

Safety and Long-Term Efficacy of Sirolimus-Eluting Stents

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ABSTRACT: Sirolimus was isolated in 1975 and was initially approved for the treatment of renal transplant rejection. The main mechanism of action is mTOR inhibition, which prevents cell cycle progression. The first-in-human study of the sirolimus-eluting stent (SES) was initiated in 1999 in Sao Paulo Brazil and Rotterdam. The study demonstrated a reduction in restenosis after SES implantation when compared with bare-metal stents. The first approved drug-eluting stent was the SES Cypher®. Several modifications in stent platform and polymer coating have been made, in an effort to improve deliverability and to reduce inflammatory response secondary to nonbiocompatible polymers. Bioabsorbable polymer and polymer-free technologies are the main characteristic of the second- and third-generation SES. Larger studies with longer follow-up are needed to prove the efficacy of those stents when compared with previous platforms.

KEYWORDS: drug-eluting stent, percutaneous transluminal coronary angioplasty, sirolimus

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Introduction

Since the introduction of balloon angioplasty by Andreas Gruetzing in 1977, percutaneous treatment of coronary artery disease has evolved substantially. With the advent of new technologies and adjuvant therapies, the use of percutaneous coronary intervention (PCI) has expanded dramatically during the past three decades. Nowadays, PCI is the preferred method of revascularization in Europe and in the United States.¹ Two main limitations of balloon angioplasty initially prevented the widespread of this therapy for the treatment of coronary artery disease: restenosis and abrupt vessel closure. Later, in 1986, Sigwart et al. implanted the first series of bare-metal stent (BMS).² The use of BMS prevented early arterial recoil and abrupt vessel closure; however, the need of repeat revascularization due to intra-stent restenosis remained high. Overall, rate of angiographic restenosis after BMS implantation was 20%.³ Clinically, intra-stent restenosis can be presented as stable angina or as an acute coronary syndrome. Endothelial injury after stent implantation stimulates cell

proliferation that leads to neointimal hyperplasia,⁴ the main characteristic of intra-stent restenosis.

Drug-eluting stents (DES) were successfully developed with the objective to reduce cell proliferation and subsequently, to decrease the rate of restenosis. In general, DES consist of three components: the stent, the drug carrier, and a pharmacologic agent. Sirolimus-eluting stents (SES) were the first DES approved for human use, receiving CE approval in April 2002, and FDA approval in April 2003. In this study, we review the reported efficacy of first-generation SES (Cypher® stent) and of newer SES designs.

Mechanism of Action, Metabolism, and Pharmacokinetic Profile

Sirolimus (also known as rapamycin) was first isolated from *Streptomyces hygroscopicus* in 1975 by Vézina and colleagues on Easter Island. The name of rapamycin was inspired by the local name of the Island, Rapa Nui.⁵ Later on, sirolimus was purified and found to be active against several fungi and some

bacteria.⁵ Chang and Sehgal identified the antiproliferative properties of the drug.⁶

Sirolimus is a macrocyclic lactone, with a very high lipophilic profile. The US Food and Drug Administration (FDA) approved the drug as Rapamune[®] for the treatment of renal transplant rejection. The main mechanism of action is its binding to an intracellular receptor protein, FK-binding protein-12 (FKBP-12). This elevates p24 levels, inhibiting activation of the mammalian target of rapamycin (mTOR) and preventing cell cycle progression from G1 to S phase⁷ (Fig. 1). After SES implantation, sirolimus is barely released into the bloodstream. Sirolimus is highly lipophilic, with rapid absorption and low systemic bioavailability. Sirolimus pharmacokinetics may vary between patients; however, blood concentration levels after SES implantation is extremely low.⁸ The effect on the suppression of neointimal hyperplasia was demonstrated in preclinical studies.^{9,10} The first-in-human feasibility study of the Cypher[®] stent was initiated in 1999 at the Institute Dante Pazzanese of Cardiology in Sao Paulo, Brazil, and the Thoraxcenter, Rotterdam, The Netherlands, demonstrated a reduction in restenosis after SES implantation.¹¹

Sirolimus has several analogs, including everolimus, zotarolimus, biolimus, and novolimus; in all of them, the inhibition of mTOR is the main mechanism of action.

Sirolimus-Eluting Stents Platforms

There are several generations of SES. After the first-generation, Cypher[®] stent was approved in 2002, it remained in the market until 2011, then it was discontinued because of business decisions related to market dynamics. Improvements in stent platforms for better deliverability, the development of

polymers with greater biological compatibility, and the use of bioabsorbable coatings or polymer-free stents characterize the second and third generations. Main SES characteristics are depicted in Table 1.

Durable polymer-based SES: the Cypher[®] stent. The majority of the information available on SES comes from clinical trials that used the Cypher[®] stent. This stent has a multi-layer coating, with an initial parylene tie-layer applied to the stent surface, followed by a polyethylene-*co*-vinyl acetate and poly-*n*-butyl methacrylate mixture that contains the sirolimus drug, and finally a top coat polymer (without drug) to control the drug-elution rate. The platform was that of the Bx VELOCITY[®] stent, made of stainless steel. The luminal and abluminal surfaces were coated with nonerodible polymers loaded with 140 $\mu\text{g}/\text{cm}^2$ of sirolimus. The Cypher[®] stent used in clinical practice released 80% of the drug within the first month after stent implantation.

Bioabsorbable polymer-based SES. The first large-scale trial of a bioabsorbable polymer-based stent used the CoStar[™] paclitaxel-eluting stent (PES),¹² and the most comprehensive clinical data are from the commercially available biolimus-eluting stents, Nobori[®]¹³ and BioMatrix[™].¹⁴ Several newer SES platforms, described below, incorporate bioabsorbable polymeric coatings.

The Yukon[®] Choice stent combines a microporous abluminal surface with a sirolimus and biodegradable polymer coating. The Orsiro[®] stent uses the platform of the PRO-Kinetic Energy stent and a bioabsorbable polymer with polylactic acid. The Supralimus[®] stent was recently introduced for routine use in Europe. It is built on a stainless steel platform, coated with a blend of biodegradable polymers. The XLIMUS[®]

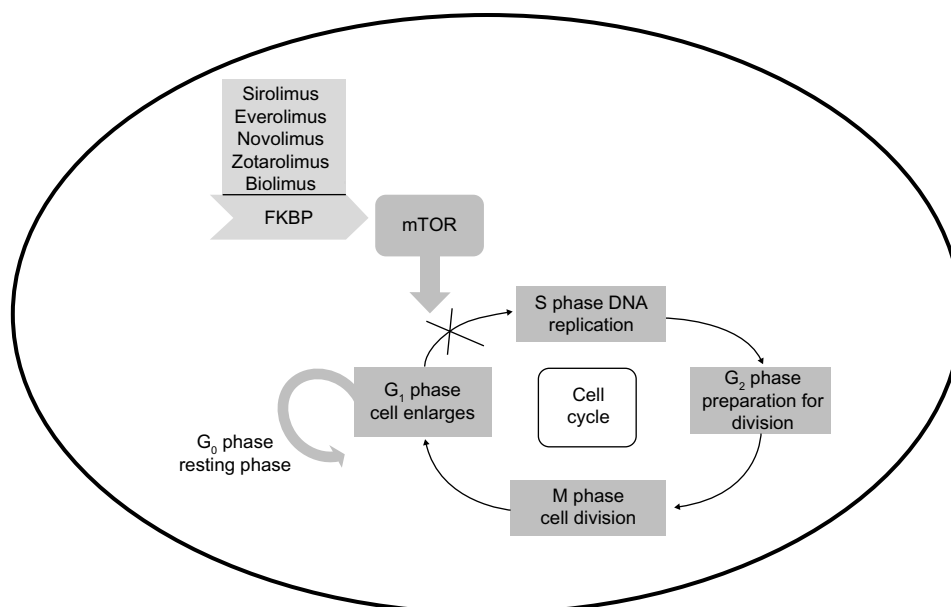


Figure 1. Mechanism of action of sirolimus and derivatives. Sirolimus binds to the cytosolic FK-binding protein (FKBP). The sirolimus-FKBP complex inhibits the mammalian target of rapamycin (mTOR) receptor, resulting in cell arrest by stopping proliferation prior to G1.

**Table 1.** Main characteristics and specification of sirolimus-eluting stents.

CLASS	STENT	STRUT THICKNESS (µm)	METAL	POLYMER	POLYMER THICKNESS (µm)	DRUG DOSE	RELEASE KINETICS (30 DAYS)
First generation	Cypher®	140	Stainless steel	Polyethylene co-vinyl acetate and poly-n-butyl methacrylate	13.7	1.4 µg/mm ²	80% release in 20 days
Biodegradable polymer	Orsiro®	60	Cobalt-chromium	Poly-L-lactic acid (PLA)	7.4	1.4 µg/mm ²	70% release in 90 days
	Supralimus® Core	60	Cobalt-chromium	Poly-L-lactic acid, Polylactic-co-glycolic acid, polyvinyl-pyrrolidone	6	1.4 mcg/mm ²	70% release in 7 days
	Nevo™	100	Cobalt-chromium	Polylactic-co-glycolic acid (PLGA)	Embedded reservoirs	166 µg in a 3 x 17 mm stent	80% release in 30 days
	Xlimus®	73	Cobalt-chromium	Poly-L-lactic acid (PLA)	2	1.25 µg/mm ²	70% release in 30 days
	Excel™	119	Stainless steel	Poly-L-lactic acid (PLA)	10–15	195–376 µg	NA
	CORACTO™	80	Stainless steel	Polylactic-co-glycolic acid (PLGA)	4	1.7 µg/mm	100% in 70 days
Polymer free	VESTASync™	65	Stainless steel			55 µg	100% in 25 days
	YUKON Choice™	65	Stainless steel			11.7–21.9 µg	100% in 90 days
	Cre8™	80	Cobalt-chromium			0.9 µg/mm ²	100% in 90 days
Cell capture	COMBO Dual™	100	Stainless steel	Abluminal biodegradable and luminal CD 34 antibody layer	5	5 µg/mm	100% in 90 days

Abbreviation: NA, Not available.

stent is composed by cobalt chromium platform with biodegradable polymer and sirolimus with crossing profile of 0.9 mm. The NEVO™ stent contained multiple laser-cut reservoirs individually filled with bioabsorbable polymer blended with sirolimus. The CORACTO™ rapamycin-eluting stent incorporates the medical grade 316 LVM stainless steel balloon-expandable Constant stent (Alvimedica Inc., Istanbul, Turkey) as platform, rapamycin (1.7 µg/mm², with a maximal drug load of the stent of 215 µg) as an antirestenotic drug, and a poly (lactic-co-glycolic acid) as biodegradable polymer.

Polymer-free SES. The VESTASync™ stent combines a stainless steel platform with a hydroxyapatite surface impregnated with a polymer-free sirolimus mixture. The CRE8™ is a stent based on Amphilimus™, a sirolimus formulated with a polymer-free amphiphilic carrier released from a reservoir machined onto the abluminal stent.

Sirolimus-eluting endothelial progenitor cell capture stent. The COMBO Dual Therapy Stent® (OrbusNeich Medical Technologies) is the first stent to combine a luminal anti-CD34 antibody with antiproliferative abluminal sirolimus elution. It has an abluminal coating of bioabsorbable polymer matrix formulated with sirolimus (5 µg/mm of stent length) for sustained release and a luminal anti-CD34 antibody cell capture coating. The antibodies bind to the CD34 membrane protein expressed on the cell surface of endothelial progenitor cells, thus anchoring the cells to the stent.

Clinical Studies

First-generation SES (Cypher® stent) vs BMS. Most of the studies that compared SES vs BMS were performed with first-generation DES. The benefit of SES in reducing the rate of restenosis was demonstrated in several pivotal trials, such as RAVEL, SIRIUS, and SCANDSTENT (Table 2).

In the RAVEL trial, 238 patients were randomized to SES or BMS. Inclusion criteria were stable angina, unstable angina, or silent ischemia. The primary end point was late luminal loss at 6 months. The use of SES was associated with significantly lower late-lumen loss (–0.01 mm vs 0.80 mm); furthermore, the rate of adverse cardiac events was significantly lower with the sirolimus stent at 1-year follow-up (29% vs 6%) due to a lower rate of target lesion revascularization (23% vs 0%).¹⁵ After 5 years of follow-up, the rate of target lesion revascularization remained lower with the SES (26% vs 11%).¹⁶

The SIRIUS trial randomized 1058 patients to SES or BMS. Inclusion criteria were stable or unstable angina. SES were superior to BMS in the primary end point of target-vessel failure at 1 year (8.6% vs 21.0%; $P < 0.001$).¹⁷ At 5 years, the benefit of SES was maintained (22.5% vs 33.5%; $P < 0.001$).¹⁸

The SCANDSTENT trial included 322 patients with complex coronary artery disease. At 3-year follow-up, patients randomized to SES had a lower rate of target lesion revascularization (33.8% vs 4.9%).^{19,20}

**Table 2.** Randomized controlled trials comparing first generation sirolimus-eluting stent.

TRIAL	TYPE OF STUDY	N. OF PATIENTS	PRIMARY ENDPOINT	PRIMARY OUTCOMES
RAVEL	SES vs. BMS	238	Late lumen loss at 6 months	SES (-0.01 ± 0.33 mm) vs. BMS (0.80 ± 0.53 mm); $P < 0.001$
SIRIUS	SES vs. BMS	1058	Failure of target vessel (composite of death from cardiac causes, MI, and repeat revascularization of TV) at one year	SES 8.6% vs. BMS 21.0%; $P < 0.001$
SCANDSTENT	SES vs. BMS	322	Difference in minimal lumen diameter at 6 months	SES 2.48 mm vs. BMS 1.65 mm; $P < 0.001$
ISAR-TEST-4	DES with permanent polymer (EES or SES) vs. biodegradable polymer stent	2603	Composite of cardiac death, TV-MI, or TL revascularization at 9 months	Biodegradable polymer (20.1%) vs. permanent polymer DES (20.9%) (HR:0.95, 95% CI 0.8–1.1; $P = 0.59$)
SIRTAX	SES vs. PES	1012	Composite of death from cardiac causes, MI, and ischemia-driven revascularization of the TL at 9 months	SES 6.2% vs. PES 10.8% (HR 0.56, 95% CI 0.36–0.86; $P = 0.009$)
RESET	SES vs. EES	3197	TL revascularization at 1 year	EES 4.3% vs. SES 5.0%; p for noninferiority < 0.0001
ENDEAVOR III	SES vs. ZES	436	Late lumen loss at 8 months	ZES (0.34 ± 0.44 mm) vs. SES (0.13 ± 0.32 mm); $P < 0.001$.
SORT OUT III	SES vs. ZES	1162	Composite of cardiac death, MI, and TV revascularisation at 9 months	ZES 6% vs. SES 3% (HR 2.15, 95% CI 1.43–3.23; $P = 0.0002$)
SORT OUT IV	SES vs. EES	1390	Composite of safety (cardiac death, MI, definite stent thrombosis) and efficacy (TV revascularization) at 9 months	EES 4.9% vs SES 5.2% (HR 0.94; 95% CI 0.67–1.31; p for noninferiority < 0.01
ZEST	SES and PES vs. ZES	2645	Composite of death, myocardial infarction, and ischemia driven TV revascularization at 12 months	ZES 10.2% vs. SES 8.3%; p for noninferiority = 0.1 ZES 10.2% vs. PES 14.1%; p for superiority = 0.01

Abbreviations: BMS, Bare-metal stent; DES, Drug-eluting stent; HR, Hazard Ratio; MI, Myocardial infarction; PES, Paclitaxel-eluting stent; SES, Sirolimus-eluting stent; TL, Target lesion; TV, Target vessel; ZES, Zotarolimus-eluting stent.

Previous studies were not powered to detect hard clinical end points (myocardial infarction (MI) or death). However, several large off-label indication registries have demonstrated a lower rate of MI deaths with the use of SES.^{21,22}

First-generation SES (Cypher® stent) vs. PES. A meta-analysis compared short-term outcomes of SES vs PES. Sixteen randomized trials with a total of 8695 patients were included. The primary efficacy end point was target lesion revascularization, and the primary safety end point was stent thrombosis. There was no significant heterogeneity. Compared with PES, SES reduced the risk of re-intervention (Hazard Ratio (HR) 0.74, 95% confidence interval (CI) 0.63–0.87) and stent thrombosis (HR 0.66, 95% CI 0.46–0.94).²³ Long-term data are available from the SIRTAX LATE trial. Patients were randomized to SES or PES with up to five years of follow-up. There was no significant difference between SES and PES in stent thrombosis rates or cardiac death, MI, and target lesion revascularization.²⁴

First-generation SES (Cypher® stent) vs SES with different polymer coatings. The ISAR-TEST-4 evaluated the use of three limus agent-eluting stents with different polymer coatings. Patients with stable coronary artery disease or acute coronary syndrome were randomized to biodegradable polymer-based SES (Yukon PC Choice®) vs durable

polymer-based DES (Cypher® or the everolimus-eluting stent (EES), Xience®). It was a noninferiority trial, and the primary end point was a composite of death, MI related to target vessel, or revascularization related to target lesion. There was no significant difference in the primary end point up to 3 years.²⁵

First-generation SES (Cypher® stent) vs second-generation DES (EES or zotarolimus-eluting stents (ZES)). Although EES have been found to be superior to PES, they appeared to be comparable to SES for clinical outcomes that include death, MI, revascularization, and stent thrombosis.^{26,27} To date, ZES appear to have clinical outcomes that are better than PES and similar to SES, despite inferior angiographic results.^{28–32}

Clinical studies with second-generation SES. The Yukon Choice™ stent was tested in the ISAR-TEST 4 trial (see above). BIOFLOW-I was a first-in-human study that used the Orsiro® stent and included 30 patients with documented myocardial ischemia. Late lumen loss was 0.12 mm at four months; two patients had target lesion revascularization. The BIOFLOW-II trial compared the Orsiro™ and Xience™ stents. The primary end point (late lumen loss at 9 months follow-up) was comparable (noninferior) for both types of stents.³ The SUPRALIMUS™ stent was evaluated in the SERIES-I study, showing a low late-lumen loss of



0.09 ± 0.28 mm.³³ The PAINT trial compared two identical stents but with different agents (INFINNIUM stent with PES vs SUPRALIMUS stent with SES) against BMS. Both experimental stent groups had lower rates of repeat revascularization at three years than BMS (29.9% vs 10%).³⁴

The XLIMUS™ stent was tested in a single-center pilot study that evaluated its performance in very complex lesions ($n = 53$), with favorable tracking and lesion-crossing performance.³⁵ The NEVO™ stent was tested in the NEVO RES-I trial that proved the superiority of the stent over PES for late lumen loss at 6-month angiographic follow-up.³⁶ The NEVO II trial (NEVO™ stent vs XIENCE® stent) was discontinued due to technical problems with the NEVO™ platform. Few OCT data were reported on this stent, which is currently off the market.³⁷

The VESTASync™ stent was evaluated in the VESTASync I single-center, nonrandomized trial ($n = 15$). At nine-month follow-up, late lumen loss was 0.36 ± 0.23 mm.³⁸

The CRE8™ stent was tested in a randomized, multicenter, noninferiority trial in terms of late lumen loss compared to Taxus Liberté™ stent. A total of 323 patients were included in the study. The CRE8™ stent showed significantly lower late-lumen loss at six months than the Taxus Liberté™ (0.14 mm vs 0.34 mm).³⁹ The RESERVOIR trial is aimed to determine whether CRE8™ stent implantation is effective in reducing hyperplasia as compared to Xience™ stent in diabetic patients.

In the REMEDEE trial, the Combo™ stent was shown to be safe and effective, meeting a noninferiority angiographic end point of late lumen loss (0.39 vs 0.44 ; P for noninferiority = 0.0012) when compared with the Taxus Liberté™ stent.³⁶

Clinical trials in specific scenarios. *Acute MI.* In this clinical scenario, six randomized controlled trials of first-generation SES vs BMS have been published, two of SES vs PES, and one of SES vs EES in STEMI (Table 3).^{40–49} With 712 patients, the TYPHOON study⁴⁰ was the largest trial to assess the effectiveness and safety of SES vs. BMS at one year. Target-vessel failure was significantly lower in the SES (7.3%) than in the BMS (14.3%) group ($P = 0.004$), driven by a decrease in the rate of target vessel revascularization (5.6% vs. 13.4%, respectively; $P < 0.001$). There was no significant difference between the two groups, respectively, in the rates of mortality (2.3% vs. 2.2%; $P = 1.00$), reinfarction (1.1% vs. 1.4%; $P = 1.00$), or stent thrombosis (3.4% vs. 3.6%; $P = 1.00$). At four-year follow-up, freedom from target lesion revascularization was significantly better in the SES group, compared to BMS (92.4% vs. 85.1%; $P = 0.002$).⁵⁰ However, no differences were observed, respectively, in freedom from cardiac death (97.6% vs. 95.9%; $P = 0.37$), freedom from repeat MI (94.8% vs. 95.6%; $P = 0.85$), or definite/probable stent thrombosis (4.4% vs. 4.8%, $P = 0.83$).

Diabetes mellitus. The DIABETES (Diabetes and SES) trial⁵¹ was the first randomized, multicenter, controlled trial specifically designed to assess the efficacy of SES vs BMS

in diabetics (Table 4). This study included 160 diabetic patients, 80 of whom received BMS, while 80 were treated with SES. Late lumen loss assessed by Quantitative Coronary Angiography (QCA) at nine-month follow-up was the primary end point. The SES-treated group showed a significant reduction of late lumen loss (relative reduction 87%). This benefit was maintained up to five-year follow-up.⁵² Subsequently, three other randomized trials also designed for diabetic patients (SCORPIUS,⁵³ DESSERT,⁵⁴ and DECODE⁵⁵) have corroborated the same positive results of SES in reducing neointimal proliferation (Table 3). A recent meta-analysis of all available data in diabetics treated with PCI demonstrated the benefit of SES in terms of restenosis and target lesion revascularization.⁵⁶

Other studies compared two different DES platforms in this clinical context. The ISAR (In-Stent Angiographic Restenosis)-DIABETES trial⁵⁷ was a prospective noninferiority trial that randomized 250 diabetic patients to the Taxus ($n = 125$) or Cypher ($n = 125$) stents. The use of SES in diabetics was associated with a decrease in late lumen loss. Recently, first-generation SES was compared against EES in the ESSENCE DIABETES trial ($n = 300$). As primary end point, late lumen loss was 0.23 ± 0.27 for EES vs 0.37 ± 0.52 mm for SES; $P < 0.001$ for noninferiority.⁵⁸

Chronic total occlusion. In this setting, few trials have compared the use of SES with BMS or with other DES. In the PRISON-II trial, treatment with SES significantly reduced the rates of binary angiographic restenosis (from 41% to 11%; $P < 0.01$), vessel re-occlusion (from 13% to 4%; $P = 0.04$), and the need for new revascularization procedures (from 22% to 8%; $P < 0.01$) in comparison with BMS.⁵⁹ In the GISSOC II-GISE multicenter randomized trial, 152 patients were randomized to implantation of SES (78 patients) or BMS (74 patients) in 13 Italian centers. The primary end point was in-segment minimal luminal diameter at eight-month follow-up. Patients treated with SES showed, at in-segment analysis, a larger minimal lumen diameter (1.98 ± 0.57 mm vs 0.98 ± 0.80 mm; $P < 0.001$), a lower late-luminal loss (-0.06 ± 0.49 mm vs 1.11 ± 0.79 mm; $P < 0.001$), and lower restenosis (9.8% vs 67.7%; $P < 0.001$) and re-occlusion (0% vs 17%; $P = 0.001$) rates. At 24-month follow-up, patients in the SES group experienced fewer major adverse cardiac events (50.0% vs 17.6%; $P < 0.001$), mainly due to a lower rate of both target lesion revascularization (44.9% vs 8.1%; $P < 0.001$) and target vessel revascularization (44.9% vs 14.9%; $P < 0.001$).⁶⁰

In the CIBELES trial, 207 patients were randomized to EES or SES. The primary end point was in-stent late loss at nine-month angiographic follow-up (noninferiority trial). In-stent late loss at nine months was 0.29 ± 0.60 mm vs 0.13 ± 0.69 mm in patients allocated to SES and EES, respectively. The observed difference in in-stent late loss between both groups was -0.16 mm (95% CI, 0.04 to -0.36 mm; P for noninferiority < 0.01). The rate of binary angiographic restenosis was 10.8% and 9.1% in patients allocated to SES

**Table 3.** Randomized controlled trials comparing sirolimus-eluting stent in patients with myocardial infarction.

TRIAL / AUTHOR	TYPE OF STUDY	N. OF PATIENTS	PRIMARY ENDPOINT	PRIMARY OUTCOMES
TYPHOON	SES vs. BMS	712	TV failure (composite of TV related death, recurrent MI, or TV revascularization) at 1-year	SES 7.3% vs. BMS 14.3%; $P = 0.004$
STRATEGY	SES vs. BMS	175	Composite of death, MI, TV revascularization at 2 years	SES 24.2% vs. BMS 38.6% (HR 0.56; 95% CI 0.33–0.98; $P = 0.038$)
SESAMI	SES vs. BMS	320	Binary restenosis at 1-year	SES 9.3% vs. 21.3%; $P = 0.032$
Díaz de Llera et al.	SES vs. BMS	114	Composite of cardiac death, recurrent MI, or TL revascularization at 1-year	SES 6.7% vs. BMS 11%; $P = 0.402$
MISSION!	SES vs. BMS	310	Late lumen loss at 9 months	SES (0.12 ± 0.43 mm) vs. BMS (0.68 ± 0.57 mm); $P < 0.001$
MULTISTRATEGY	SES vs. BMS	744	Composite of death, reinfarction, and clinically driven TV revascularization at 8 months	SES 7.8% vs. BMS 14.5%; $P = 0.004$
Juwana et al	SES vs. PES	397	Late lumen loss at 9 months	SES (0.01 ± 0.42 mm) vs. PES (0.21 ± 0.50 mm); $P = 0.001$
ZEST-AMI	SES vs. PES vs. ZES	328	Composite of death, MI, ischemia-driven TV revascularization at 12 months	SES 8.2% vs. ZES 11.3% vs. PES 8.2%; $P = 0.834$
KOMER	SES vs. PES vs. ZES	611	Composite of cardiac death, recurrent MI, ischemia-driven TL revascularization at 12 months	SES 3.4% vs. ZES 5.9% vs. PES 5.7%; $P = 0.457$
XAMI	SES vs. EES	625	Composite of cardiac death, nonfatal MI, TV revascularization	SES 7.7% vs. EES 4.0%; $P = 0.048$

Abbreviations: BMS, Bare-metal stent; CTO, Chronic total occlusion; DES, Drug-eluting stent; DM, Diabetes Mellitus; HR, Hazard Ratio; MI, Myocardial infarction; PES, Paclitaxel-eluting stent; SES, Sirolimus-eluting stent; TL, Target lesion; TV: Target vessel; ZES, Zotarolimus-eluting stent.

and EES, respectively ($P 0.709$). At 12 months, the rate of probable or definitive stent thrombosis occurred in 3.0% and 0.0% of patients, respectively ($P 0.075$).⁶¹

One trial tested the use of biodegradable polymer-based SES in chronic total occlusion. In the CORACTO trial, 95 patients were randomized to BMS ($n = 47$) or SES ($n = 48$). The primary end points were late lumen loss and in-segment restenosis after 6 months. At follow-up, late lumen loss and angiographic restenosis were significantly better with the CORACTO® stent (1.8 mm vs 0.77 mm and 60% vs 17.4%, respectively; both $P < 0.0001$).⁶²

Safety Concerns

Although RCTs did not identify any safety issues with first-generation DES, this topic became a firestorm during the 2006 European Society of Cardiology Annual Meeting. Meta-analysis of pooled data showed that first-generation DES increased mortality and MI compared to BMS.⁶³ High rates of early- and late-stent thrombosis after discontinuation of dual antiplatelet agents in patients treated with first-generation DES also raised safety concerns.⁶⁴ Pathology studies demonstrated that the durable polymers used in first-generation DES could cause a delay in arterial healing, characterized by persistent fibrin deposits, delayed hypersensitivity reactions, and poor endothelialization of the vessel wall, all of which increased the thrombotic risk. Second-generation DES performed otherwise.⁶⁵ The risk of stent thrombosis after

DES implantation is not class specific and is more related to increased inflammatory response and the poorer stent platforms of first-generation DES. A lack of uniform definition of stent thrombosis has made it difficult to compare different studies of first-generation SES. Data from the Bern-Rotterdam registry showed a steady rate of stent thrombosis of 0.6% per year with the use of first-generation SES.⁶⁶ This rate reached 0.8% at nine months in the German-Italian registry.⁶⁷ The j-Cypher registry included 10 778 patients with up to 2 years of follow-up; the incidence of definite stent thrombosis was 0.34% at 30 days, 0.54% at 1 year, and 0.77% at 2 years.⁶⁸ In a small long-term study, SES had incomplete neointimal coverage by angiography at 21 months in most of the 17 patients evaluated. Furthermore, the presence of mural red thrombi was only seen in patients with SES and incomplete neointimal coverage.⁶⁹ Although the risk of very late stent thrombosis in patients receiving newer generations of SES has not yet been studied, the lower-than-expected rates of stent thrombosis reported to date suggest that this risk is more related to the stent platform and the presence of certain polymer coatings than to the drug used.⁷⁰ As discussed above, sirolimus has an antiproliferative effect and, as a result, incomplete neointimal coverage due to delayed reendothelialization in first-generation SES was observed; however, second-generation stents have greater neointimal coverage in OCT evaluation,⁷¹ without an increase in neointimal hyperplasia and subsequent restenosis. Evolution from first-generation to second- and third-generation SES was characterized by

Table 4. Randomized controlled trials comparing sirolimus-eluting stent in patients with diabetes mellitus.

TRIAL / AUTHOR	TYPE OF STUDY	N. OF PATIENTS	PRIMARY ENDPOINT	PRIMARY OUTCOMES
DIABETES	SES vs. BMS	160 (all DM)	Late lumen loss at 9 months	SES (0.06 ± 0.4 mm) vs. BMS (0.47 ± 0.5 mm); <i>P</i> < 0.001
SIRTAX	SES vs. PES	1012 (250 DM)	Composite of cardiac death, MI, and ischemia-driven TL revascularization	SES 14.8% vs. BMS 25.8%; <i>P</i> = 0.05
ISAR-DIABETES	SES vs. PES	250 (all DM)	In-segment late lumen loss at 9 months	SES (0.43 ± 0.45 mm) vs. PES (0.67 ± 0.62 mm); <i>P</i> = 0.002
ESSENCE DIABETES	SES vs. EES	300 (all DM)	In-segment late lumen loss at 8 months	SES (0.37 ± 0.52 mm) vs. EES (0.23 ± 0.27 mm); <i>p</i> for noninferiority < 0.001
SCORPIUS	SES vs. BMS	200 (all DM)	In-segment late lumen loss at 8 months	SES (0.17 ± 0.45 mm) vs. BMS (0.75 ± 0.59 mm); <i>P</i> = <0.0001
DESSERT	SES vs. BMS	75 (all DM)	In-stent late lumen loss at 8 months	SES (0.14 ± 0.33 mm) vs. BMS (0.96 ± 0.61 mm); <i>P</i> = <0.001
DECODE	SES vs. BMS	200 (all DM)	In-stent late lumen loss at 6 months	SES (0.23 ± 0.32 mm) vs. BMS (1.1 ± 0.59 mm); <i>P</i> = <0.001

Abbreviations: BMS, Bare-metal stent; CTO, Chronic total occlusion; DES, Drug-eluting stent; DM, Diabetes Mellitus; HR, Hazard Ratio; MI, Myocardial infarction; PES, Paclitaxel-eluting stent; SES, Sirolimus-eluting stent; TL, Target lesion; TV, Target vessel; ZES, Zotarolimus-eluting stent.

changes in polymer coating to reduce the inflammatory reaction; narrowing of struts, with increased stent coverage and as a result lower stent thrombosis⁷² and fewer jailed side branches⁷³; and modified release patterns of drugs⁷⁴ to improve the safety and clinical outcomes of newer stent designs.

Double antiplatelet treatment (DAPT) after SES implantation was recommended for at least one year in American Societies guidelines⁷⁵ and between 6 and 12 months in European guidelines.⁷⁶ DAPT is typically the combination of aspirin with a P2Y12 inhibitor such as clopidogrel, prasugrel, or ticagrelor. In the era of first-generation SES, premature discontinuation of DAPT (<6 months) increased the risk of stent thrombosis.⁷⁷ When triple therapy with an oral vitamin K inhibitor is required due to a high CHADS₂ score, mechanical valve, or recurrent embolism, the treatment should be prescribed for the shortest necessary duration with frequent INR measurement (target INR 2–2.5).⁷⁶

Another issue that may be related to the use of DES in general and first generation SES in particular is the development of neoatherosclerosis. A pathology study demonstrated that this phenomenon occurs earlier after the implantation of first-generation DES than that of BMS.⁷⁸ Larger clinical studies with longer follow-up are required to assess the use of second-generation SES.

Conclusions

The Cypher[®] stent, the most thoroughly studied of the SES and the first of the DES approved in the United States and Europe, was commercially discontinued in 2011. Beyond one-year follow-up, there were no safety concerns about those first-generation SES. In recent years, considerable advances have been made in the development of SES, including improvements in platform and polymer coating. First-in-human trials

have demonstrated the safety and effectiveness of the second-generation SES that are currently available. However, larger studies with longer follow-up are needed to prove the absence of undesirable long-term effects.

Author Contributions

Wrote the first draft of the manuscript: AR. Contributed to the writing of the manuscript: MS. Agree with manuscript results and conclusions: AR, MS. Jointly developed the structure and arguments for the paper: AR, MS. Made critical revisions and approved final version: AR, MS. All authors reviewed and approved of the final manuscript.

Abbreviations

BMS: Bare-metal stent
 DES: Drug-eluting stent
 EES: Everolimus-eluting stent
 mTOR: Mammalian target of rapamycin
 PCI: Percutaneous coronary intervention
 PES: Paclitaxel-eluting stent
 SES: Sirolimus-eluting stent
 ZES: Zotarolimus-eluting stent

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