Dual DES	Sirolimus and probucol	6–8 months BR 11.0% vs 12.0% (*p* = 0.68) vs 19.3% (*p* = 0.002) LLL 0.23±0.50 vs 0.24±0.51 (*p* = 0.78) vs 0.58±0.55 (*p* < 0.001) TLR 6.8% vs 7.2% (*p* = 0.83) vs

			13.6% (*p* = 0.001) 2 years Death and MI 7.8% vs 10.2% vs 9.2% (*p* = 0.61) TLR 7.7% vs 10.7% vs 14.3% (*p* = 0.009) BR 13.9% vs 18.6% vs 20.9% (*p* = 0.047) LLL 0.30±0.54 vs 0.35±0.60 vs 0.57±0.57 (*p* < 0.001)
ISAR-TEST 3 [53] (NP *n* = 201 vs BP *n* = 202 vs PP *n* = 202) Completed	Yukon (Translumina)	Sirolimus	6–8 months LLL 0.47±0.56 vs 0.17±0.45 vs 0.23±0.46 (*p* = 0.94) 2 years TLR 13.9% vs 8.4% vs 10.4% (*p* = 0.19) Death and MI 7.0% vs 6.9% vs 6.4% (*p* = 0.97) ST 1.0% vs 0.5% vs 1.0% (*p* = 0.82)
ISAR-TEST 5 [57] (DD *n* = 2002 vs ZES *n* = 1000) Completed	Dual DES	Sirolimus and probucol	6–8 months BR 13.3% vs 13.4% (*p* = 0.95) LLL 0.31±0.58 vs 0.30±0.56 (*p* = 0.50) 1 year MACE 13.1% vs 13.5% (*p* = 0.74) ST 1.1% vs 1.2% (*p* = 0.80)
VESTASync II [58] (NP *n*=50 vs BMS *n* = 25) Ongoing	VESTASync (MIV Therapeutics)	Sirolimus	9 months LLL 0.39±0.20 vs 0.74±0.52 (*p* = 0.03)
FIM [59] (NP SD *n*=60 vs PES *n* = 60) Ongoing	BioFreedom (Biosensors)	Biolimus A9	1 year LLL 0.17±0.22 vs 0.35±0.22 (*p* = 0.001) 2 years

			MACE 6.8% vs 10.0% (p = NS)

BR, binary restenosis; DD, non-polymeric dual DES; FIM, first-in-man; LLL, in-stent late lumen loss (mm); MACE, major adverse cardiovascular events; NP, non-polymeric DES; ST, definite/probable stent thrombosis; TLF, target lesion failure; PP, permanent polymer; BP, biodegradable polymer; SD, standard dose; NS, not significant.

Table 2. Biodegradable polymer drug eluting stents.

Study (*n*) **Current status**	**Stent (Manufacturer)**	**Drug**	**Polymer type**	**Results/endpoints**
LEADERS [37] (BES n = 857 vs SES n = 850) Completed	BioMatrix (Biosensors)	Biolimus A9	Abluminal PLA	5 years MACE 22% vs 26% (p = 0.07) Definite VLST 0.66% vs 2.5% (p = 0.003)
COMFORTABLE AMI [38] (BES n = 575 vs BMS n = 582) Completed	BioMatrix (Biosensors)	Biolimus A9	Abluminal PLA	1 year MACE 4.3% vs 8.7% (p = 0.004) ST 2.5% vs 3.7% (p = 0.25)
COMPARE II [41] (BES n = 1795 vs EES n = 912) Ongoing	Nobori (Terumo)	Biolimus A9 Abluminal	PLA	1 year MACE 5.2% vs 4.8% (p = 0.69) ST 0.8% vs 1.0% (p = 0.58)
BASKETPROVE- II [42] (target n = 2400, BES vs EES vs BMS) Recruiting	Nobori (Terumo)	Biolimus A9 Abluminal	PLA	Primary endpoint of MACE at 2 years
PAINT [46] (SES n = 106 vs PES n = 111 vs BMS	Supralimus (Sahajanand Medical)	Sirolimus	PLLA, PLGA, PLC, PVP	9 months LLL 0.32±0.43 vs 054±0.44 vs

n = 57) Completed				0.90±0.45 ($p < 0.001$) 3 years MACE 12.5% vs 16.6% vs 33.3% ($p < 0.01$)
CREATE registry [45] (*n* = 2077) Completed	Excel (JW Medical System)	Sirolimus	PLA	3 years MACE 4.5% ST 1.0%
REMEDEE [49] (SES *n* = 124 vs PES *n* = 59) Ongoing	Combo (OrbusNeich)	Sirolimus + EPC	Abluminal	9 months LLL 0.39±0.45 vs 0.44±0.56 ($p = 0.55$)
EVOLVE [43] (SYNERGY *n*=94 vs SYNERGY half-dose *n*=99 vs PROMUS Element *n* = 98) Completed	SYNERGY (Boston Scientific)	Everolimus	PLGA Rollcoat Abluminal	6 months LLL 0.10±0.25 vs 0.13±0.26 vs 0.15±0.34 (paired *p* = ns) TLF 2.2% vs 4.1% vs 3.1% (*p* = NS) ST 0.0% vs 0.0% vs 0.0%
OCTDESI [50] (JACTAX *n*=20 vs JACTAX low-dose *n*=21 vs TAXUS *n* = 19) Ongoing	JACTAX Liberte (Boston Scientific)	Paclitaxel	Juxtaposed Abluminal Coating technology	6 months USS 7.0±12.2% vs 4.6±7.3% vs 5.3±14.7% ($p = 0.81$) LLL 0.25±0.32 vs 0.39±0.43 vs 0.24±0.44 ($p = 0.39$)

LLL, in-stent late lumen loss (mm); MACE, major adverse cardiovascular events; PLA,poly-L-lactide; PLC, 75:25 poly-L-lactide-co-caprolactone; PLGA, 50:50 poly-D,L-lactide-co-glycolide; PLLA, poly-L-lactic acid; PVP, polyvinyl pyrrolidone; ST, definite/probable stent thrombosis; TLF, target lesion failure; USS, uncovered stent struts; NS, not significant.

Table 3: Ongoing Clinical Trials

Clinical Trial (NCT identifier)	Official Title	Study Type	Primary Outcome Measures	Designed as Safety Issue	Estimated Study Completion Date	Current Status
DESTINY TRIAL (Inspiron x Biomatrix) (NCT01856088)	Stents Coated With the Biodegradable Polymer on Their Faces and Elution of Sirolimus Abluminais Versus Elution Biolimus for the Treatment of Coronary Lesions Again - Randomized Destiny	Interventional Allocation: Randomized	Lumen Loss [Time Frame: 9 months after the procedure]	Yes	February 2018	Recruiting Last verified: May 2013
PONTINA (NCT01060306)	Prospective Optical cohereNce Tomography Evaluation of neoINtimal Coverage of a biodegrAdable Polymer-based Drug-eluting Stent	Observational: Case Control Time Perspective: Prospective	Assessment of neointimal coverage of the biodegradable polymer-based Biolimus A9-eluting stent (Biomatrix stent) after full drug elution and polymer biodegradation [Time Frame: 6 months]	No	January 2011	Unknown Last verified: January 2010
BESS (NCT01268371)	Comparison of Biolimus-eluting Biodegradable Polymer, Everolimus-eluting and Sirolimus-eluting Coronary Stents	Interventional. Allocation: Randomized	MACE	Yes	July 2015	Recruiting Last verified: April 2013
BIO-RESORT (NCT01674803)	Comparison of BIOdegradable Polymer and DuRablE	Interventional. Allocation: Randomized	Target vessel failure (TVF) [Time Frame: 1 year]	Yes	November 2016	not yet open for participant recruitm

	Polymer Drug-eluting Stents in an All COmeRs PopulaTion: Randomized Multicenter Trial in an All Comers Population Treated Within thE NeThErlands 3 (TWENTE 3)					ent Last verified : August 2012
EVOLUTION (NCT00825773)	A Randomized Study to Evaluate Safety and Efficacy of the ExcelTM Sirolimus Eluting Stent With a Biodegradable Polymer Versus SirOlimus ELUting Stent With Non-Biodegradable Polymer in the Treatment of PatIents With de nOvo Coronary Artery LesioNs	Interventional. Allocation: Randomized	Ischemia-driven Target Vessel Failure which is a composite of cardiac death, myocardial infarction (Q and non-Q wave) and target vessel revascularization (TVR) at 12 months. [Time Frame: 12 months]	Yes	April 2014	Recruiting Last verified : January 2009
OCTOBER(NCT01012583)	Optical Coherence TomOgraphy Assessment of the Excel Drug-Eluting Stent With BiodegradablE polymeR vs. the Cypher Drug-Eluting Stent With Permanent Polymer	Observational: Case Control Time Perspective: Prospective	To quantitate the presence of neointimal stent strut coverage at 6 month via Optical Coherence Tomography follow-up. [Time Frame: 6 month]	Yes	October 2010	Unknown Last verified : November 2009

Pro-HOPE (NCT01880879)	A Prospective Multicenter Trial Evaluating Helios Biodegradable Polymer Sirolimus-eluting Stent Safety and Effectiveness in Treatment of Coronary Artery Disease	Interventional Single Group Assignment	1 year incidence of target lesion [Time Frame: 1 year]	No	January 2015	Recruiting Last verified: January 2013
Evaluate Safety And Effectiveness Of The Tivoli® DES and The Firebird2® DES For Treatment Coronary Revascularization (NCT01681381)	A Prospective, Open Label, Randomized Study to Evaluate Safety And Effectiveness Of The Tivoli® Biodegradable Polymer Rapamycin-Eluting Stent and The FIREBIRD2® Rapamycin-Eluting Coronary CoCr Stent For Treatment Coronary Revascularization	Interventional. Allocation: Randomized	Ischemia-driven Target Lesion Failure (TLF) which is a composite of cardiac death, myocardial infarction (Q and non-Q wave) and target lesion revascularization (TLR) at 12 months post-procedure. [Time Frame: 12 months]	Yes	September 2018	Recruiting Last verified: November 2012
CREDIT-I (NCT01909869)	A PILOT First-In-Man Study to Evaluate Safety and Efficacy of the EXCEL-□ With Cobalt Chromium Alloys Sirolimus Eluting Biodegradable Polymer Stent in the Treatment of Patients With de Novo	Interventional Single Group Assignment	MACE	Yes	March 2018	Recruiting Last verified: July 2013

	Coronary Artery Lesions(CREDIT-I)					
DISCOVERY123 (NCT01844843)	Evaluation With OFDI of Strut Coverage of Terumo New Drug Eluting Stent (Development Code TCD-10023) With Biodegradable Polymer at 1, 2 and 3 Months	Interventional Single Group Assignment	OFDI assessed percent stent strut coverage [Time Frame: 3 months post procedure.]	No	December 2014	Recruiting Last verified : April 2013
OPTIMA (NCT01137019)	Optical Coherence Tomography Assessment of Intimal Tissue and Malapposition: A Randomized Comparison of the Biolimus A9-eluting and Everolimus-eluting Coronary Stents	Interventional. Allocation: Randomized	Rate of stent strut malapposition [Time Frame: 0 Days]	No	October 2012	Unknown Last verified : May 2010

(www.clinicaltrials.gov; As accessed on 9/8/2013)

References:

[1] Garg S, Serruys PW. Coronary stents: looking forward. J Am Coll Cardiol 2010;56:S43–78.

[2] Ko BS, Meredith IT. New DES: a new step forward? Minerva Cardioangiol 2012;60:41–56.

[3] Alfonso F, Fernandez C. Second-generation drug-eluting stents. Moving the field forward. J Am Coll Cardiol 2011;58:26–9.

[4] Stone GW, Rizvi A, Sudhir K, Newman W, Applegate RJ, Cannon LA, et al. Randomized comparison of everolimusand

paclitaxel-eluting stents, 2-year follow-up from the SPIRIT (Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System) IV trial. J Am Coll Cardiol 2011;58:19–25.

[5] Smits PC, Kedhi E, Royaards K-J, Joesoef KS, Wassing J, Rademaker-Havinga TAM, et al. 2-year follow-up of a randomized controlled trial of everolimus- and paclitaxeleluting stents for coronary revascularization in daily practice. COMPARE (Comparison of the everolimus eluting XIENCEV stent with the paclitaxel eluting TAXUS LIBERTE stent in all-comers: a randomized open label trial). J AmColl Cardiol 2011;58:11–8.

[6] Jensen LO, Thayssen P, Hansen HS, Christiansen EH, Tilsted HH, Krusell LR, et al. Randomized comparison of everolimus-eluting and sirolimus-eluting stents in patients treated with percutaneous coronary intervention: the Scandinavian Organization for Randomized Trials with Clinical Outcome IV (SORT OUT IV). Circulation 2012;125:1246–55.

[7] de Waha A, Dibra A, Byrne RA, Ndrepepa G, Mehilli J, Fusaro M, et al. Everolimus-eluting versus sirolimus-eluting stents: a meta-analysis of randomized trials. Circulation 2011;4:371–7.

[8] Rasmussen K, Maeng M, Kaltoft A, Thayssen P, Kelbaek H, Tilsted HH, et al. Efficacy and safety of zotarolimus-eluting and sirolimus-eluting coronary stents in routine clinical care (SORT OUT III): a randomised controlled superiority trial. Lancet 2010;375:1090–9.

[9] Park D-W, Kim Y-H, Yun S-C, Kang S-J, Lee S-W, Lee CW, et al. Comparison of zotarolimus-eluting stents with sirolimus- and paclitaxel-eluting stents for coronary revascularization: the ZEST (comparison of the efficacy and safety of zotarolimus-eluting stent with sirolimus-eluting and paclitaxel-eluting stent for coronary lesions) randomized trial. J Am Coll Cardiol 2010;56:1187–95.

[10] Park S-J, Kang S-J, Virmani R, Nakano M, Ueda Y. In-stent neoatherosclerosis: a finalcommonpathway of late stent failure. J Am Coll Cardiol 2012;59:2051–7.

[11] Joner M, Finn AV, Farb A, Mont EK, Kolodgie FD, Ladich E, et al. Pathology of drug-eluting stents in humans: delayed healing and late thrombotic risk. J Am Coll Cardiol 2006;48:193–202.

[12] Brugaletta S,RaduMD, Garcia-GarciaHM,HeoJH, FarooqV, Girasis C, et al. Circumferential evaluation of the neointima by optical coherence tomography after ABSORB bioresorbable vascular scaffold implantation: can the scaffold cap

the plaque? Atherosclerosis 2012;221:106–12.

[13] Foerst JR, Ball TC, Nakano M, Virmani R, Kaplan AV. Late complication: Xience V stent fractures with restenosis. JACC Cardiovasc Interv 2012;5:239–42.

[14] Raber L, Magro M, Stefanini GG, Kalesan B, van Domburg RT, Onuma Y, et al. Very late coronary stent thrombosis of a newer-generation everolimus-eluting stent compared with early-generation drug-eluting stents: a prospective cohort study. Circulation 2012;125:1110–21.

[15] Stone GW, Witzenbichler B, Guagliumi G, Peruga JZ, Brodie BR, Dudek D, et al. Heparin plus a glycoprotein IIb/IIIa inhibitor versus bivalirudin monotherapy and paclitaxel-eluting stents versus bare-metal stents in acute myocardial infarction (HORIZONS-AMI): final 3-year results from a multicentre, randomised controlled trial. Lancet 2011;377:2193–204.

[16] Stefanini GG, Kalesan B, Serruys PW, Heg D, Buszman P, Linke A, et al. Long-term clinical outcomes of biodegradable polymer biolimus-eluting stents versus durable polymer sirolimus-eluting stents in patients with coronary artery disease (LEADERS): 4 year follow-up of a randomised noninferiority trial. Lancet 2011;378:1940–8.

[17] Holmes Jr DR, Louis AC, Cannon AD, Stahle E, Morice M-C, Mack MJ, et al. Four-year follow-up of theSYNTAXtrial: optimal revascularization strategy in patients with three-vessel disease and/or left main disease. In: Presented at Transcatheter Cardiovascular Therapeutics. 2011. Available at http://wwwsyntaxscorecom/indexphp?option=com content &view=article&id=40&Itemid=75 [accessed 7/22/2013].

[18] Kappetein AP, Feldman TE, Mack MJ, Morice M-C, Holmes DR, Stahle E, et al. Comparison of coronary bypass surgery with drug-eluting stenting for the treatment of left main and/or three-vessel disease: 3-year follow-up of theSYNTAX trial. Eur Heart J 2011;32:2125–34.

[19] Stone GW. Comparison of Everolimus-Eluting (XIENCE V) and Paclitaxel-Eluting (TAXUS Express) stents: first report of the five-year clinical outcomes from the SPIRIT III trial. In: Presented at Transcatheter Cardiovascular Therapeutics. 2011.

[20] Claessen BE, Beijk MA, Legrand V, Ruzyllo W, Manari A, Varenne O, et al. Two-year clinical, angiographic, and intravascular ultrasound follow-up of the XIENCE V everolimus-eluting stent in the treatment of patients with de novo native coronary artery lesions: the SPIRIT II trial.

Circulation 2009;2:339–47.

[21] Byrne RA, Kastrati A, Massberg S, Wieczorek A, Laugwitz K-L, HadamitzkyM, et al. Biodegradable polymerversus permanent polymer drug-eluting stents and everolimus- versus sirolimus-eluting stents in patients with coronary artery disease: 3-year outcomes from a randomized clinical trial. J Am Coll Cardiol 2011;58:1325–31.

[22] Byrne RA, Kastrati A, Tiroch K, Massberg S, Wieczorek, Laugwitz K, et al. Two-year outcomes after everolimus- or sirolimus-eluting stents in patients with coronary artery disease in the ISAR-TEST 4 trial. In: Presented at Transcatheter Cardiovascular Therapeutics. 2010.

[23] Valgimigli M, Campo G, Monti M, Vranckx P, Percoco G, Tumscitz C, et al. Short- versus long-term duration of dualantiplatelet therapy after coronary stenting: a randomized multicenter trial. Circulation 2012;125:2015–26.

[24] Bittl JA. Bioresorbable stents: the next revolution. Circulation 2010;122:2236–8.

[25] Hofma SH, van der Giessen WJ, van Dalen BM, Lemos PA, McFadden EP, Sianos G, et al. Indication of long-term endothelialdysfunction after sirolimus-eluting stent implantation. Eur Heart J 2006;27:166–70.

[26] Togni M, Windecker S, Cocchia R, Wenaweser P, Cook S, Billinger M, et al. Sirolimus-eluting stents associated with paradoxic coronary vasoconstriction. J Am Coll Cardiol 2005;46:231–6.

[27] Levine GN, Bates ER, Blankenship JC, Bailey SR, Bittl JA, Cercek B, et al. 2011 ACCF/AHA/SCAI guideline for percutaneous coronary intervention: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines and the Society for Cardiovascular Angiography and Interventions. Circulation 2011;124:e574–651 [Erratum appears in Circulation 2012 Feb 28;125(8):e412. Note: Dosage error in article text].

[28] Task Force on Myocardial Revascularization of the European Society of Cardiology, The European Association for Cardio-Thoracic Surgery, European Association for Percutaneous Cardiovascular Interventions, Wijns W, Kolh P, Danchin N, et al. Guidelines on myocardial revascularization. Eur Heart J 2010;31:2501–55.

[29] Mintz GS,PopmaJJ, PichardAD,KentKM,Satler LF,Wong C, et al. Arterial remodeling after coronary angioplasty: a serial intravascular ultrasound study. Circulation 1996;94:35–43.

[30] Serruys PW, de Jaegere P, Kiemeneij F, Macaya C, RutschW, Heyndrickx G, et al. A comparison of balloon-expandablestent implantation with balloon angioplasty in patients with coronary artery disease. Benestent Study Group. N Engl J Med 1994;331:489–95.

[31] Serruys PW, Kutryk MJB, Ong ATL. Coronary-artery stents. N Engl J Med 2006;354:483–95.

[32] Serruys PW, Onuma Y, Dudek D, Smits PC, Koolen J, Chevalier B, et al. Evaluation of the second generation of a bioresorbable everolimus-eluting vascular scaffold for the treatment of de novo coronary artery stenosis: 12-month clinical and imaging outcomes. J Am Coll Cardiol 2011;58:1578–88.

[33] Onuma Y, Ormiston J, Serruys PW. Bioresorbable scaffold technologies. Circ J 2011;75:509–20.

[34] Ormiston JA, Serruys PW, Regar E, Dudek D, Thuesen L, Webster MWI, et al. A bioabsorbable everolimus-eluting coronary stent system for patients with single de-novo coronary artery lesions (ABSORB): a prospective open-label trial. Lancet 2008;371:899–907.

[35] Ormiston JA, Serruys PWS. Bioabsorbable coronary stents. Circulation 2009;2:255–60.

[36] Okamura T, Garg S, Gutierrez-Chico JL, Shin E-S, Onuma Y, Garcia-Garcia HM, et al. In vivo evaluation of stent strut distribution patterns in the bioabsorbable everolimus-eluting device: anOCTad hoc analysis of the revision 1.0andrevision 1.1 stent design in the ABSORB clinical trial. EuroIntervention 2010;5:932–8.

[37] Waksman R. The disappearing stent: when plastic replaces metal. Circulation 2012;125:2291–4.

[38] Heublein B, Rohde R, Kaese V, Niemeyer M, Hartung W, Haverich A. Biocorrosion of magnesium alloys: a new principle in cardiovascular implant technology? Heart 2003;89:651–6.

[39] Dudek D, Onuma Y, Ormiston JA, Thuesen L, Miquel-Hebert K, Serruys PW. Four-year clinical follow-up of the ABSORB everolimus-eluting bioresorbable vascular scaffold in patients with de novo coronary artery disease: the ABSORB trial. EuroIntervention 2012;7:1060–1.

[40] Banning A. ABSORB clinical program – the latest!. In: Presented

at EuroPCR. 2012.

[41] Serruys PW, Ormiston JA, Onuma Y, Regar E, Gonzalo N, Garcia-Garcia HM, et al. A bioabsorbable everolimuseluting coronary stent system (ABSORB): 2-year outcomes and results from multiple imaging methods. Lancet 2009;373:897–910.

[42] Serruys P, Onuma Y. 5-Year Cohort A and 2-year Cohort B results: integrated insights. In: Presented at Transcatheter Cardiovascular Therapeutics. 2011.

[43] ClinicalTrials.gov. Abbott Vascular. Identifier: NCT01023789. ABSORB EXTEND Clinical Investigation: A Continuation in the Clinical Evaluation of the ABSORB Bioresorbable Vascular Scaffold (BVS) System in the Treatment of Subjects With de Novo Native Coronary Artery Lesions. Last updated: 02/01/2013. Available at http://clinicaltrialsgov/ct2/show/NCT01023789 [accessed 7/22/2013].

[44] ClinicalTrials.gov. Abbott Vascular. Identifier: NCT01425281. Absorb II Randomized Controlled Trial: A Clinical Evaluation to Compare the Safety, Efficacy and Performance of Absorb Everolimus Eluting Bioresorbable Vascular Scaffold System Against XIENCE Everolimus Eluting Coronary Stent System in the Treatment of Subjects With Ischemic Heart Disease Caused by de Novo Native Coronary Artery Lesions. Last updated: 3/20/2013. Available at http://clinicaltrialsgov/ct2/show/NCT01425281?term=bioresorbable+AND+scaffold+ [accessed 7/22/2013].

[45] Abizaide A, Bartorelli A, Whitbourn R, Clark L, Chevalier B, Miquel-Herbert K, et al. Preliminary data from ABSORB EXTEND: a report of the 6-month clinical outcomes from the first 200 patients enrolled. In: Presented at Transcatheter Cardiovascular Therapeutics. 2011.

[46] Nishio S, Kosuga K, Igaki K, Okada M, Kyo E, Tsuji T, et al. Long-term (>10 years) clinical outcomes of first-in-human biodegradable poly-L-lactic acid coronary stents: Igaki-Tamai stents. Circulation 2012;125: 2343–53.

[47] Verheye S. DESolve Myolimus Eluting Bioresorbable Coronary Scaffold First-in-ManTrial 6month imaging and clinical results. In: Presented at EuroPCR. 2012.

[48] Haude M, Erbel R, Verheye S, Waksman R, Degen H, Bose D, et al. Twelve-month clinical and angiographic results of

the multicenter first-in-man BIOSOLVE-1 study with the paclitaxel-eluting bioabsorbable magnesium scaffold. In: Presented at EuroPCR. 2012.

[49] ClinicalTrials.gov. REVA Medical, Inc. Identifier: NCT01262703. Pilot Study of the ReZolveTM Sirolimus-Eluting Bioresorbable Coronary Stent. Last updated: 07.06.12. Available at http://clinicaltrialsgov/ct2/show/ NCT01262703?term=reva&rank=2 [accessed 7/22/2013].

[50] Elixir Medical Corporation (online). DESolve Bioabsorbable Coronary Scaffold; 2012. Available at http:// http://elixirmedical.com/index.php?page=ous-desyne-novolimus-eluting-coronary-stent-system [accessed 7/22/2013].

[51] Arterial Remodelling Technologies (Online).ARTproducts; 2012. Available at http://www.art-stent.com/products.php [accessed 7/22/2013].

[52] Onuma Y, Serruys PW, Ormiston JA, Regar E, Webster M, Thuesen L, et al. Three-year results of clinical follow-up after a bioresorbable everolimus-eluting scaffold in patients with de novo coronary artery disease: the ABSORB trial. EuroIntervention 2010;6:447–53.

[53] Stefanini GG, Byrne RA, Serruys PW, de Waha A, Meier B, Massberg S, et al. Biodegradable polymer drug-eluting stents reduce the risk of stent thrombosis at 4 years in patients undergoing percutaneous coronary intervention: a pooled analysis of individual patient data from the ISAR-TEST 3, ISAR-TEST 4, and LEADERS randomized trials. Eur Heart J 2012;33:1214–22.

[54] ClinicalTrials.gov. Biosensors Europe SA. Identifier: NCT01623180. A Prospective Randomized Comparison of the BioFreedom Biolimus A9 Drug Coated Stent Versus the Gazelle Bare Metal Stent in Patients With High Risk of Bleeding. Last updated 01/01/2013. Available at http://clinicaltrialsgov/ct2/show/NCT01623180?term= leaders+free&rank=1 [accessed 07/22/2013].

[55] Mehilli J, Kastrati A, Wessely R, Dibra A, Hausleiter J, Jaschke B, et al. Randomized trial of a nonpolymer-based rapamycin-eluting stent versus a polymer-based paclitaxeleluting stent for the reduction of late lumen loss. Circulation 2006;113:273–9.

[56] Mehilli J, Byrne RA,Wieczorek A, Iijima R, Schulz S, Bruskina O, et al. Randomized trial of three rapamycin-eluting stents with different coating strategies for the reduction of coronary restenosis. Eur Heart J 2008;29:1975–82.

[57] Byrne RA, Kufner S, Tiroch K, Massberg S, Laugwitz KL,

Birkmeier A, et al. Randomised trial of three rapamycineluting stents with different coating strategies for the reduction of coronary restenosis: 2-year follow-up results. Heart 2009;95:1489–94.

[58] Byrne RA, Mehilli J, Iijima R, Schulz S, Pache J, Seyfarth M, et al. A polymer-free dual drug-eluting stent in patients with coronary artery disease: a randomized trial vs. polymerbased drug-eluting stents. Eur Heart J 2009;30:923–31.

[59] Byrne RA, Kastrati A, Tiroch K, Schulz S, Pache J, Pinieck S, et al. 2-year clinical and angiographic outcomes from a randomized trial of polymer-free dual drug-eluting stents versus polymer-based Cypher and Endeavor [corrected] drug-eluting stents. J Am Coll Cardiol 2010;55: 2536–43.

[60] Massberg S, Byrne RA, Kastrati A, Schulz S, Pache J, Hausleiter J, et al. Polymer-free sirolimus- and probucoleluting versus new generation zotarolimus-eluting stents in coronary artery disease: the Intracoronary Stenting and Angiographic Results: Test Efficacy of Sirolimus- and Probucol-Eluting versus Zotarolimus-eluting Stents (ISARTEST 5) trial. Circulation 2011;124:624–32.

[61] Grube E. The BioFreedom DES: late results, technology challenges, and next steps. In: Presented at Global Summit on Innovations in Interventions. 2012.

[62] de Ribamar Costa J, Abizaid A, Costa R, Almeida B, Feres F, Perin M, et al. Two-year sustained efficacy of a novel, polymer-free sirolimus eluting stent: late results of the VESTASync II trial. J Am Coll Cardiol 2012;59:E212.

[63] Nakazawa G, Finn AV, Kolodgie FD, Virmani R. A review of current devices and a look at new technology: drug-eluting stents. Expert Rev Med Devices 2009;6:33–42.

[64] Windecker S, Serruys PW, Wandel S, Buszman P, Trznadel S, Linke A, et al. Biolimus-eluting stent with biodegradable polymerversus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial. Lancet 2008;372:1163–73.

[65] Serruys P. LEADERS: five-year follow-up from a prospective, randomized trial of Biolimus A9-eluting stents with a biodegradable polymer vs. sirolimus-eluting stents with a durable polymer: final report of the LEADERS study. In: Presented at Transcatheter Cardiovascular Therapeutics. 2012.

[66] Raber L, Kelbaek H, Ostoijc M, Baumbach A, Heg D, Tuller D, et al. Effect of biolimus-eluting stents with biodegradable polymer vs bare-metal stents on cardiovascular events

among patients with acute myocardial infarction: the COMFORTABLE AMI randomized trial. JAMA 2012;308:777–87.

[67] Chevalier B, Silber S, Park S-J, Garcia E, Schuler G, Suryapranata H, et al. Randomized comparison of the Nobori Biolimus A9-eluting coronary stent with the Taxus Liberte paclitaxel-eluting coronary stent in patients with stenosis in native coronary arteries: the NOBORI 1 trial – Phase 2. Circulation 2009;2:188–95.

[68] Ostoijc M, BeleslinSD, Jung B, Persic R, Jagic Z, Nedljkovic N, et al. First clinical comparison of Nobori–Bioloimus A9 eluting stents with Cypher–Sirolimus eluting stents: NOBORI CORE nine months angiographic and one year clinical outcomes. EuroIntervention 2008;3:574–9.

[69] Smits P, vanBovenA,Goy J-J, denHeyer P, Serra A, Slagboom T, et al. COMPARE II trial. In: Presented at EuroPCR. 2012.

[70] Jeger R, Pfisterer M, Alber H, Eberli F, Galatius S, Naber C, et al. Newest-generation drug-eluting and bare-metal stents combined with prasugrel-based antiplatelet therapy in large coronary arteries: the BAsel Stent Kosten Effektivitats Trial PROspective Validation Examination part II (BASKET-PROVE II) trial design. Am Heart J 2012;163, 136–41.e1.

[71] Drug-eluting stent with biodegradable polymer in patients with STEMI – short and long term outcomes: data from e-NOBORI and NOBORI 2 trials

[72] Lemos PA, Moulin B, Perin MA, Oliveira LARR, Arruda JA, Lima VC, et al. Late clinical outcomes after implantation of drug-eluting stents coated with biodegradable polymers: 3-year follow-up of the PAINT randomised trial. EuroIntervention 2012;8:117–9.

[73] Lemos PA, Moulin B, Perin MA, Oliveira LARR, Arruda JA, Lima VC, et al. Randomized evaluation of two drug-eluting stents with identical metallic platform and biodegradable polymer but different agents (paclitaxel or sirolimus) compared against bare stents: 1-year results of the PAINT trial. Catheter Cardiovasc Interv 2009;74: 665–73.

[74] Han Y, Jing Q, Xu B, Yang L, Liu H, Shang X, et al. Safety and efficacy of biodegradable polymer-coated sirolimuseluting stents in “real-world” practice: 18-month clinical and 9-month angiographic outcomes. JACC Cardiovasc Interv 2009;2:303–9.

[75] Han Y, Jing Q, Li Y, Yang L, Liu H, Shang X, et al. Sustained clinical safety and efficacy of a biodegradable-polymer coated sirolimus-eluting stent in “real-world” practice:

three-year outcomes of the CREATE (Multi-Center Registry ofEXCELBiodegradablePolymerDrugEluting Stents) study. Catheter Cardiovasc Interv 2012;79:211–6.

[76] Meredith IT, Verheye S, Dubois CL, Dens J, Fajadet J, Carrie D, et al. Primary endpoint results of the EVOLVE trial: a randomized evaluation of a novel bioabsorbable polymercoated, everolimus-eluting coronary stent. J AmColl Cardiol 2012;59:1362–70.

[77] Guagliumi G, Sirbu V, Musumeci G, Bezerra HG, Aprile A, Kyono H, et al. Strut coverage and vessel wall response to a new-generation paclitaxel-eluting stent with an ultrathin biodegradable abluminal polymer: Optical Coherence Tomography Drug-Eluting Stent Investigation (OCTDESI). Circulation 2010;3:367–75.

[78] Haude M. The REMEDEE study: insights from the angiographic and intravascular ultrasound comparison of a combination siroimus eluting EPC capture stent with a paclitaxel eluting stent. J Am Coll Cardiol 2012;59:E209.

[79] Byrne RA, Kastrati A, Kufner S, Massberg S, Birkmeier KA, Laugwitz K-L, et al. Randomized, non-inferiority trial of three limus agent-eluting stents with different polymer coatings: the Intracoronary Stenting and Angiographic Results: Test Efficacy of 3 Limus-Eluting Stents (ISAR-TEST-4) Trial. Eur Heart J 2009;30:2441–9.

[80] Raber L, Wohlwend L, Wigger M, Togni M, Wandel S, Wenaweser P, et al. Five-year clinical and angiographic outcomes of a randomized comparison of sirolimus-eluting and paclitaxel-eluting stents: results of the sirolimus-eluting versus paclitaxel-eluting stents for coronary revascularization LATE trial. Circulation 2011;123:2819–28.