

Clinical Studies with Sirolimus, Zotarolimus, Everolimus and Biolimus A9 Drug-Eluting Stent Systems

Bimmer E. Claessen^{1,2}, José P.S. Henriques² and George D. Dangas^{1,3,*}

¹Cardiovascular Research Foundation, New York, NY, ²Academic Medical Center, University of Amsterdam, ³Mount Sinai Medical Center, New York, NY

Abstract: The introduction of the drug-eluting stent (DES) has revolutionized the field of interventional cardiology during the past decade. Initial pivotal randomized clinical trials showed a large reduction in restenosis rates and the need for repeat intervention with DES compared with bare-metal stents. The three main components of a DES are 1) the stent platform, 2) a coating facilitating elution of the drug (mostly a polymer), and 3) an antiproliferative/anti-inflammatory drug. Currently, two classes of drugs are widely used in DES, Taxanes, including its best-known member Paclitaxel, and Rapamycins, which include Sirolimus and its analogues such as Everolimus, Zotarolimus and Biolimus A9. The first DES to receive United States Food and Drug Administration approval was the Sirolimus-eluting stent. Recently, two other stent types eluting a Sirolimus-analogue were approved; the Zotarolimus-eluting stent and the Everolimus-eluting stent. Biolimus A9-eluting stents, using biodegradable polymers, are currently approved and marketed outside of the United States. This review article focusses on the clinical studies that have been performed with DES eluting Sirolimus or its analogues.

Keywords: Drug-eluting stents, Sirolimus, Rapamycin derivatives.

INTRODUCTION

Percutaneous coronary intervention (PCI) has undergone an impressive evolution since Andreas Gruentzig first performed percutaneous coronary angioplasty in 1977 [1]. The introduction of the first commercially available intracoronary stent, the Palmaz-Schatz stent [2], reduced the incidence of restenosis and acute vessel closure, two common complications of balloon angioplasty. However, depending on patient and lesion characteristics, in-stent restenosis occurs in about 10-30% of patients treated with a bare-metal stent (BMS) for coronary artery disease. The drug-eluting stent (DES) was engineered to reduce the incidence of in-stent restenosis. In theory, coating a stent with a polymer which facilitates controlled release of an antiproliferative drug allows for local prevention of in-stent restenosis. This theory was confirmed by the first pivotal randomized clinical trials comparing BMS and DES. The use of DES was associated with markedly reduced rates of in-stent restenosis and target lesion revascularization (TLR) [3-5]. The drugs used in contemporary DES can be divided into two classes; 1) the Taxanes, including the drug Paclitaxel, and 2) the Rapamycins, including Sirolimus, and its analogues, such as Zotarolimus, Everolimus and Biolimus A9. The purpose of this article is to review and discuss the clinical studies that were performed with DES coated with Sirolimus or its analogues.

PHARMACOLOGICAL CHARACTERISTICS OF SIROLIMUS AND ITS ANALOGUES

Sirolimus is a natural macrocyclic lactone with potent immunosuppressive and antiproliferative properties, it is also known as Rapamycin, as it was first discovered in a soil sample from Easter Island (also known as Rapa Nui) [6]. It is synthesized by the bacterium *Streptomyces hygroscopicus*. The United States Food and Drug Administration (FDA) approved Sirolimus in 1999 for the prophylaxis of renal transplant rejection, for which it is still being used. The chemical structure of Sirolimus and its analogues is shown in Fig. (1), and their antirestenotic properties are depicted schematically in Fig. (2). In short, Sirolimus is a pro-drug that binds to specific cytosolic proteins. After binding to FK506-binding

protein 12 (FKBP12), the sirolimus/FKBP12 complex binds to the cell cycle regulatory protein mammalian target of Rapamycin (mTOR), inhibiting its action. mTOR is involved with critical steps of the cell cycle, and inhibition of mTOR by Rapamycin has a cytostatic effect, causing the cell cycle to arrest in the late G1 phase [7, 8]. Other antirestenotic properties of Sirolimus have been reported, but are not as well understood, these include: inhibition of total protein and collagen synthesis involved in extracellular matrix formation, inhibition of smooth muscle cell migration, and promoting a contractile rather than a proliferative phenotype [9-11].

FEASIBILITY OF SIROLIMUS AND ITS ANALOGUES TO REDUCE RESTENOSIS

The feasibility of Sirolimus as a stent-delivered drug to reduce restenosis was tested by Suzuki *et al.* in a porcine model [12]. After 4 weeks, the mean neointimal area in Sirolimus-eluting stent (SES) treated lesions was significantly reduced relative to BMS treated lesions. After successful implementation of Sirolimus on a DES, the feasibility of stent based delivery of Sirolimus-analogues was investigated. The molecular structures of the three well-studied Sirolimus analogues Zotarolimus, Everolimus and Biolimus A9 are shown in Fig. (1). Their molecular structures differ from Sirolimus by substituting the hydroxyl group at position 40 of the Sirolimus molecule for other chemical structures. These substitutions result in similar antirestenotic properties but with improved lipophilicity.

SIROLIMUS-ELUTING STENTS

Prototype Stent Design

The most widely used SES (Cyphertm, Cordis, Warren, NJ) is composed of the Bx velocitytm 316L stainless steel stent platform with a closed cell geometry, coated with a two-layer polyethylene-co-vinyl acetate and poly-n-butyl methacrylate polymer. The polymer facilitates the release of Sirolimus which is blended in a concentration of 1.4µg/mm². This non-erodable polymer had been applied previously in bone cement, ocular devices and a drug-releasing intrauterine device [13, 14]. Because of its high strut thickness (140 µm, the highest of currently available DES), and its closed-cell design, the SES has gained a reputation of being difficult to deliver to more complex coronary lesions. In an attempt to tackle this problem, the Cyphertm SES was recently fitted with a new delivery system, this updated version of the SES is marketed as Cypher select plustm.

*Address correspondence to this author at the Cardiovascular Institute, Mount Sinai Medical Center, New York, NY 10029; Tel: +1-212-241-7014; Fax: +1-212-241-0273; E-mail: George.Dangas@mssm.edu

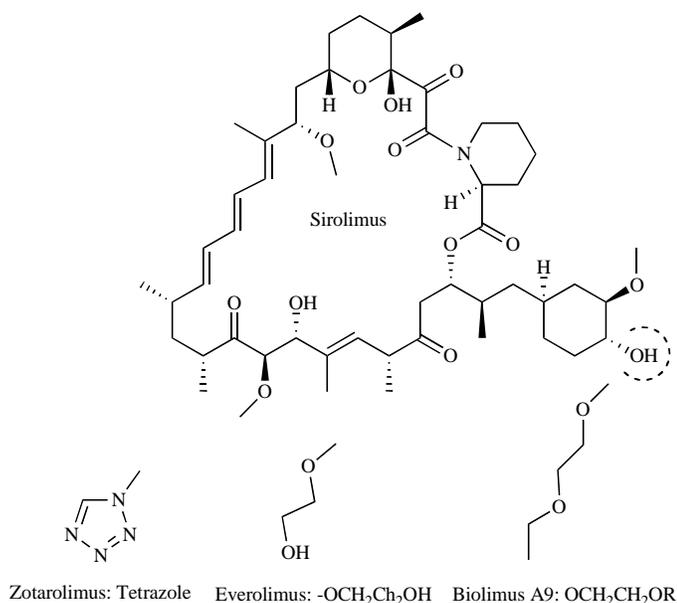


Fig. (1). Chemical structure of Sirolimus, Zotarolimus, Everolimus, and Biolimus A9. Hydroxyl group in dotted circle is substituted with shown chemical structures to form the sirolimus-analogues zotarolimus, everolimus, and biolimus A9.

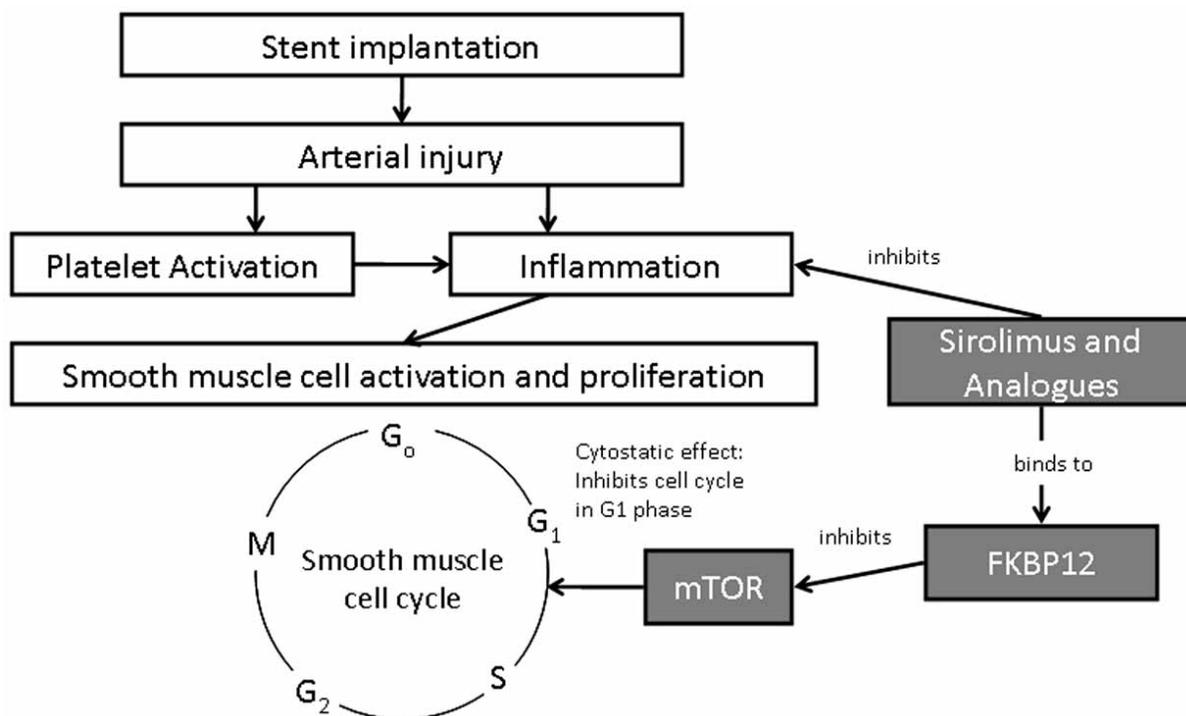


Fig. (2). Antirestenotic properties of Sirolimus and its analogues.

First-in-Man Clinical Experience

The first-in-man implantation of a SES occurred in 1999 in Sao Paulo, Brazil [15]. A total of 30 patients received a SES with one of two drug release formulations; a fast release (FR) formulation (<15 days of drug release [n=15]) or a slow release (SR) formulation (≥28 days of drug release [n=15]). Quantitative coronary angiography (QCA) and intravascular ultrasound (IVUS) analysis revealed only minimal neointimal hyperplasia at four months follow-up; in-stent late loss was $-0.1\pm 0.3\text{mm}$ in the FR-treated group and $0.09\pm 0.3\text{mm}$ in the SR-treated group [15]. Subsequent randomized clinical trials were performed with the SR SES. The longevity of

the antiproliferative action of the SES was confirmed at repeat QCA and IVUS measurements at four years follow-up. In-stent late loss at four years was $0.41\pm 0.5\text{mm}$ and $0.09\pm 0.2\text{mm}$ in the FR and SR groups, respectively [16].

Randomized Clinical Trials with the Sirolimus-Eluting Stent

The “Randomized study with the sirolimus-eluting bx VElocity balloon-expandable stent” (RAVEL) trial was the first randomized clinical trial comparing the SES with BMS for the treatment of coronary artery disease [3]. In the RAVEL trial, 238 patients with single *de novo* lesions were randomized to treatment with either a 18 mm SES or a similar but uncoated BMS. The treated lesions

were relatively simple, ACC-AHA type C lesions were excluded and 57% of patients in RAVEL had a type B2 lesion. After six months, in-stent late loss was significantly lower in the SES group ($-0.01 \pm 0.3\text{mm}$) compared with the BMS ($0.8 \pm 0.5\text{mm}$, $p < 0.01$). Moreover, an IVUS substudy showed significant differences between the SES and the BMS in terms of neointimal hyperplasia volume ($2 \pm 5\text{mm}^3$ vs. $37 \pm 28\text{mm}^3$, $p < 0.01$) and percent of volume obstruction ($1 \pm 3\%$ vs. $29 \pm 20\%$, $p < 0.01$) [17]. In terms of clinical endpoints, the SES was superior to the BMS in preventing TLR (0% vs 23%, $p < 0.01$), with similar rates of death and myocardial infarction at one year.

The "Sirolimus-eluting stent in *de novo* coronary artery lesions" (SIRIUS) trial randomized 1058 patients with single *de novo* coronary artery lesions to either a SES ($n=533$) or an identical BMS ($n=525$) [4]. Compared with the RAVEL trial, patients in SIRIUS had slightly more complex coronary artery lesions with 33% type B2 lesions and 23% Type C lesions. The SIRIUS trial confirmed the superiority of the SES over the BMS at 6 months in terms of angiographic in-stent late loss ($0.17 \pm 0.5\text{mm}$ vs. $1.00 \pm 0.7\text{mm}$, $p < 0.01$) and IVUS-measured neointimal volume (4.4mm^3 vs. 57.6mm^3 , $p < 0.01$) and percent of volume obstruction (3.1% vs. 33.4%, $p < 0.01$). Furthermore, one-year TLR rates were significantly lower in the SES group compared to the BMS group (4.9% vs. 20%, $p < 0.01$) [18]. At 12 months, there were no differences in death or myocardial infarction rates.

These impressive results led to the FDA approval of the SES in April 2003. However, subgroup analyses of SIRIUS raised a number of concerns. For example, the TLR rate was 6.3% in lesions with a reference vessel diameter $< 2.75\text{mm}$ compared to 1.9% in patients with a reference vessel diameter $\geq 2.75\text{mm}$. Furthermore, restenosis occurred predominantly at the proximal stent margin after SES placement, suggesting a causative role for balloon injury outside of the stent. Finally, patients with diabetes mellitus (DM) had high rates of TLR, even with the SES (all DM 7.2%, insulin-dependent DM 13.9%). Further evaluation of the SES in randomized clinical trials revealed a 70% reduction in the need for TLR relative to BMS throughout all lesion an patient subsets [19, 20]. However, the problem of in-stent restenosis remains significant even with SES, particularly in diabetic patients, patients with ST-elevation myocardial infarction and patients with complex lesion types such as chronic total occlusions, bifurcation lesions, saphenous vein graft lesions and in-stent restenosis lesions (Table 1) [3, 4, 21-42].

Head-to-Head Drug-Eluting Stent Trials with the Sirolimus-Eluting Stent

The relative performance in terms of safety and efficacy of the SES vs. the Paclitaxel-eluting stent (PES, TAXUS[™], Boston Scientific, Natick, MA) has been extensively studied. Both SES and PES were shown to be effective in reducing restenosis compared with BMS in large pivotal randomized trials [3-5, 43, 44]. However, a number of meta-analyses of head-to-head trials comparing SES vs. PES showed a significantly reduced risk of repeat revascularization in patients receiving a SES, with similar rates of death and myocardial infarction [19, 45, 46]. Several large randomized clinical trials are currently being performed comparing the SES with newer DES.

Observational Studies with the Sirolimus-Eluting Stent

It has been estimated that only 30% of lesions treated in 'real-world' clinical practice would have been eligible for inclusion in the initial pivotal randomized clinical trials evaluating the safety and efficacy of the SES. In daily clinical practice, the SES has been used for off-label indications in the majority of cases [47]. Several registry studies have examined the use of the SES in unselected patient cohorts. The first results from the "Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital" (RESEARCH) registry were published in 2004 [48]. The RESEARCH investigators

compared clinical outcomes in a cohort of 508 patients with *de novo* lesions treated with SES with a historical control cohort of 450 BMS-treated patients. Even in the presence of more complex lesion characteristics, a significantly reduced rate of TVR was observed in the SES group compared with the BMS group after one year [48]. More recently, Daemen *et al.* reported the 4-year clinical outcome of this cohort, confirming the efficacy of the SES in reducing TVR at long-term follow-up [49]. This study was instrumental in confirming the safety and efficacy of the SES in unselected populations with greater patient and lesion complexity compared to pivotal randomized clinical trials. Over the last years, a number of large real-world registry studies have shown that the use of SES is associated with low rates of major adverse cardiac events, and TVR in particular [50-53].

Other Types of Sirolimus-Eluting Stents

Although the Cypher[™] SES currently is the only SES available in the United States, several other SES have either been studied, or are currently being studied. Hausleiter *et al.* reported successful inhibition of neointimal hyperplasia with a polymer-free microporous 316L stainless steel SES compared with the same drug-free BMS [54]. These investigators also compared the efficacy of a polymer-free SES, a biodegradable polymer SES, and the permanent-polymer Cypher[™] SES in terms of reducing in-stent late loss at 6-8 months follow-up. The authors reported similar efficacy of the biodegradable polymer SES and the permanent-polymer SES and inferior efficacy with the polymer free SES [55]. Experiments with dual-drug-eluting stents (dual-DES) by the same group showed non-inferiority of dual-DES combining 17- β -estradiol or probucol to stents eluting Sirolimus alone [56, 57]. The VESTA-sync[™]-eluting stent (MIV Therapeutics, Atlanta, Ga) is a non-polymeric SES that has been tested in small patient cohorts and preliminary data have been promising [58-59]. Larger randomized clinical trials are warranted to confirm the safety and efficacy of these types of SES. The Nevo[™] SES (Cordis, Warren, NJ) is another nonpolymeric SES that elutes the drug from reservoirs in the stent surface. The RES-ELUTION I trial randomized 394 patients with single *de novo* coronary artery lesions to treatment with the Nevo[™] SES ($n=202$) or the PES ($n=192$). At 6-month angiographic follow-up, in-stent late loss was significantly lower with the Nevo[™] SES ($0.13 \pm 0.31\text{mm}$) compared with the PES (0.36 ± 0.46 , $p < 0.01$). Although not powered to detect differences in clinical outcome, the RES-ELUTION I investigators observed a trend towards a lower incidence of a composite endpoint of death, myocardial infarction and TLR in the Nevo[™] SES group (6.1%) compared with the PES group (10.8%, $p=0.14$) at one-year follow-up [59-60].

ZOTAROLIMUS-ELUTING STENTS

The Endeavor[™] Zotarolimus-eluting stent (ZES, Medtronic CardioVascular, Santa Rosa, CA) is based upon the thin-strut ($91\mu\text{m}$) Cobalt-Chromium alloy Driver[™] stent platform upon which three layers of phosphorylcholine polymer are sprayed. This polymer is a synthetic copy of a component of the outer surface of the erythrocyte bi-layer, and was found to be non-thrombogenic in preclinical studies [61]. First, a primer layer is applied to the stent surface, then a layer of polymer mixed with zotarolimus in a concentration of $10\mu\text{g}/\text{mm}$, and finally a top layer of polymer is applied. Zotarolimus was specifically designed for use in DES, made by substituting a tetrazole ring for the native hydroxyl group at position 40 in Sirolimus (Fig. 1). It is a lipophilic compound with very low water solubility, facilitating drug diffusion into the vessel wall [62]. Zotarolimus is released during the first four weeks after ZES implantation, which is a relatively short period when compared with other DES. The Endeavor[™] ZES received FDA-approval in February 2008.

Currently, a new type (next-generation) ZES (Endeavor Resolute[™], Medtronic CardioVascular, Santa Rosa, Ca) is undergoing

Table 1. Event Rates with Sirolimus-Eluting Stents from Major Randomized Clinical Trials.

	Year	N of Patients Treated with SES	Duration of Follow-up	TLR	MI	Death	Longest Available Follow-up	TLR	MI	Death
Initial pivotal trials										
RAVEL	2002	120	1 year	0.0%	0.8%	1.7%	5 years (pooled meta-analysis)	11.9%	8.3%	15.9%
SIRIUS	2003	533	9 months	4.1%	2.8%	0.9%				
E-SIRIUS	2003	175	9 months	4.0%	4.6%	1.1%				
C-SIRIUS	2004	50	9 months	4.0%	2.0%	0.0%				
All-comer populations										
LEADERS	2008	850	9 months	5.9%	4.6%	2.8%	2 years	7.3%	5.8%	5.1%
SORT-OUT II	2008	1065	18 months	4.5%	4.2%	1.7%				
SORT-OUT III*	2010	1170	18 months	2.0%	1.0%	1.0%				
Diabetes Mellitus										
DES-DIABETES	2008	200	9 months	2.0%	0.5%	0.0%	2 years	3.5%	0.5%	0.0%
ISAR-DIABETES	2007	125	9 months	6.4%	4.0%	3.2%				
Bifurcation Lesions										
CACTUS	2009	350	6 months	7.7%	9.7%	0.3%				
Chronic total occlusions										
PRISON II	2006	100	1 year	4.0%	2.0%	0.0%	3 years	7%	5%	4.0%
Saphenous vein grafts										
RRISC	2006	38	6 months	4.3%	10.6%	2.6%	32 months	24%	18%	29.0%
In-stent restenosis										
ISAR DESIRE	2005	100	1 year	8.0%	1.0%	2.0%				
SISR	2006	259	9 months	8.5%	2.7%	0.0%	3 years	19%	6.2%	3.9%
ISAR DESIRE 2	2010	225	1 year	16.6%	2.7%	3.4%				
Multivessel disease										
ARTS II	2010	607	1 year	7.4%	1.2%	1.0%	5 years	20.3%	5.8%	5.4%
Myocardial Infarction										
TYPHOON	2006	355	1 year	3.7%	1.1%	2.3%	4 years	7.2%	4.8%	4.0%

* This trial excluded all postprocedural events for a 5 day period.

SES= Sirolimus-eluting stent, TLR= Target lesion revascularization, MI= Myocardial infarction

clinical evaluation in a number of large randomized clinical trials. This ZES is based upon the same stent platform as the Endeavor™ ZES, but is coated with a different polymer with a top-coat which elutes 85% of its Zotarolimus content within the first 60 days post-procedure (i.e. slower than with the earlier type) and the remainder of the drug is completely eluted by 180 days [63].

Another Type of ZES, the nonpolymeric ZoMaxx™ stent (Abott Vascular, Santa Clara, Ca) was been discontinued after disappointing clinical trial results [64].

First-in-Man Clinical Experience

The ENDEAVOR I first-in-man study was the first clinical study to evaluate the safety and feasibility of the ZES in the treat-

ment of *de novo* coronary artery disease [65]. It was designed as a prospective, multicenter, nonrandomized, single-arm study in which 100 patients were enrolled. In-stent late loss assessed by repeat angiography at one year was 0.61 ± 0.44 mm, relatively high compared with other types of DES. However, patients had low rates of clinical events up to one year follow-up; 2 patients (2%) underwent TLR, 1 patient (1%) had a myocardial infarction and no patients died.

ENDEAVOR II: Endeavor™ ZES vs. Bare-Metal Stents

After the promising first-in-man results, the ENDEAVOR II trial was conducted, a randomized controlled trial in 1197 patients with a single *de novo* lesion [66]. A total of 598 patients were treated with ZES and 597 patients were treated with the same BMS. The primary endpoint of target vessel failure (TVF, a composite of death, myocardial infarction or TVR) at 9 months was 7.3% in the ZES group and 15.1% in the BMS group ($p<0.01$), entirely due to a lower rate of TVR in the ZES group (5.6% vs. 12.5%, $p<0.01$).

Head-to-Head Drug-Eluting Stent Trials with the Endeavor™ ZES

After the promising results from these initial trials, a number of other randomized clinical trials were performed to evaluate the performance of the ZES relative to the two FDA-approved DES at that time. In ENDEAVOR III, 323 patients with a single *de novo* coronary artery lesion received a ZES and 113 patients received a SES [67]. This trial was designed to demonstrate non-inferiority in terms of in-segment late loss at 8-month angiographic follow-up. However, the primary endpoint was not met; in-segment late loss was 0.34 ± 0.44 in the ZES group and 0.13 ± 0.32 in the SES group ($p<0.01$). Despite the higher late loss in the ZES group, the ENDEAVOR III investigators reported no differences in clinical endpoints at 9-month follow-up. Long-term follow-up of the ENDEAVOR III trial showed a significantly lower rate of a composite endpoint of death or myocardial infarction at 5 years in the ZES group (1.3%) compared with patients in the SES group (6.5%, $p<0.01$) [68]. However, the small ENDEAVOR III trial was not powered to detect differences in clinical event rates.

The recent “Danish Organization for Randomized Trials with Clinical Outcome III” (SORT OUT III) trial randomized 1162 unselected patients in a 1:1 ratio to either ZES or SES [33]. At 18 months, the primary endpoint of cardiac death, myocardial infarction or TVR occurred in 10% in the ZES arm compared to 5% in the SES arm ($p<0.01$). This difference was largely driven by a higher TVR rate in the ZES arm (8% vs 3%, $p<0.01$). The definitive answers about the relative safety and efficacy of the ZES and the SES will be provided by the “Patient Related Outcomes with Endeavor versus Cypher stenting Trial” (PROTECT) [69]. Enrollment in this 8800-patient trial has been completed and the results of the primary endpoint of definite/probable stent thrombosis at three-year follow-up according to the Academic Research Consortium definition [70] are eagerly awaited.

The large-scale ENDEAVOR IV trial randomized 1,548 patients with a single *de novo* coronary artery lesion in a 1:1 ratio to treatment with ZES or PES [71]. The primary endpoint of ENDEAVOR IV, TVF at 9-month follow-up, occurred in 6.6% and 7.1% in patients treated with ZES and PES, respectively ($p=0.685$). An angiographic substudy performed in 279 patients at 8 months revealed that the ZES was inferior in reducing in-segment and in-stent late-loss compared with the SES. However, as previously observed in the ENDEAVOR III trial, this was not associated with a significantly increased rate of TLR. Moreover, the ENDEAVOR IV investigators constructed a multivariate logistic regression model to identify predictors of TLR. Assignment to angiographic follow-up was the only significant independent predictor of TLR in the ZES group.

Finally, the ZES was compared to a stent coated with a durable polymer eluting the sirolimus-analogue novolimus in the small-scale EXCELLA II study. A total of 210 patients with a maximum of 2 *de novo* native coronary artery lesions were randomized to either the ZES or the novolimus-eluting stent (NES). At 9 months, late loss was significantly lower in the NES group (0.11 ± 0.32 mm vs. 0.63 ± 0.42 mm, $p<0.01$). Clinical event rates at 9 months were low and comparable in both groups. Definite/probable stent thrombosis occurred in 1.4% of the NES group and 0.0% in the ZES group [72].

Observational Studies with the Endeavor™ Zotarolimus-Eluting Stent

The large-scale E-Five registry was designed in order to investigate the safety and effectiveness of the ZES in the treatment of more complex patients and lesions than those in the randomized controlled trials [73]. Over 12,000 stents were implanted in 10,339 lesions in 8,314 patients at 188 sites in this worldwide registry. The prevalence of diabetes was 32.7%, 60% of patients had type B2/C lesions, and 47.8% of patients were treated for an acute coronary syndrome. The primary composite endpoint of death, myocardial infarction or TLR occurred in 7.5% of patients at one year follow-up. These results are consistent with results of previous clinical trials.

Clinical Studies with the Endeavor Resolute™ Zotarolimus-Eluting Stent

The RESOLUTE trial was a first-in-man, prospective, nonrandomized, multicenter study of the next-generation Endeavor Resolute™ ZES [74]. A total of 139 patients were enrolled, of whom 100 underwent 9-month angiographic and IVUS follow-up. In-stent late loss was 0.12 ± 0.26 mm, which compares very favorably to the 0.61 ± 0.44 mm found in ENDEAVOR I with the first-generation ZES. The Endeavor Resolute™ ZES also showed promising clinical outcomes; at 2-year follow-up, rates of death, myocardial infarction, and TLR were 2.9%, 5.8%, and 1.4%, respectively [75].

The RESOLUTE III trial was a large randomized clinical trial comparing the Resolute™ ZES with the everolimus-eluting stent (EES, Xience V™, Abbot Vascular, Santa Clara, Ca, or Promus™, Boston Scientific, Natick, Ma) [76]. A total of 2300 patients representing a real-world patient population were randomized 1:1 to either the Resolute™ ZES or the EES in this all-comer trial. Compared with the ZES group, the EES group had a higher number of stents used per patient (2.0 ± 1.3 vs. 1.9 ± 1.2 , $p=0.02$) and a longer stent length (37.0 ± 26.5 mm vs. 34.4 ± 24.5 mm, $p=0.02$). At one year, rates of the primary endpoint of target lesion failure (TLF, cardiac death, myocardial infarction and ischemia-driven TLR) were 8.2% in the ZES arm and 8.3% in the EES arm, rendering the ZES non-inferior to the EES (Table 2). However, ARC-defined definite stent thrombosis occurred in 13 patients (1.3%) in the ZES arm compared with 3 (0.3%) in the EES arm ($p=0.01$). Clinical follow-up will continue up to five years. The Resolute™ ZES is currently being further studied in a number of ongoing trials (Table 3).

EVEROLIMUS-ELUTING STENTS

The feasibility of the use of Everolimus on a DES was initially tested in the first-in-man “First Use To Underscore Restenosis reductions with Everolimus” (FUTURE) I and II trials. In these trials, a stainless-steel stent was covered on the abluminal surface with a biodegradable polylactic acid polymer which elutes Everolimus. A Pooled analysis of 106 patients from the FUTURE I and II trials showed that the Everolimus-eluting stent (EES) with biodegradable polymer was efficacious in reducing in-stent neointimal hyperplasia and restenosis regardless of vessel size [77, 78]. A similar version of this stent using the same stent platform and biodegradable poly-

Table 2. One-Year Clinical Outcomes of the RESOLUTE III Randomized Clinical Trial.

	Resolute ZES	EES	p value
Target lesion failure	8.2%	8.3%	<0.01*
Cardiac death	1.3%	1.7%	0.61
Target vessel myocardial infarction	4.2%	4.1%	0.92
Clinically driven target lesion revascularization	3.9%	3.4%	0.5
Definite stent thrombosis	1.3%	0.3%	0.01

* p for non-inferiority

ZES= Zotarolimus eluting stent, EES= Everolimus-eluting stent

Table 3. Ongoing Trials Evaluating Sirolimus(Analogue)-Eluting Stents.

Study Name	Number of Patients	Study Arms	Inclusion Criteria (Selected)	Powered for
RESOLUTE US	1574	Resolute ZES	up to two <i>de novo</i> native coronary arterie lesions	Clinical endpoints
RESOLUTE international	2200	Resolute ZES	all-comers	Clinical endpoints
RESOLUTE Japan	100	Resolute ZES	<i>de novo</i> lesion(s) in native coronary arteries	Angiographic endpoints
TWENTE	1380	Resolute ZES vs. EES	all-comers	Clinical endpoints
PROTECT	8800	Endeavor ZES vs. SES	Patients with on-label indications for both ZES and SES	Clinical endpoints/ Stent thrombosis rates
SPIRIT WOMEN registry	1550	EES vs. SES	up to four <i>de novo</i> native coronary artery lesions	Clinical endpoints
SPIRIT WOMEN randomized substudy	450	EES vs. SES	up to four <i>de novo</i> native coronary artery lesions	Clinical endpoints
RESET	3200	EES vs. SES	all-comers	Clinical endpoints
SORT OUT IV	2678	EES vs. SES	all-comers	Clinical endpoints
EXCELLENT	1400	EES vs. SES	<i>de novo</i> native coronary artery lesions	Angiographic endpoints
COMPARE 2	unknown	EES vs. Nobori BES	all-comers	Clinical endpoints
EXCEL	2500	EES vs. CABG	Left-main disease and syntax score <32	Clinical endpoints

ZES= Zotarolimus-eluting stent, EES=Everolimus-eluting stent, SES=Sirolimus-eluting stent, BES=Biolumus-eluting stent, CABG= Coronary artery bypass grafting

mer but with the Sirolimus-analogue Biolimus A9 instead of Everolimus underwent further clinical testing.

Design of the Xience Vtm/Promustm Everolimus-eluting Stent

The EES (EES, Xience V, Abbot Vascular, Santa Clara, Ca, or Promus, Boston Scientific, Natick, Ma) was approved by the FDA in July 2008, and has the lowest strut and polymer thickness of currently FDA-approved DES. It is based upon the thin-strut (81µm) medical grade L-605 cobalt chromium alloy stent platform. The durable (non-biodegradable) thin copolymer (6-8 µm) used on the EES consists of poly n-butyl methacrylate (PBMA) which is applied as a primer and vinylidene fluoride and hexafluoropropylene as the drug matrix layer. Everolimus is mixed with the fluoropolymer in a concentration of 100µg/cm² and applied to the PBMA coated stent surface. In contrast to the previously mentioned EES and ZES, no topcoat is used. The first 25% of Everolimus on the stent is released during the first day after stent implantation, 75% is released after one month, and all drug is released after four months

[79]. Everolimus and Sirolimus are similar in pharmacology and potency, but differ in solubility, with Everolimus being more lipophilic than Sirolimus [80]. An updated version of the EES (Xience Primetm, Abbott Vascular, Santa Clara, CA) has recently been introduced in out-of-US markets. Xience Primetm uses the same polymer and drug combination on a novel cobalt chromium stent platform designed for enhanced deliverability and flexibility. The Promus Elementtm EES (Boston Scientific, Natick, MA), based upon a platinum chromium alloy stent system is currently under development.

First-in-Man Clinical Experience

A total of 60 patients were randomized at nine European sites to the Xience Vtm/Promustm EES or an identical BMS for the treatment of a single *de novo* lesion in a native coronary artery in the first-in-man SPIRIT FIRST study of this EES [81]. Angiographic in-stent late lumen loss at 6 months was 0.10±0.19mm vs. 0.87±0.37mm in the EES group and the BMS group, respectively. Repeat angiography at 12 months showed a non-significant increase in in-stent late

loss in the EES arm (0.24 ± 0.27 mm), while in-stent late loss in the BMS arm remained virtually unchanged (0.84 ± 0.45 mm). The TVF rate at 12-month follow-up was 15.4% in the EES group and 21.4% in the BMS group [82]. No additional clinical events occurred up to five-year follow-up in the EES arm, suggesting a favorable safety and efficacy profile [83].

Head-to-Head Noninferiority Drug-Eluting Stent Trials with the Everolimus-Eluting Stent

In addition to the previously mentioned RESOLUTE III trial, the EES has been studied in a number of non-inferiority randomized trials. The SPIRIT II trial enrolled 300 patients in a 3:1 ratio to the EES or the PES. Inclusion criteria were a maximum of two *de novo* native coronary artery lesions with a diameter between 2.5 and 3.75mm and <28mm in length. Although this trial was powered to detect non-inferiority in terms of in-stent late loss at 6-month angiographic follow-up, the EES was found to be superior to the PES (0.11 ± 0.27 mm vs 0.36 ± 0.39 mm, $p<0.01$) [84]. At two-year angiographic follow-up in a subset of 152 patients, a late increase in neointimal hyperplasia was detected in the EES arm; two-year in-stent late loss was 0.33 ± 0.37 mm and 0.34 ± 0.34 mm in the EES and PES arms, respectively [85]. However, this late “catch-up” in neointimal hyperplasia did not translate into an increased rate of clinical events in the EES arm. At three-year follow-up a trend towards a lower incidence of the composite endpoint of cardiac death, myocardial infarction or ischemia-driven TLR was found with the EES compared with the PES (7.2% vs 15.9%, $p=0.053$) [86].

A total of 1002 patients with up to two *de novo* lesions in a native coronary artery were randomly allocated in a 2:1 manner to treatment with the EES or the PES in the US-based SPIRIT III trial [87]. The trial was powered to detect non-inferiority in terms of the primary endpoint of 8-month angiographic in-segment late loss and 12-month ischemia-driven TVF (a composite of cardiac death, myocardial infarction, and ischemia-driven TVR). In fact, SPIRIT III proved superiority of the EES over the PES in terms of in-segment late loss (0.14 ± 0.39 mm vs 0.26 ± 0.46 mm, $p<0.01$) and non-inferiority in terms of ischemia-driven TVF (8.6% vs. 11.3%, $p=0.20$).

The SPIRIT V diabetic randomized controlled trial included 218 diabetic patients treated with the EES and 106 patients treated with the PES [88]. The primary endpoint of in-stent late loss at 9 months was significantly lower in the EES group (0.19 ± 0.37 vs. 0.39 ± 0.49 , $p<0.01$). Rates of TLF at one year were similar in both groups, 11.2% and 12.5% in the EES and PES arms, respectively ($p=0.71$).

Head-to-Head Superiority Drug-Eluting Stent Trials with the Everolimus-Eluting Stent

The large-scale SPIRIT IV trial included 3,690 patients with relatively complex lesions (up to 3 *de novo* native coronary artery lesions) were randomized in a 2:1 fashion to receive treatment with the EES or the PES [89]. Of note, patients in SPIRIT IV did not undergo routine angiographic follow-up to minimize the influence of the “occulo-stenotic reflex” on clinical outcomes. At one year the incidence of the composite primary endpoint of TLF was 4.2% in the EES arm and 6.8% in the PES arm ($p<0.01$). This difference was due to significantly lower rates of myocardial infarction (1.8% vs 2.9%, $p=0.04$) and ischemia-driven TLR (92.5% vs 4.6%, $p<0.01$). Moreover, a significant reduction in the incidence of ARC definite/probable stent thrombosis at one year was observed with the EES relative to the PES (0.29% vs 1.06%, $p<0.01$). However, no difference in TLF between the two stents was observed in the 1,100 patient diabetic subgroup. The superiority of the EES over the PES was confirmed in the randomized COMPARE trial in which 6% of the 897 patients in the EES group and 9% of the 904 patients in the PES group ($p=0.02$) had a primary outcome event

(composite of all-cause mortality, myocardial infarction, and TVR) at 12-month follow-up. In contrast to the previous randomized trials with strict inclusion and exclusion criteria, a real-world population was enrolled in COMPARE, with 60% of patients treated for an acute coronary syndrome. As in SPIRIT IV, the incidence of ARC definite/probable stent thrombosis was significantly lower in the EES arm (0.7% vs 3%, $p<0.01$). Although long-term results of these trials are eagerly anticipated, these findings suggest that the next-generation EES is superior to the first-generation PES. These findings are supported by a recent meta-analysis of 6,683 patients (4,194 treated with EES, 2,489 treated with PES) from the SPIRIT II, III, IV and COMPARE trials [90]. At one-year, the use of EES resulted in significantly reduced rates of myocardial infarction (risk ratio [RR] 0.57, $p<0.01$), TLR (RR 0.57, $p<0.01$) and ARC definite/probable stent thrombosis (RR 0.36, $p=0.02$), with similar rates of all-cause mortality when compared with PES (Fig. 3). Of note, there was no heterogeneity in the results according to the TAXUS Express vs. Liberté stent platforms. Several other randomized clinical trials are currently being conducted to evaluate the relative efficacy of the EES vs. various types of SES, ZES, and BES (Table 3).

Observational Studies with the Everolimus-Eluting Stent

The favorable outcomes with the EES in randomized trials have been replicated in several non-randomized registry studies. In the 2700-patient international SPIRIT V registry, the 1-year rates of cardiac death, myocardial infarction, and TLR were 1.1%, 2.7%, and 1.3%, respectively [91]. Latib *et al.* report slightly higher event rates after a median follow-up of 378 days in a cohort of 345 unselected EES-treated patients. In this study, cardiac death, myocardial infarction, and TLR occurred in 2.1%, 2.1%, and 7.9%, respectively [92]. Furthermore, Onuma *et al.* compared a cohort of 649 consecutive patients treated with the EES against three historical control groups (BMS, $n=450$, SES, $n=508$, and PES, $n=576$). Despite the fact that patients treated with the EES were older, more often treated for myocardial infarction, and had more complicated lesions, the clinical outcome at one year was significantly better than in patients treated with BMS and PES and comparable to patients treated with SES [93].

Clinical Trials with a Bioabsorbable Everolimus-Eluting Stent

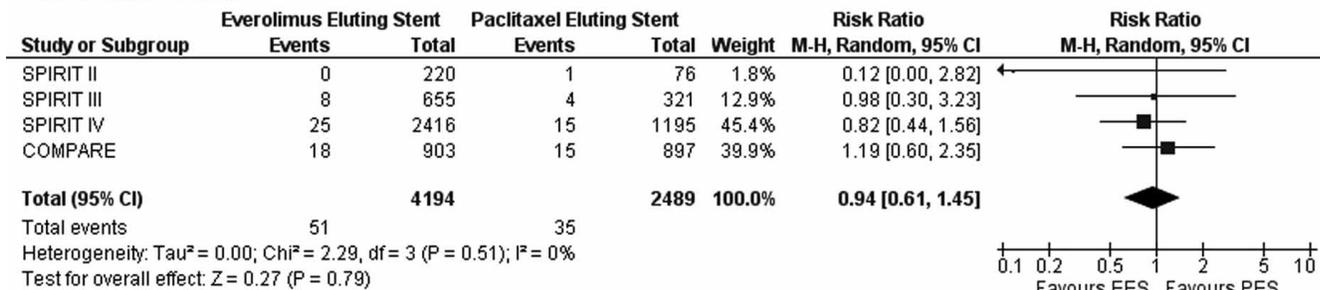
The safety and feasibility of a fully bioabsorbable EES was investigated in the ABSORB trial [94]. A total of 30 patients with a single *de novo* native coronary artery lesion were enrolled in the ABSORB trial. All patients in this single-arm trial were treated with a bioabsorbable EES, made of polylactic acid. At 6-month follow-up angiography, in-stent late loss was 0.44 ± 0.35 mm, mainly due to a mild reduction of stent area resulting from late recoil [95]. At 6 month follow-up, only one adverse event had occurred, one patient (3.6%) had a myocardial infarction. At 2 years after implantation, the stent was bioabsorbed and vasomotion was restored. Moreover, no additional adverse events had occurred and in-stent late loss remained stable (0.48mm) [96]. Additional trials with the bioabsorbable EES using an updated stent design to minimize recoil are currently being performed.

BIOLIMUS A9-ELUTING STENTS

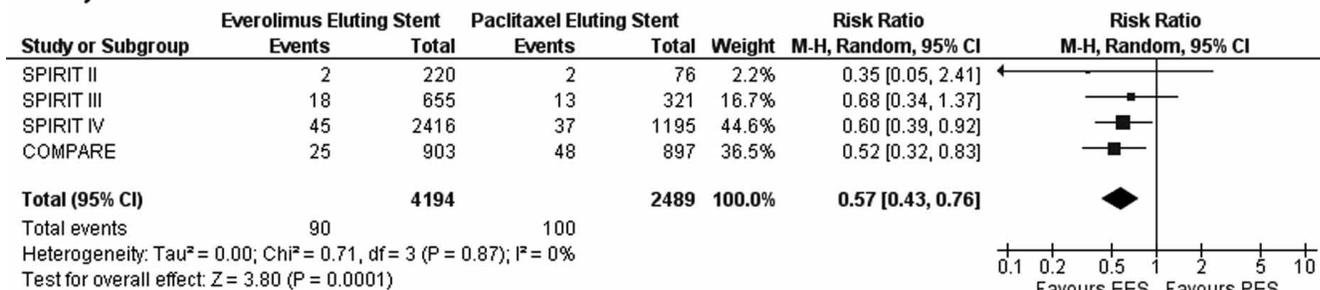
Stent Design

Biolimus A9 is a very lipophilic semi-synthetic Sirolimus analogue designed specifically to be used in DES. Its chemical structure is shown in Fig. (1). Biolimus A9 is a white powder that is synthesized by chemical modification of Sirolimus. Considerations for the use of pharmacologic agents on DES include the biocompatibility of the drug matrix and a high lipophilicity to ensure release from the carrier coating directly into the coronary vessel wall. Preclinical studies of Biolimus A9 showed it was well tolerated with a safety profile similar to that of other Sirolimus-analogues [97].

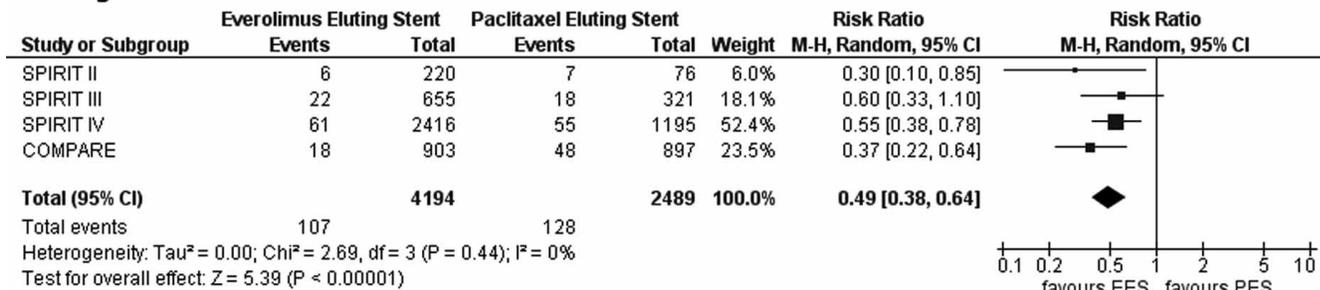
A All-cause death



B Myocardial infarction



C Target lesion revascularization



D Definite/probable stent thrombosis

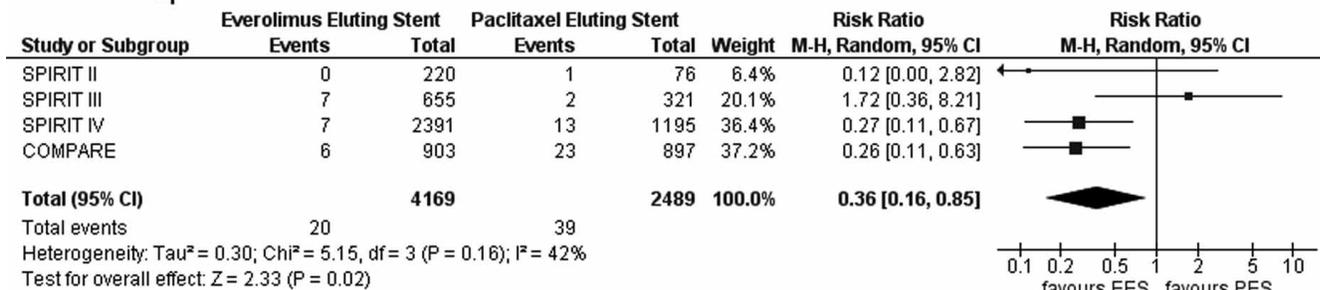


Fig. (3). Outcomes from randomized trials comparing the everolimus eluting stent versus the paclitaxel eluting stent. Size of data markers indicates the weight of the study
EES= Everolimus eluting stent, PES= Paclitaxel eluting stent

The Biomatrix™ Biolimus-eluting stent (BES, Biosensors International, Singapore) comprises a stainless steel, quadrature-link design S-stent (strut thickness 112 μm) and a poly(lactic acid) polymer/Biolimus A9 coating. This 15 μm thick coating consists of a 1:1 combination by weight of Biolimus A9 and poly(lactic acid), resulting in a standard dose of 15.6 μg of drug per mm of stent. Of note, the coating is only applied to the abluminal stent surface. Moreover, the poly(lactic acid) polymer is biodegradable and breaks down into carbon dioxide and water concurrent with drug release in 6-9 months after stent implantation. A biodegradable polymer was de-

veloped because permanent polymers in first-generation DES are thought to play a causal role in the development of late and very late stent thrombosis [98].

First-in-Man Clinical Experience

The safety and feasibility of the Biomatrix™ BES was evaluated in the first-in-man “Stent Eluting A9 bioLimus Trial in Humans” (STEALTH) trial [99]. A total of 120 patients with single *de novo* native coronary artery lesions were randomized in a 2: 1 ratio to treatment with the BES or an identical BMS. In-stent late loss at 6-

months was $0.26\pm 0.43\text{mm}$ in the BES group and $0.74\pm 0.45\text{mm}$ in the BMS group ($p<0.01$) [100].

Head-to-Head Drug-eluting Stent Trials with the Biolimus-Eluting Stent

The safety and efficacy of an updated version of the BES, called Biomatrix Flex[™] (BES, Biosensors International, Singapore), which uses the same biodegradable drug/polymer matrix on a stainless steel stent platform with a slightly altered strut design, was subsequently studied in the “Limus Eluted from A Durable versus ERodable Stent coating” (LEADERS) trial [39]. This large-scale all-comer trial randomized 857 patients to BES and 850 patients to SES. The primary endpoint was a composite of cardiac death, myocardial infarction, or clinically-driven TVR at 9 months follow-up. In LEADERS, the BES performed similar to the SES in terms of the primary clinical endpoint (9% vs 11%, $p=0.39$). An angiographic substudy in 427 patients showed similar in-stent late loss at 9 months in patients treated with BES ($0.13\pm 0.46\text{mm}$) compared to patients treated with SES (0.19 ± 0.50 , $p=0.34$). Since the biodegradable polymer degrades in 6-9 months after stent implantation, long-term results of this study will be needed to show if possible long-term differences in clinical endpoints arise between both stent types. The two-year results of LEADERS were recently presented, the primary composite endpoint had occurred in 13% of BES the group and 15.4% of the SES group, $p=0.18$) [28]. Follow-up will continue up to five years.

The Nobori[™] BES (Terumo Corporation, Tokyo, Japan) is in fact identical to the Biomatrix[™] BES but is distributed by another company through a licensing agreement. The Nobori[™] BES has been studied in a separate clinical trial program. The 243-patient NOBORI 1 trial showed superiority in reducing 9-month in-stent late loss with the BES compared to the PES ($0.11\pm 0.30\text{mm}$ vs. $0.32\pm 0.50\text{mm}$, $p<0.01$) [101]. The small nonrandomized NOBORI CORE study enrolled 107 patients, of whom 54 received a BES and 53 received a SES. Clinical event rates were low up to one year follow-up and similar between both cohorts. The large randomized all-comer BES vs. EES COMPARE 2 trial is currently enrolling and will provide important further insight into the clinical performance of the BES.

Observational Studies with the Biolimus A9-Eluting Stent

The NOBORI-2 registry included 3,068 unselected patients treated with a BES. A total of 53.3% of patients had multivessel disease, 29.8% had diabetes mellitus, 18.6% were treated for an acute myocardial infarction, 21.9% were treated in a bifurcation lesions, and 3.2% were treated for a chronic total occlusion. One-year follow-up was obtained in 97% of patients and clinical event rates were encouraging: One-year TLF, cardiac death, MI, TLR, and definite/probable stent thrombosis rates were 3.6%, 1.0%, 1.4%, 2.2% and 0.6%, respectively [102].

VERY LATE CLINICAL OUTCOME WITH SIROLIMUS (ANALOGUE)-ELUTING STENTS

Sirolimus(analogue)-eluting stents have been introduced relatively recently, at the beginning of the 21st century. The FDA approved the SES in 2003, and the ZES and EES in 2008. Therefore, very late (five-year) follow-up data on stents eluting Sirolimus or its analogues are scarce, and uncertainty exists about their long-term safety and efficacy. Particular concern exists about the permanent polymer coating and delayed neointimal stent strut coverage of many DES, which may have pro-thrombotic properties leading to an increased risk of stent thrombosis >1 year [98]. In an attempt to address these concerns, next-generation DES were designed to optimize safety and efficacy outcomes. Table 4 shows the differences in stent design between the various DES that are the topic of this review.

Table 5 shows five-year results from clinical trials and observational studies with Sirolimus(analogue)-eluting stents [21, 41, 103-106]. Five-year outcomes seem encouraging for the SES. Long-term revascularization rates are favorable, although they rise with increasing patient and lesion complexity. Of note, five-year ARC definite/probable stent thrombosis rates vary from 1%-8%. High stent thrombosis rates were reported in studies evaluating patients with ST-elevation myocardial infarction (6.9%) and patients with multivessel disease (8%), requiring long and multiple stents [41, 106]. However, results from many thousands of patients will be needed to make any conclusive statements about the long-term safety of SES.

Table 4. Differences in Stent Design Between Various Sirolimus(Analogue)-Eluting Stents

	Stent Material	Strut Thickness	Polymer	Polymer Thickness	Drug Concentration	Drug Lipophilicity	Drug Release Kinetics
Cypher [™] SES	316L stainless steel	140 μm	3-layer permanent polymer	14 μm	1.4 $\mu\text{g}/\text{mm}^2$	+	80% within 30 days, followed by gradual release in subsequent months
Endeavor [™] ZES	L-605 cobalt chromium alloy	91 μm	3-layer permanent biomimetic polymer	4 μm	1.6 $\mu\text{g}/\text{mm}^2$	+++	100% within 28 days
Endeavor Resolute [™] ZES	L-605 cobalt chromium alloy	91 μm	3-layer permanent biomimetic polymer		1.6 $\mu\text{g}/\text{mm}^2$	+++	85% within 60 days, 100% after 6 months
Xience V [™] /Promus [™] EES	L-605 cobalt chromium alloy	81 μm	2-layer permanent polymer	5 μm	1 $\mu\text{g}/\text{mm}^2$	++	80% within 30 days, 100% after 4 months
Biomatrix Flex [™] /Nobori [™] BES	316L stainless steel	112 μm	Abluminal side-only Bioabsorbable polymer (fully absorbed within 6-9 months)	15 μm (abluminal side only)	15.6 $\mu\text{g}/\text{mm}$	+++	Burst release post-implantation, gradual release up to 6-9 months

Table 5. Published Studies with Five-Year Follow-up After Sirolimus(Analogue)-Eluting Stent Implantation

	Year of Publication	Inclusion Criteria	Number of DES Treated Patients	TVF	Death/MI	Death	MI	TVR	TLR	Stent Thrombosis*
Sirolimus-eluting stent										
Randomized trials										
RAVEL, SIRIUS, E-SIRIUS, and C-SIRIUS pooled analysis	2009	Single <i>de novo</i> lesions	878	26.2%	15.1%	8.9%	7.9%	15.2%	9.6%	2.1%
STRATEGY	2009	ST-elevation myocardial infarction	87	29.9%	18.4%	21.8%	11.2%	10.3%	n/a	6.9%
Observational studies										
ARTS-II	2010	Multivessel disease	607	n/a	n/a	5.4%	4.4%	14.5%	n/a	8%
Goy <i>et al.</i>	2009	All-comers	350	n/a	n/a	8%	2%	n/a	8%	2.1%
Shen <i>et al.</i>	2009	Chronic total occlusions	76	n/a	n/a	11.8%	2.6%	n/a	6.6%	2.0%
Zotarolimus-eluting stent										
ENDEAVOR I	2009	Single <i>de novo</i> lesions	100	5.2%	n/a	4.1%	1.0%	n/a	3.1%	1.0%

*Definite/probable stent thrombosis according to ARC definition

Direct cross-trial comparisons are discouraged.

TVF= Target Vessel Failure, MI= Myocardial Infarction, TVR= Target vessel revascularization, TLR= Target lesion revascularization, n/a= not available

The ENDEAVOR I study is currently the only non-SES study with published five-year outcomes. As this first-in-man study randomized only 100 patients with single *de novo* native coronary artery lesions, it is impossible to make any definite statements on the long-term safety of the Endeavor[™] ZES. Currently, no five-year data for the EES and BES have been published.

CONCLUSION

A large number of coronary stents eluting sirolimus or its analogues are currently marketed or under development. Newer DES incorporate sirolimus-analogues developed specifically for use on a DES, biodegradable polymers, non-polymeric drug delivery, and even fully bioabsorbable coronary artery stents. Large randomized clinical trials enrolling thousands of patients are currently being performed to investigate whether these advances in stent design translate in improved safety and efficacy outcomes. These results are eagerly anticipated to guide the evidence-based decision making process in stent selection for patients with coronary artery disease.

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