Current perspective

Drug-eluting stents. The third revolution in percutaneous coronary intervention

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Local stent-based drug delivery (drug-eluting stent - DES) is a new technology aimed to prevent the development of neointimal hyperplasia and restenosis following percutaneous coronary interventions. A number of DESs have been developed using different carrier stents, different kind of coatings, and different drugs. However, to date only two polymer-coated DESs (the Cypher™ sirolimus-eluting stent from Cordis, Johnson & Johnson, Miami Lake, FL, USA; and the Taxus™ paclitaxel-eluting stent, Boston Scientific, Natick, MA, USA) have become commercially available after a number of randomized trials showed their ability to reduce late luminal loss, binary restenosis and the need for repeat revascularization when compared to bare metal stents.

This review describes the general concept of DES and summarizes the results of the principal clinical trials on DESs, both approved for clinical use or under development. For the marketed stents, we also report the results of the first clinical evaluations in real life and a few insights into the most controversial issues.

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Introduction

Coronary stenting, by reducing both the acute risk of major complications and the incidence of restenosis, has gradually replaced conventional balloon angioplasty as the standard technique to accomplish percutaneous coronary interventions (PCIs)[1,2]. However, in-stent restenosis still occurs in 10 to 50% of the patients, depending upon a number of clinical, angiographic, and procedural variables[3-5].

In April 2002, the first drug-eluting stent (DES) became commercially available in Europe, beginning what has been called the third revolution in PCI following the introduction of balloon angioplasty and stents. The DES combines the advantages of a stainless steel scaffold with controlled release of an antiproliferative agent to prevent restenosis[6]. Local drug delivery allows to achieve appropriate drug concentration at the treatment site while avoiding systemic toxic effects.

Although DESs are likely to become soon the new standard strategy for PCI, a major debate regarding their correct utilization is ongoing. Evidence-based medicine, cost-effectiveness ratio, and necessity to complete scientific evaluation in every subset of patients and lesions, have resulted in different strategies between different countries and different hospitals[7-10].

A number of issues are still unsolved, such as long-term outcome, optimal duration of dual antiplatelet therapy following DES implantation, predictors and treatment of failures, equivalence/difference among DESs, economical impact for hospitals and health service resources compared to alternative strategies.

In the present article we sought to summarize the main clinical data available on DESs, and to provide a few insights into the most controversial issues on DES utilization.

The devices

A DES has three basic components: the stent, the coating, and the biological agent. A number of DESs have been developed using different carrier stents, different kinds of coating, and different drugs[6,11].

Although stent designs dedicated to drug delivery have been developed, and clinical investigations are currently ongoing, the best results obtained to date have been achieved using available conventional bare-metal stents (BMSs) as drug carriers. Nevertheless, compounds with narrow tox-

ic-therapeutic windows or different physicochemical properties may require a customized stent platform. To ensure uniform drug delivery, the ideal DES should have a large surface area, minimal gaps between cells, and minimal strut deformation after deployment. Furthermore, these stents would need to maintain a good deliverability even in more complex lesions, through a low profile, good conformability and radial support, and appropriate flexibility.

A variety of different formulations have been developed that provide appropriate stent coating for clinical use, including direct drug binding, coatings with phosphorylcholine, non-erodible or bioabsorbable polymers, or ceramic layers. The coating should not induce an excessive vascular reaction[12], should be suitable for sterilization, it must follow the geometric change of configuration during stent expansion, be resistant to mechanical abrasion during stent implantation, and it should be able to release the drug in a controlled way. A potential universal coating is unlikely, and different pharmacological agents may require different delivery vehicles.

The biological agent carried by the stent should interfere with one or more steps involved in the restenosis process, yet preserving vascular healing. A number of antiproliferative, immunosuppressive, anti-inflammatory, antithrombotic, and prohealing drugs have been tested or are under investigation (Table I).

To date, only two DESs have received CE (Conformité Européenne) and FDA (Food and Drug Administration) approval for clinical use in Europe and in the United States, respectively: the Cypher™ sirolimus-eluting stent (SES) (Cordis, Johnson & Johnson, Miami Lake, FL, USA), and the TAXUS™ paclitaxel-eluting stent (PES) (Boston Scientific, Natick, MA, USA). In randomized trials, both these stents have been shown to dramatically reduce late luminal loss, binary restenosis, and the need for repeat revascularization when compared to BMSs[13-17] (Figs. 1 and 2).

Sirolimus (rapamycin) is a macrocyclic lactone produced by *Streptomyces hygroscopicus*, which inhibits cellular proliferation by blocking cell cycle progression at the G1 to S transition[18-20], and inhibits vascular smooth muscle cell migration[18]. In the Cypher™ stent, a combination of two non-erodible polymers (polyethylene-co-vinyl acetate, and poly n-butyl methacrylate [PBMA]) mixed with sirolimus (67%/33%) makes up the basecoat formulation which is applied to a parylene C-treated stent. A drug-free topcoat of PBMA polymer is applied to the stent surface to control the release kinetics of sirolimus (> 28 days)[6].

Paclitaxel (taxol) is an antineoplastic agent that shifts the microtubule equilibrium toward assembly. This enhances the assembly of extraordinarily stable microtubules, interrupting proliferation, migration, and signal transduction[21-23]. In the Taxus™ stent, 1 $\mu g/mm^2$ paclitaxel is incorporated in a poly(lactide-co-Σ-caprolactone) copolymer attached to a conventional stent. Two different release kinetics were evaluated: slow release (continuous drug release throughout the first 15-20 days), and moderate release (the drug is released within the first 2 days after stent implantation).

Other DESs are undergoing clinical or preclinical evaluation: some appear very promising and are likely to enter the market soon, other gave less brilliant results, whilst a few have been clearly disappointing (Table II)[24-27].

Randomized trials

To date, many randomized controlled trials on DESs have been completed. However, while studies on SESs represent a homogeneous group utilizing one single de-

Table I. Potential candidates for drug elution and principal mechanisms of action.

Antiproliferative	Antithrombins	Immunomodulators	Migration inhibitors/ ECM modulators	Promote healing/ endothelialization
Paclitaxel	Heparin	Sirolimus	Halofuginone	VEGF
Taxol derivative (QP-2)	Hirudin	Tacrolimus	Propyl hydroxylase inhibitors	17-β estradiol
Vincristin	Iloprost	Everolimus	C-proteinase inhibitors	Tkase inhibitors
Methotrexate	Abciximab	Mizoribine	Metalloproteinase inhibitors	BCP-671
Angiopeptin		Cyclosporin	Batimastat	HMG-CoA reductase inhibitors
Mitomycin		Biorest	Probucol	Nitric oxide donors
BCP-678		Interferon-γ1b		EPC antibody
Antisense c-myc		Leflunomide		
ABT-578		Tranilast		
Actinomycin D		Cyclosporin		
RestenASE		Corticosteroids		
1-Chloro-deoxyadenosine		Mycophenolic acid		
PCNA ribozyme		Biphosphonates		
Celecoxib				

ECM = extracellular matrix; EPC = endothelial progenitor cell; HMG-CoA = 3-hydroxy-3-methylglutaryl coenzyme A; VEGF = vascular endothelial growth factor.

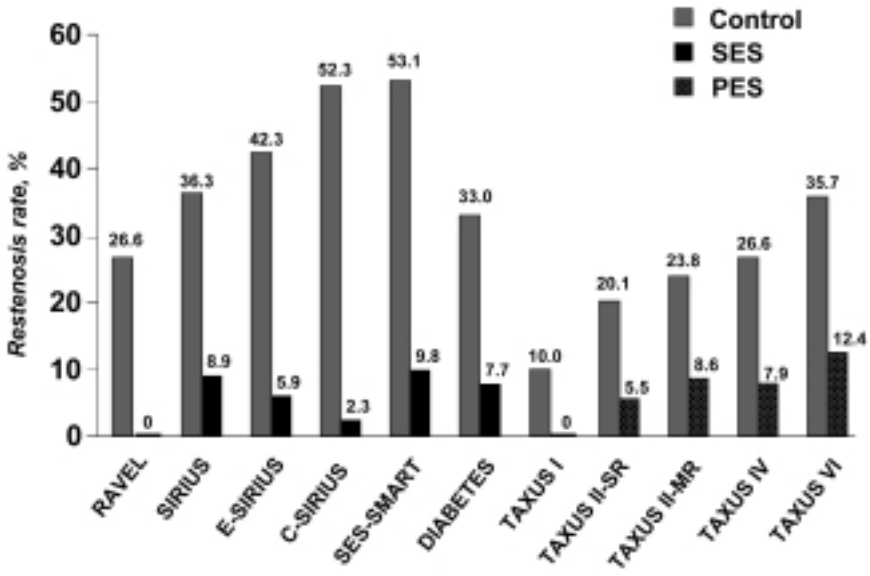

Figure 1. *Restenosis rates in randomized clinical trials on polymer-coated sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES).*

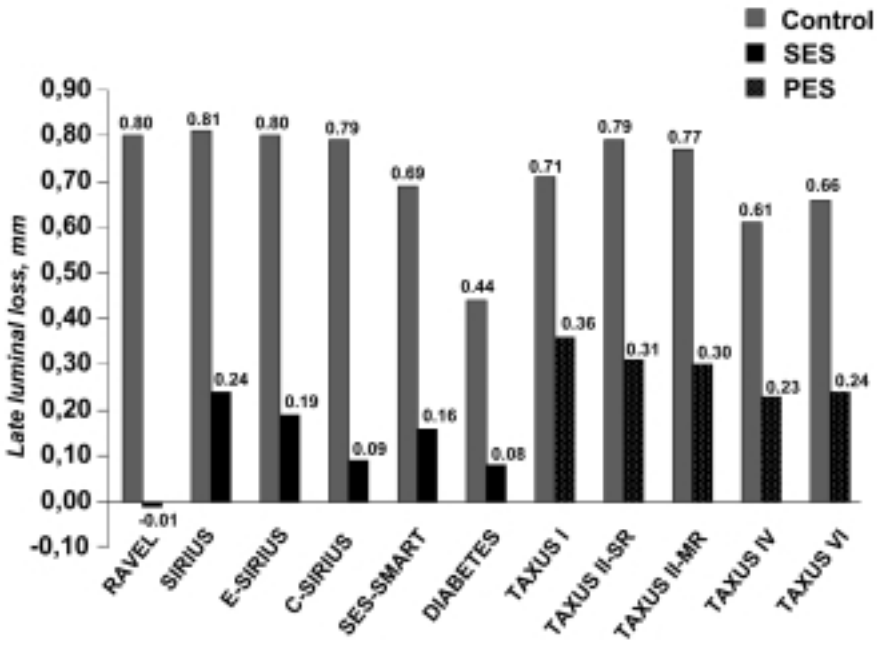

Figure 2. *Late luminal loss in randomized clinical trials on polymer-coated sirolimus-eluting stents (SES) and paclitaxel-eluting stents (PES).*

vice, studies on PESs comprised a variety of devices, both non-polymer-based and polymer-based, which therefore need to be evaluated separately.

In all these trials chronic total occlusion, ostial lesion, thrombus-containing lesion, unprotected left main PCI, acute myocardial infarction, low left ventricular ejection fraction, and multivessel stenting were exclusion criteria.

The main angiographic results are depicted in figures 1 and 2.

The first large trial designed to compare two different DESs is the REALITY trial, which enrolled 1300 patients randomized to the Cypher or Taxus stent in *de novo* lesions. The trial has been recently completed, and 8-month follow-up results should be available shortly.

The sirolimus-eluting stent. Six randomized trials comparing the outcomes of patients treated with SESs and conventional BMSs have been concluded to date[13,14,16,28-32]. In these studies, SESs were evaluated in the treatment of *de novo* coronary lesions, < 33 mm long, in native coronary arteries 2.5 to 3.5 mm in diameter.

The landmark Randomized Study with the Sirolimus-Eluting Velocity Balloon-Expandable Stent

Table II. Negative clinical trials with drug-eluting stents.

Trial	Agent	Vehicle	Stent platform	Reason of clinical failure
SCORE[24]	Taxol derivative QP2 (4000 μg)	Polymer sleeves	QuaDS-QP2 stent	Excessive incidence of stent thrombosis and myocardial infarction possibly due to the polymer sleeves
DELIVER[25]	Paclitaxel (3 μg/mm^2)	Direct binding	Multilink penta	Lack of efficacy
ACTION[26]	Actinomycin D) (10 and 2.5 μg/mm^2)	Polymeric coating	Multilink tetra	Lack of efficacy
BRILLIANT-EU[27]	Batimastat	Phosphorylcholine coating	BiodivYsio stent	Lack of efficacy
PRESENT trials	Tacrolimus (60 and 230 μg)	Nanoporous ceramic coating	FlexMaster ceramic stent	Lack of efficacy
EVIDENT	Tacrolimus (352 μg)	PTFE	PTFE-covered stent graft	Lack of efficacy
IMPACT	Mycophenolic acid (14- or 45-day release 3.3 μg/mm^2)	"Unicoat" polymer	Duraflex stent	Lack of efficacy

PTFE = polytetrafluoroethylene.

in the Treatment of Patients with de Novo Native Coronary Artery Lesions (RAVEL) trial included 238 patients with single non-complex *de novo* lesions. Remarkably, the 6-month angiographic restenosis rate of the SES group was zero, as well as the late loss. Intravascular ultrasound examination at follow-up further confirmed the marked neointimal inhibition after SES implantation[33]. The clinical outcomes were significantly better among patients treated with the sirolimus stents, with 94% of patients being free of any major cardiac events at 1 year compared to 71% in the BMS group ($p < 0.01$) (Table III)[13-17,28-32,34].

The Sirolimus-Eluting Bx Velocity™ Balloon-Expandable Stent (SIRIUS) trial randomized 1101 patients with *de novo* lesions to sirolimus or bare stents[14]. In-stent binary restenosis (within the margins of the stent) was reduced by 91% (3.2 vs 35.4%, $p < 0.01$) and in-segment restenosis (including the stented portion and the 5-mm segments proximal and distal to the stent) was reduced by 75% (8.9 vs 36.3%, $p < 0.01$)[14]. At 9 months, the incidence of major adverse cardiac events was significantly lower in the sirolimus group (7.1 vs 18.9%, $p < 0.01$), mainly due to a decrease in the need of target lesion revascularization (TLR) (4.1 vs 16.6%, $p < 0.01$) (Table III). At 12 months, the absolute difference in TLR continued to increase (4.9 vs 20%, $p < 0.001$)[35].

The E-SIRIUS trial enrolled 352 patients with longer lesions and smaller vessels than the RAVEL and SIRIUS trials[16]. Nevertheless, the 8-month in-stent restenosis rate was 3.9% in the sirolimus and 41.7% in the bare stent group ($p < 0.01$). Similarly, the incidence of in-segment restenosis (5-mm edges included) was significantly reduced (5.9 vs 42.3%, $p < 0.01$). The 9-month incidence of major adverse cardiac events was 8 vs 22.6% in the sirolimus and bare stent groups ($p < 0.01$) (Table III).

In the C-SIRIUS trial, which randomized 100 patients to sirolimus or conventional stenting, in-stent restenosis was not detected in any patient after SES implantation[28]. In-segment restenosis occurred in 2.3% of SES patients and 52.3% of BMS patients ($p < 0.001$). At 270 days, clinically-driven TLR was 4% in the SES group and 18% in the BMS group ($p = 0.05$). The Kaplan-Meier estimate of freedom from major adverse cardiac events at 270 days was 96.0% for SES patients and 81.7% for BMS patients ($p = 0.029$).

The Sirolimus-Eluting Stent in Small Arteries (SES-SMART) study was specifically designed to evaluate SESs in small vessels[31]. The mean vessel size in the patients was 2.2 mm. At 8 months, in-segment binary restenosis was 9.8% in the SES group and 53.1% in the control group ($p < 0.001$). Acute myocardial infarction and overall clinical events were also significantly reduced in patients who received the DES. All findings appeared to be independent of gender, diabetic status, and stent size[31].

The Diabetes and Sirolimus-Eluting Stent Trial (DIABETES) assessed the efficacy of SESs in 160 diabetic patients with *de novo* coronary stenoses, half of whom received BMSs[32]. Abciximab was recommended for all patients. There was an 88% reduction in late lumen loss in the SES group compared to the BMS group (from 0.44 to 0.08 mm, $p < 0.0001$). Binary restenosis was reduced from 33% in the BMS group to 7.7% in the SES group. At 9-month follow-up, there was a significant difference in TLR (7.5 vs 31.3%, $p < 0.0001$) and major adverse cardiac events (11.3 vs 36.3%, $p < 0.0001$) in favor of the SES group.

Paclitaxel (polymer-coated). The large variety of PESs should lead us to consider that variations in drug

Table III. Clinical outcomes for polymer-coated sirolimus- or paclitaxel-eluting stents in randomized trials.

Trial	Follow-up (months)	Death (%)	Myocardial infarction (%)	Repeat revascularization (%)	Any event (%)	Stent thrombosis (%)
Sirolimus						
RAVEL[13,29,30]	12					
Sirolimus		1.7	3.3	0*	5.8*	0
Bare stent		1.7	4.2	22.9	28.8	0
SIRIUS[14]	9					
Sirolimus		0.9	2.8	3.8*	7.1*	0.4
Bare stent		0.6	3.2	15.8	18.9	0.8
E-SIRIUS[16]	9					
Sirolimus		1.1	4.6	4.0*	8.0*	1.1
Bare stent		0.6	2.3	20.9	22.6	0
C-SIRIUS[28]	9					
Sirolimus		0	2	4	4	0
Bare stent		0	4	18	18	2
SES-SMART[31]	8					
Sirolimus		0	1.6*	7.0*	9.3*	0.8
Bare stent		1.6	7.8	21.1	31.3	3.1
DIABETES[32]	9					
Sirolimus		1.3	2.6	7.5*	11.3*	0
Bare stent		2.5	6.3	31.3	36.3	0
Paclitaxel (polymer-coated)						
TAXUS I[34]	24					
Paclitaxel		0	0	3	3	0
Bare stent		0	0	10	10	0
TAXUS II[15]	12					
Paclitaxel-SR		0	2.3	10.1*	10.9*	0.7**
Bare stent-SR		1.5	5.1	15.9	22.0	0
Paclitaxel-MR		0	3.7	6.9*	9.9*	0**
Bare stent-MR		0	5.2	19.1	21.4	0
TAXUS IV[17]	12					
Paclitaxel		1.4	3.5	6.8*	10.6*	0.6
Bare stent		1.2	4.6	16.7	19.8	0.8
TAXUS VI	9					
Paclitaxel		0	8.2	9.1*	16.4*	0.5
Bare stent		0.9	6.1	19.4	22.5	1.3

MR = moderate release; SR = slow release. * $p < 0.05$ vs control; ** rates of angiographically documented stent thrombosis.

dosing, release kinetics, stent design, and stent coating technologies may result in different vascular reactions and efficacy.

Four clinical trials utilizing polymer-coated PESs have been reported[15,17,34]. Overall, more than 2300 patients with *de novo* lesions have been enrolled in the TAXUS I[34], II[15], IV[17], and VI trials, and randomized to paclitaxel or bare stents. Different stent platforms with different release kinetics were used in these studies. The Taxus NIRx stent coated with paclitaxel (1 μg/mm^2 paclitaxel per unit of stent surface area) in a slow-release formulation was employed in the TAXUS I, the same stent with both a slow-release and a moderate-release formulation was used for the TAXUS II. In TAXUS IV and VI, the drug was loaded onto the Express stent, in the slow-release formulation in the former, and the moderate-release formulation in the latter. A marked reduction in neointimal proliferation and binary restenosis was observed in the active groups of all the trials, leading to a significant reduction in revascularization procedures and overall adverse cardiac events compared to controls[15,17,34]. Interestingly, the TAXUS VI is the only trial specifically designed for long lesions (lesion length for inclusion 18-42 mm). In this trial, PESs reduced restenosis from 35.7 to 12.4% and repeat revascularizations from 19.4 to 9.1% (Grube E., personal communication). In all these studies, DESs and BMSs showed similar rates of subacute stent thrombosis.

Paclitaxel (direct dip-coating). Paclitaxel elution from a metal stent without a polymer coating is an attractive choice because some polymers were associated with an exaggerated inflammatory response and increased neointimal hyperplasia in animal studies. However, contradictory clinical results have been obtained with devices utilizing direct dip-coating of paclitaxel stents[25,36,37]. Some of the studies evaluating paclitaxel or paclitaxel derivatives never came to full completion due to an unacceptable adverse event rate (9.4% stent thrombosis in the active arm of the Study to Compare

Restenosis Rate between QueST and QuaDS-QP2 [SCORE] trial)[38] or did not yield sufficient clinical benefit to justify commercialization of the device. The European Evaluation of Paclitaxel Eluting Stent (ELUTES) trial[37] and the Asian Paclitaxel-Eluting Stent Clinical Trial (ASPECT)[36] have shown a significant dose-dependent reduction in restenosis with paclitaxel stents, whereas the larger RX Achieve™ Drug-Eluting Coronary Stent System in the Treatment of Patients with de Novo Native Coronary Lesions (DELIVER-I) study failed to demonstrate the beneficial effect of these devices[25]. In the ASPECT, two different types of antiplatelet therapy were given to patients treated with PESs[36]. This choice contributed to the relative increase in adverse events in the group treated with aspirin and cilostazol compared to those treated with aspirin and clopidogrel.

Other stents/drugs. To date, SESs and PESs have the most extensive accumulated clinical experience and are the only DESs commercially available for clinical use. However, a myriad of new devices have recently been tested and are currently in various stages of development for clinical use. New DESs that have already been evaluated in preliminary clinical studies are summarized in table IV[39-47].

The FUTURE I and II trials evaluated a new DES covered by everolimus (a sirolimus-like agent) within a polyhydroxyacid biodegradable polymer (Guidant, Santa Barbara, CA, USA). In both studies the 6-month angiographic in-stent restenosis rate was zero for the study stent, with a very low incidence of in-segment restenosis[41,48]. The FUTURE program has now been expanded with two large-scale multicenter studies, FUTURE III and IV, which will evaluate this stent design in a larger patient population.

Tacrolimus is a well-known potent antiproliferative agent which was already used in various therapeutic areas. Although effective in preclinical studies, the first tacrolimus-eluting stent system in the treatment of native coronary lesions (PRESENT I, II) and saphenous vein graft lesions (EVIDENT) failed to prove any clinical benefit[48] (Table II). Another tacrolimus-eluting stent has recently been developed, the JANUS Carbostent™ (Sorin Biomedica Cardio, Saluggia-VC, Italy), which is designed to elute more drug toward the vessel wall than into the bloodstream so that the drug does not inhibit endothelial re-growth post-stenting. In the JUPITER I trial a dichotomous effect in diabetics and non-diabetics was observed. The 6-month incidence of target vessel revascularization was low (4.9%) in non-diabetic patients, but high (30%) in diabetics. No further events were recorded between 6 and 12 months in both groups.

Animal data indicated that local delivery of 17-beta-estradiol promotes re-endothelialization, inhibits cell migration and proliferation, and prevents restenosis. The Estrogen and Stents to Eliminate Restenosis (EASTER) trial examined the safety and efficacy of 17-beta-estradiol-eluting stent implantation on *de novo* coronary lesions[45]. In 30 patients, the restenosis rate was 6.7% with a late loss of 0.31 mm, and TLR was 3.4%[45].

ABT-578 is a new synthetic analogue of sirolimus. In order to evaluate safety, feasibility and efficacy of the ABT-578-eluting ENDEAVOR stent system (Medtronic Inc., Minneapolis, MN, USA) the ENDEAVOR clinical program has been started, including three randomized clinical trials. ENDEAVOR I is the first-in-man trial including 100 patients with native *de novo* coronary lesions. The 12-month follow-up data, recently presented, demonstrated the safety and feasibility of this new DES concept with a major adverse cardiac event rate of 2.0% at 12 months[42]. One-year binary restenosis rate was 3.3% and TLR 1%. In order to evaluate this stent system in a larger patient population as well as in more complex lesion subsets, the multicenter study ENDEAVOR II has been started including a total of 1200 patients. The study enrollment was completed in January 2004 and the results will be presented at the American College of Cardiology annual conference in March 2005. The aim of the US multicenter study ENDEAVOR III is a head-to-head comparison of the ENDEAVOR ABT-578-eluting stent system with the already approved Cypher™ SES in 436 patients. Enrollment has been completed in September 2004. Medtronic has extended the ENDEAVOR program with the ENDEAVOR IV trial, which has recently been launched to compare the safety and efficacy of the ENDEAVOR eluting stent with the Taxus™ stent.

The Conor Medsystems (Menlo Park, CA, USA) Medstent™ is the first stent specifically designed to drug delivery. The stent is crafted with more than 500 laser-cut holes per stent that could serve as drug reservoirs for different drugs. Different release kinetics could be programmed by the application of the stent bioabsorbable polymer. In the Paclitaxel In-Stent Controlled Elution Study (PISCES) trial[44], paclitaxel was loaded onto the Medstent and used in 191 patients randomized to one of six forms of drug dose/delivery/directional release or to a BMS. The two long-term (30-day) release formulations, 10 and 30 µg, produced at 4 months an in-segment late loss of 0.20 and 0.28 mm, respectively, compared with 0.60 mm for the BMS. In-stent late loss for these two doses over the same time period was 0.38 and 0.37 mm, compared with 0.88 mm in the BMS[44]. These two doses are now being explored in the larger EuroSTAR trial.

"Real world"

As already pointed out, only two devices are commercially available, therefore data on DESs in clinical conditions and lesions excluded from randomized trials are limited to these devices.

Table IV. Clinical studies with new drug-eluting stents.

Trial	Design	Inclusion criteria	Study groups	In-lesion restenosis (%)	In-lesion late loss (mm)
Everolimus					
FUTURE I[40,41]	Randomized (2:1), single-blind	Single de novo lesions Length < 18 mm Vessel diameter 2.75-4.0 mm	Bioabsorbable polymer-coated everolimus-eluting stent (n=27)	0	0.11*
			Bare stent control for MR-paclitaxel (n=15)	9.1	0.85
FUTURE II[41]	Randomized (1:2), single-blind	Single de novo lesions Length < 18 mm Vessel diameter 2.75-4.0 mm	Bioabsorbable polymer-coated everolimus-eluting stent (n=21)	0	0.12*
			Bare stent control for MR-paclitaxel (n=43)	19.4	0.85
ABT-578					
ENDEAVOR I[42]	Series of cases	Single, de novo lesions Vessel size 3.0 to 3.5 mm	Phosphorylcholine-coated Driver™ cobalt alloy stent (n=100)	2.1** 3.3§	0.21** 0.40§
Tacrolimus					
JUPITER I[43]	Series of cases	Single de novo lesions Vessel size 3.0 to 4.0 mm Length < 12 mm	Carbofilm™-coated Janus tacrolimus-eluting stent (n=58)	NA	NA
Paclitaxel					
PISCES[44]	Series of cases	Single de novo lesions Vessel size 3.0 to 3.5 mm	Bioabsorbable polymer-coated cobalt alloy stent with laser cut holes as drug reservoirs (n=191)	0§§ 7.4§§§	0.20§ 0.28§
17β-estradiol					
EASTER[45]	Series of cases	Single de novo lesions Vessel size 3.0 to 4.0 mm	Phosphorylcholine-coated estrogen-eluting stent (2.54 μg/mm^2) (n=30)	6.7	0.31
Dexamethasone					
STRIDE[46]	Series of cases	Single de novo lesions Vessel size 2.75 to 4.0 mm	BiodivYsioMatrix LO stent immersed in dexamethasone solution (15 mg/ml) (n=71)	13.3	0.45
Nitric oxide drug elution					
NOBLESSE[47]	Series of cases	Single de novo lesions Vessel size 2.75 to 3.5 mm	Bioabsorbable polyesteramide-coated Genic stent with oxygen free scavenger covalently bounded (n=45)	9.5	0.69

MR = moderate release; NA = not available. * $p < 0.05$ vs controls; ** 4-month follow-up; § 12-month follow-up; §§ 10 μg dose in 30-day release formulation; §§§ 30 μg dose in 30-day release formulation.

The Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH) study was a single-center registry which included patients treated with SESs according to a non-restrictive inclusion criterion. Virtually all consecutive patient subsets were considered eligible. Long-term (12-month) outcomes of the first 508 patients with *de novo* lesions treated exclusively with a SES were compared with 450 patients treated with a BMS in the period just prior to the introduction of DESs[49]. Only 2 (0.4%) presented with thrombotic stent occlusion in the first month after the procedure, while the stent thrombosis rate in the BMS group was 1.6% ($p = 0.1$). There were no further thrombotic events up to 1 year. SESs reduced by 38% the 1-year risk of major cardiac events (9.7 vs 14.8%, $p < 0.01$), mainly due to a risk reduction of 65% in clinically-driven repeat intervention (3.7 vs 10.9%, $p < 0.01$). Importantly, approximately 68% of patients included in the registry would have been excluded from the earlier clinical trials (e.g. patients with previous coronary surgery, patients admitted with acute myocardial infarction, and those with multivessel stenting, among other characteristics). SES implantation was associated with a risk reduction that ranged from 28 to 79% across the subgroups evaluated. However, the benefit of SESs did not reach statistical significance in some subgroups (women, diabetics, patients treated with bifurcation stenting, and patients receiving ≥ 33-mm stents).

These findings highlighted the need for further analyses with larger numbers of patients to fully estimate the clinical impact of SESs in these patients.

In the Swiss Registry, a total of 183 patients treated with SESs were included. At 7 ± 2 months, 95.6% of the patients were event-free, and TLR was required in only 3 patients (1.6%)[50].

The German Cypher Registry[51] was launched in April 2002. From April 2002 until December 2003, 3579 interventions using a SES at 102 centers were included in the registry. This reflects a proportion of this DES compared to all stents implanted at the participating centers of < 10%. In a large proportion of interventions, SESs were implanted in lesions or in clinical situations not yet evaluated by randomized clinical trials: 10.1% ST-elevation myocardial infarction, 1.8% cardiogenic shock, 2.1% left main stenosis, 5.5% coronary artery bypass graft lesion, 23.2% in-stent stenosis, and 6% chronic total occlusion. Acute complication rate was low, with 0.2% for death, 0.3% for subacute stent thrombosis, 1.3% for myocardial infarction, 2.1% for urgent PCI, and 0.2% for coronary artery bypass graft. In about one half of the patients included in the German Cypher Registry, the DES was implanted in lesions that were excluded from randomized clinical trials. The use of this SES in "real life" conditions was found to be safe concerning acute complications. Long-term follow-up will be reported shortly.

In the Milan registry, 486 patients with 1027 lesions were treated with SESs[52]. Of all patients studied, around 80% had multivessel disease, and 20% diabetes mellitus. At 6 months, the major adverse cardiac event rate was low (13.8%), TLR was performed in 9.5% of the patients, and target vessel revascularization in 11.5%. Target vessel revascularization was 4.5% for single-vessel disease, and 13.2% for multivessel disease. Diabetes mellitus was the only significant predictor of target vessel revascularization[52].

In a prospective survey, which included 12 hospitals in Northern Italy, the REAL registry (Registro Angioplastiche Emilia-Romagna), 4237 patients who underwent PCI (SES, n = 872; BMS, n = 3365) were evaluated. At 9 months, the use of SESs was associated with a 57% reduction in TLR which increased to 63% in a prespecified high-risk subgroup of patients when compared to BMS. Interestingly enough, in the "low-risk" patients the reduction in TLR associated with SES was not statistically significant, thus supporting the hypothesis that, when a selective SES use strategy is chosen, selection of higher-risk patients is reasonable and effective (Marzocchi A., personal communication).

Less data are so far available for PES utilization in the real world, because this device was introduced in the market in February 2003.

The WISDOM registry is a post-marketing registry conducted with the objective of evaluating unselected patients treated with PESs in the "real world". Preliminary results of this multinational registry on 778 patients confirmed the 30-day safety of PESs in complex patients, with only 0.4% of the patients presenting stent thrombosis. In the Asia-Indian arm of the study, at 9-month clinical follow-up (complete for 80%), the major adverse cardiac event-free survival was 95.7% and survival free from reinterventions was 98.1% (Chan C., personal communication).

In an *interim* analysis from the Taxus Eluting-Stent Evaluated at Rotterdam Cardiology Hospital (T-SEARCH) registry, unrestricted PES utilization in a consecutive cohort of 479 patients was safe and associated with a low revascularization rate at 6 months[53]. At 6-month follow-up, the event-free survival and rate of repeat revascularization was similar to that observed in patients treated with SESs in the previous RESEARCH period (Serruys P.W., personal communication).

Subgroup analyses. An increasing number of studies are focusing on the results of SES and PES utilization in several subgroups of patients and lesions.

Not surprisingly, SESs have been shown to be very effective in patients with multivessel disease[54], diabetes mellitus[55], acute myocardial infarction[56,57], chronic total occlusion[58], in-stent restenosis[59-62], saphenous vein graft[63], left main disease[64], long lesions[65], small vessels[66], and ostial lesions[67]. In the treatment of bifurcation lesions, SESs improved the results compared with historical controls using BMSs, with an overall restenosis rate around 23-26%[68,69]. However, there are some uncertainties about the most appropriate technique to

use with these devices. In a randomized trial designed to compare stenting of both branches with stent of the main branch only, from 3.5 to 4.6% (including sudden death) subacute stent thrombosis was observed, increasing up to 6.3% considering only the double stenting group[68]. Almost all the procedures in this trial were performed with the T-stenting technique[68]. In another series, 58 patients with 65 *de novo* bifurcation stenoses were treated with SES implantation in both vessels[69]. Four methods of stenting were used: T-stenting (63%), culotte stenting (8%), kissing stents (3%), or the "crush" technique (26%). No case of angiographic stent thrombosis was observed. Angiographic restenosis rates of the main and side branches were 9.1 and 13.6%, respectively, with an overall restenosis rate of 22.7%[69]. In both studies, regardless of the technique used, and despite single or double stenting, restenosis in the side branch remained a problem[68,69].

SESs showed promising results also in the treatment of in-stent restenosis[59-62], with a recurrent restenosis rate ranging from 0 to 20%, and a low incidence of adverse clinical events. In the RESEARCH in-stent restenosis study[61], late loss was 0.17 ± 0.76 mm, and overall post-SES restenosis was 14.6%. No restenosis was observed in focal lesions. In a non-randomized comparison at the same institution, the 9-month clinical outcome of this strategy was comparable to the gold standard vascular brachytherapy (VBT)[70]. The multicenter TROPICAL study compared 162 patients with in-stent restenosis to 256 patients treated with VBT in the active arm of the GAMMA II trial[71]. Even taking into account the limitations of the study design, the apparent reduction in late loss (0.68 VBT vs 0.08 SES, p < 0.001), and in 6-month restenosis (40.3% VBT vs 9.7% SES, p < 0.001) obtained with SESs is noteworthy[71].

In the TAXUS III trial, PESs were implanted to treat in-stent restenosis lesions in 28 patients[72]. Exclusion criteria were lesion length > 30 mm, total occlusion, and vessel diameter > 3.0 mm. No subacute stent thrombosis occurred up to 12 months. Angiographic restenosis rate was 25%, with a mean late loss of 0.54 mm. Incomplete lesion coverage and stent underexpansion were reported by the authors as important determinants of further interventions[72].

The non-polymer coated ACHIEVE™ PES (Cook) was compared to intracoronary beta-radiation therapy in a matched-pair analysis[73]. Angiographic binary in-lesion restenosis at 6 months was 20% in the PES group and 16% in the VBT group (p = 1.0), but in-stent diameter stenosis was lower in the PES group (27 ± 8 vs 34 ± 13%, p = 0.05), and larger in-stent minimal lumen diameter (2.10 ± 0.71 vs 1.75 ± 0.36, p = 0.03). At 12-month follow-up, TLR was performed in 9% of the PES patients and 24% of the VBT patients (p = 0.25)[73].

The Intracoronary Stenting and Angiographic Results-Drug-Eluting Stents for In-stent Restenosis (ISAR-DESIRE) trial, 300 patients with in-stent restenosis were randomly assigned to one of three treatment groups: SES, PES, or balloon angioplasty[74]. The incidence of the 6-month angiographic restenosis was 44.6% in the balloon angioplasty group, 14.3% in the SES group (p < 0.001 vs balloon angioplasty), and 21.7% in the PES group (p = 0.001 vs balloon angioplasty). The secondary analysis showed a trend toward a lower rate of angiographic restenosis (p = 0.19) and a significantly lower rate of target vessel revascularization (p = 0.02) among SES compared with PES patients[74].

Data about treatment of recurrent in-stent restenosis in previously irradiated sites with DESs are limited to SESs. In two small series of patients, there were no major in-hospital complications, and the incidence of subacute thrombosis was low[75,76]. Mid-term clinical follow-up showed a reintervention rate of 25-26%[75,76], and 40% recurrent binary restenosis in the first series, suggesting acceptable clinical outcome compared to historical series but also the need for further investigation before this strategy could be routinely recommended[75].

Potential limitations

Stent thrombosis and incomplete apposition. Initial enthusiasm about DESs has been tempered by concerns regarding potential untoward effects such as an increased incidence of acute and subacute stent thrombosis and late acquired-stent malappositions/aneurysms. Indeed, in the RAVEL and SIRIUS trials acquired-stent malapposition (as observed by intravascular ultrasound) was more frequent in SES patients than in the control arms[33]. Conversely, in the TAXUS II trial patients treated with BMSs or PESs showed similar rates of late-acquired malapposition[15]. Remarkably, these intravascular ultrasound observations were not associated with any adverse event throughout the follow-up period in any of these studies[15,33,77,78].

Stent thrombosis, especially delayed cases due to incomplete endothelialization of the stent struts, has been described with DESs[79,80]. This issue has been addressed by two recent meta-analyses of randomized trials comparing BMSs and SESs or PESs[81,82]. In the first report, the incidence of late thrombotic stent occlusion was not seen to be more frequent in patients treated with DESs (odds ratio [OR] 1.08, 95% confidence interval [CI] 0.53-2.20)[81]. In the second meta-analysis from 10 randomized trials, the rate of stent thrombosis was similar for DESs and BMSs (0.58 vs 0.54%, OR 1.05, 95% CI 0.51-2.15, p = NS), as well as the rate of late thrombosis (0.23 vs 0.25%, OR 0.99, 95% CI 0.35-2.84, p = NS)[82]. The same holds true for the registries which included "real world" more complex patients, and off-label indications[49,51,52]. In another large single-center experience, the incidence of stent thrombosis after SES implantation was about 1%, which is within the expected range for BMSs. The incidence of this com-

plication was strongly associated with discontinuation of antiplatelet therapy within the first month (about a 30-fold increased risk)[79]. Remarkably, in the DIABETES trial that is the only trial that truly used long-term (i.e. 12-month) dual antiplatelet treatment in both the DES and BMS groups, the incidence of stent thrombosis was zero, despite the high-risk population enrolled. Chieffo et al.[83] reported 5 cases of intraprocedural stent thrombosis following SES implantation (0.7% of their patients), which is a very rare event with BMSs (< 0.01%). None of these patients was pretreated with glycoprotein IIb/IIIa inhibitors. Univariate exact logistic regression analysis demonstrated an association between intraprocedural stent thrombosis and total stent length per vessel, in millimeters (exact OR 1.03, 95% CI 1.011-1.046, p = 0.0028), suggesting some caution when very long SESs are implanted[83].

To summarize, DESs do not seem to increase the overall incidence of stent thrombosis compared to BMSs, even in more complex patient and lesion subsets. However, optimal duration of dual antiplatelet therapy is still unclear (several different schemes used in different studies). Notably, prolonged (≥ 6 months) dual antiplatelet treatment might be able to virtually abrogate stent thrombosis and should be adopted whenever possible. Some high-risk subsets of patients might require glycoprotein IIb/IIIa inhibitors during the procedure to avoid acute complications.

Is there a late "catch-up" phenomenon? A late catch-up has been described after implantation of a high dose (800 μg) paclitaxel derivative QP2-eluting stent, with the restenosis rate increasing from 13% at 6 months to 62% at 12 months, raising concerns for all other DESs[84,85]. However, long-term efficacy should be evaluated separately for each DES assembly, since a "class effect" is unlikely for these devices. The SES has the largest body of long-term data available. The First-in Man (FIM) study has shown persistent positive results up to 4 years, without any evidence of late catch-up restenosis[86,87]. After 4 years, in-stent and in-lesion loss have remained low (0.1 and 0.2 mm, respectively), while TLR has held at 2.8%. In the RAVEL[29], SIRIUS[88], and E-SIRIUS trials (Schofer J., personal communication), no further events due to restenosis were observed up to 2 years. Recently, the 3-year follow-up results of the RAVEL trial have been presented, showing TLR rates of 5% in the SES group and 14.4% in the BMS control patients (p = 0.01). With paclitaxel, no rebound effect was seen from 6 to 12 months in TAXUS I[34], TAXUS II[15], TAXUS IV[17], ELUTES[37], and ASPECT[36] trials. The 2-year results of TAXUS II and IV have recently been reported (Colombo A. and Stone G., respectively, personal communications). In these studies the clinical benefit of the Taxus stent continues to increase with no apparent evidence of late catch-up. The angiographic and intravascular ultrasound analysis of 207 patients enrolled in the TAXUS II study (104 BMS, 49 moderate release, 54 slow release) did not show any significant changes in minimal lumen diameter, late loss, and neointimal volume between 6 months and 2 years in the PES groups. Thus, all clinical data to date seem to contradict animal results showing delayed cellular proliferation following DES implantation[89]. However, longer follow-up and larger experience are required to draw definitive conclusions.

Restenosis following drug-eluting stent implantation: predictors, patterns, insights, and treatment. Subgroup analyses of patients included in the RAVEL and SIRIUS have shown that the overall benefit of SESs was also observed across many subsets of patients and lesion types[14,30]. However, in the SIRIUS trial, the post-sirolimus restenosis was significantly increased in diabetics, long lesions, and small vessels. These randomized studies have largely been restricted to selected patients treated with single lesion elective stenting. In the angiographic substudy of the RESEARCH registry[90], which comprised more complex patients, the following characteristics were identified as independent multivariate predictors of post-SES restenosis: treatment of in-stent restenosis (OR 4.16, 95% CI 1.63-11.01, p < 0.01), ostial location (OR 4.84, 95% CI 1.81-12.07, p < 0.01), diabetes (OR 2.63, 95% CI 1.14-6.31, p < 0.02), total stented length (per 10-mm increase: OR 1.42, 95% CI 1.21-1.68, p < 0.01), reference diameter (per 1.0-mm increase: OR 0.46, 95% CI 0.24-0.87, p < 0.03), and left anterior descending coronary artery (OR 0.30, 95% CI 0.10-0.69, p < 0.01)[90]. Multivariate analysis from patients included in the TAXUS IV trial[17] has identified several multivariate predictors of 9-month TLR. Apart from the utilization of BMSs (OR 4.58, 95% CI 2.64-7.95, p < 0.0001), other independent predictors were: diabetes (OR 1.78, 95% CI 1.10-2.88, p = 0.02), an increase in stent length (OR 1.04, 95% CI 1.01-1.07, p = 0.006), a decrease in acute gain (OR 2.08, 95% CI 1.11-3.88, p = 0.02), and lesion angulation (OR 0.98, 95% CI 0.97-0.99, p < 0.03). Indeed, the post-DES restenosis has been shown to frequently occur in association with higher complexity characteristics, which might be responsible for local trauma outside the stented segment, incomplete lesion coverage, uneven distribution of drug release because of asymmetrical stent expansion or damage of the stent coating[91]. This may represent the new face of "geographic miss", previously described for brachytherapy, in the DES era[11]. In this setting, diligent stent placement in various plaque morphologies may be more important than ever. If complete lesion coverage is important to avoid longitudinal geographic miss, proper stent sizing is also a critical stage to prevent what has been called "axial" geographic miss[11]. Oversized stents may produce extensive trauma to the media, adventitia, and surrounding tissues, with an enhanced proliferative reaction that cannot be counteracted by usual drug concentrations. Conversely, placing a

stent too small in a large vessel may lead to underdosing at the tissue level due to the lack of contact between the stent and the vessel wall secondary to incomplete stent apposition, or because the struts are expanded beyond the limit for optimal drug delivery, leading to a decreased concentration of drug per unit of surface area[11]. The STLLR trial has recently been launched as the first large, multicenter, prospective study to assess stent deployment techniques, define factors associated with suboptimal deployment, and establish the association between geographic miss and clinical outcomes in patients treated with SESs in real-world practice[92].

The vast majority of in-stent restenoses after SES implantation present a focal pattern, i.e. are very localized and bordered by segments with no evidence of neointima[14,91,93]. Results of the SIRIUS and E-SIRIUS trials, where most of the post-SES were located at the proximal stent border, suggested a possible edge effect of SESs[14,16]. This finding was not confirmed in other studies, where the operators were strongly advised to avoid both residual dissection at stent borders and gaps between stents, and to cover the entire injured vessel area[90,93].

In randomized trials, angiographic and intravascular ultrasound examinations of vascular response and restenosis cases after the implantation of polymer-coated PESs, suggested that the pattern was much more likely to be focal than diffuse or proliferative[17]. No edge effect was observed and, conversely, a possible protective effect at the distal edge has been suggested[94]. However, in ischemia-driven cases, investigators from Milan reported a predominantly diffuse or totally occlusive pattern of recurrent restenosis post-PES implantation[95]. In a randomized comparison between SESs and PESs in complex *de novo* lesions, the incidence of binary restenosis was similar. However, post-SES restenosis was focal in 88% of the cases, whilst post-PES restenosis occurred only in 43% (Kaul U., personal communication, available at www.tctmd.com).

The treatment of restenosis following DES implantation is a matter of intense debate. Only a few data have been reported to date. Investigators from Rotterdam evaluated the clinical and angiographic outcomes of patients presenting with restenosis after SES implantation treated with repeated PCI[96]. From the 27 in-stent restenosis lesions, 4% were re-treated with a BMS, 11% were treated with balloon dilation, and the remaining 85% were treated with repeated DES implantation (44% SES, 41% PES). The overall recurrent restenosis rate was 42.9%. Remarkably, the recurrent restenosis rate of originally *de novo* lesions re-treated with DESs was 18.2%, but further investigations are warranted to confirm this finding[96]. VBT for the treatment of these cases has been evoked[97], and there are some anecdotic reports in the literature. However, the role of this strategy in post-DES restenosis has to be defined in larger studies.

Cost-effectiveness. The costs of currently marketed DESs (i.e. SESs and PESs) have been perceived as a major limitation for a more widespread use of these devices. In an analysis from the RAVEL trial, the utilization of the SES resulted in a mean additional procedural cost of € 1286, as compared to the control group based on costs in the Netherlands[7]. However, due to the decrease in reinterventions attributable to the SES use at the end of the first year of follow-up the estimated cost difference had decreased to € 54. In other words, in the RAVEL trial the reduction in the risk of major events from 28.8 to 5.8% after SES was accomplished at an extra cost of € 54 per patient.

Clinical outcomes, resource use, and costs were assessed prospectively for all patients enrolled in the SIRIUS trial over a 1-year follow-up period[98]. SESs increased initial hospital costs by $2881 per patient, but reduced follow-up costs by $2571 per patient mainly because of a minor number of subsequent revascularization procedures. Overall, aggregate 1-year costs remained $309 per patient higher. The incremental cost-effectiveness ratio for SESs was $1650 per repeat revascularization event avoided or $27 540 per quality-adjusted year of life gained, values that have been considered to compare reasonably with other accepted medical interventions[98]. Obviously, this figure within the US healthcare system cannot be directly extrapolated to other locations, nor to different (real-life) clinical scenarios. In addition, stent market and prices are extremely dynamic, and could be driven down by the introduction of new effective competitor devices. Cost-effectiveness of DESs should therefore be constantly re-evaluated. Furthermore, although this analysis well represents a societal point of view, it does not represent the economic impact of DESs from other points of view, such as hospital administrations[99]. In this peculiar time frame, selective DES utilization in prespecified subgroups of patients and lesions could be a reasonable and cost-effective choice, although there are no data available to support this hypothesis.

Comparison with cardiac surgery. As compared to coronary artery bypass graft surgery in patients with multivessel disease, coronary stents achieved the same degree of protection against death, stroke, and myocardial infarction. However, after 1 year stenting was associated with a greater need for repeated revascularization[100]. The ARTS II study was designed to assess the efficacy of SESs in patients with multivessel disease, and to compare these results to the historical controls enrolled in the ARTS I[101]. At the 6-month follow-up the event-free survival rate for the SES group was 93.6%, which compares favorably with the 80% observed in the stent arm of the ARTS I, and is similar to the 91% of the bypass surgery arm of the same study (Serruys P.W., personal communication).

The FREEDOM trial is an international, multicenter ongoing trial that randomized 2400 patients with

multivessel coronary disease and diabetes mellitus to bypass surgery or SES implantation. The patients will be followed up for 5 years. The SYNTAX study has been designed to randomize around 1500 patients with three-vessel disease and/or left main disease to bypass surgery or multivessel PCI with the Taxus stent. A parallel registry for patients not enrolled is also planned for both studies. Hopefully, these trials will provide important information to guide the choice of the optimal revascularization strategy for patients with multivessel disease.

Conclusions

DESs represent the last revolution in interventional cardiology. Polymer-based SESs and PESs have been shown to be very effective in reducing restenosis rate and repeat revascularizations in randomized trials. Very promising results are emerging from the utilization of these two devices in the real-world scenario. As restenosis rates are still not "zero", the search for and testing of new drugs will continue. A tailored DES for each patient/lesion could be hypothesized for the future. Ongoing studies will address a number of unsolved issues, such as duration of dual antiplatelet therapy, differences among DESs, comparison with surgery in patients with multivessel disease. The DES era is just at the beginning, and a number of new devices are likely to be released in the next future. Furthermore, the way is open for a number of new therapeutic options that could be associated with drug elution, such as stent-based local gene delivery, and endothelial cell seeding of the stent to restore the integrity of the endothelial cell lining among the others.

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