Drug-eluting coronary stents – focus on improved patient outcomes

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Abstract: The development of stent has been a major advance in the treatment of obstructive coronary artery disease since the introduction of balloon angioplasty. Subsequently, neointimal hyperplasia within the stent leading to in-stent restenosis emerged as a major obstacle in long-term success of percutaneous coronary intervention. Recent introduction of drug-eluting stents is a major breakthrough to tackle this problem. This review article summarizes stent technology, reviews progress of drug-eluting stents and discusses quality of life, patient satisfaction, and acceptability of percutaneous coronary intervention.

Keywords: drug-eluting stent, coronary intervention, patient outcomes

Introduction

Percutaneous transluminal coronary angioplasty (PTCA), introduced by Andreas Gruntzig in 1977, revolutionized coronary artery revascularization from open heart surgery to a percutaneous procedure. However, PTCA was limited by periprocedural complications including coronary dissection and vascular recoil resulting in emergent coronary occlusion, and a significant (30%–50%) incidence of recurrence or restenosis, which compromised long-term efficacy.^{1,2} The development of a scaffolding metal mesh tube called a “stent” that could be delivered on the balloon catheter improved both problems. The widespread adoption of bare metal stents (BMS) was hindered by two limitations: the risk of sudden occlusion due to stent thrombosis and a high (30%–40%) incidence of in-stent restenosis (Figure 1).³ More aggressive dual antiplatelet therapy and high-pressure stent deployment dramatically lowered the risk of stent thrombosis and restenosis.⁴

Understanding the processes and mechanisms involved in in-stent restenosis was the key driver for the development of drug-eluting stent (DES) technology. In-stent restenosis is a result of a response to injury to the arterial wall, which triggers an inflammatory process resulting in proliferation and migration of smooth muscle cells from the arterial media. Exuberant neointimal growth, encroaching on the vessel lumen leads to in-stent restenosis.^{5,6} DES delivered antiproliferative and immunosuppressive drugs to the arterial wall, dramatically reducing in-stent restenosis and they have now become mainstream therapy for percutaneous coronary intervention (PCI).

DES design

The goal of stent design, in addition to deliverability and effective lesion scaffolding, is that the stent should minimize the neointimal host response and not be toxic. A DES consists of three components: a metal scaffold, the active pharmacological

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Figure 1 The response to stent implantation.

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agent, and a carrier for the drug. The metal stent platform must be flexible enough for deliverability, radiopaque for visibility, biocompatible for long-term mechanical stability after implantation. Modern stents are made of stainless steel or cobalt chromium, and they vary in their strut pattern and length of radially expandable elements (Figure 2).⁷ There is an association between stent strut thickness and restenosis with thinner struts associated with less restenosis.⁸ Cobalt chromium exhibits superior radial strength and improved radiopacity when compared to stainless steel. This permits thinner stent struts for cobalt chromium stents and leads to a reduction in device profile, increasing the ease of stent deliverability to the target lesion.⁹ Other alternatives to a metallic stent platform, such as biodegradable and bioabsorbable stent platforms are also being explored.¹⁰

The metal stent backbone is coated with a thin polymer film containing the active drug, which is released in controlled

amounts locally at the site of implantation. Wide ranges of polymers are available as carriers of the active drug. Polymers are classified as biodegradable, such as poly-L lactic acid, or nonbiodegradable (durable), such as polyurethane derivatives and silicone based polymers.^{11,12} Coatings have several engineering challenges of their own as they may crack, decompose, and dissolve over time. In addition, the biocompatibility of polymers used for coating stents is critical. Nonbiodegradable polymers have been implicated in delayed healing, impaired stent strut endothelialization, and a hypersensitivity reaction which can contribute to stent thrombosis.¹³ The nonbiodegradable phosphorylcholine polymer used in the Endeavor[®] Sprint Zotarolimus-Eluting Coronary Stent System (Medtronic, Inc, Minneapolis, MN) releases 95% of the sirolimus analog, zotarolimus, within 14 days of stent deployment; although nonbiodegradable it is biocompatible (a natural component of cell membrane), causing less inflammation compared with the polymers used on the Cypher[®] Stent (Cordis Corporation, Warren, NJ).¹⁴ Current research is looking into stents that will have novel coatings or are completely polymer free.¹⁵

Pharmacology of DES

Pharmacological agents incorporated on the stent surface prevent restenosis by interfering with the cell cycle in some way. For example, paclitaxel and sirolimus both have antiproliferative properties (inhibit proliferation of vascular smooth muscle and endothelial cells) and also have potent anti-inflammatory function and affect cell migration and motility.^{16,17} Compartmentalizing these agents as either antiproliferative or anti-inflammatory will understate the breadth of their biological activity. Below is a brief description of the mechanism of action of the current Food and Drug Administration-approved agents for coronary stent application: sirolimus, paclitaxel, zotarolimus, and everolimus.

Sirolimus, zotarolimus, and everolimus all interfere with the cell cycle in the presynthetic (G1) phase. Sirolimus (previously called rapamycin) is a natural macrolide antibiotic produced by the fungus *Streptomyces hygrissopicus* that is able to inhibit cytokine and growth factor mediated proliferation of lymphocytes and smooth muscle cells, resulting in reduced neointimal proliferation.¹⁸ Zotarolimus is a semisynthetic (made by substituting a tetrazole ring for the native hydroxyl group at position 42 in rapamycin) analog of sirolimus.¹⁹ Everolimus is a synthetic derivative of sirolimus (40-O-[2-hydroxyethyl]-rapamycin).²⁰ Paclitaxel is an antineoplastic agent isolated from the bark of the Pacific Yew tree, *Taxus brevifolia*. It acts on the postsynthetic G2 phase,

Figure 2 Coronary stents. (A) Taxus[®] stent (Boston Scientific Corporation, Natick, MA) with stainless steel metallic platform; (B) Xience V[®] Everolimus Eluting Coronary Stent (Abbott Laboratories, Abbott Park, IL) with cobalt chromium platform.

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stabilizing microtubule assembly, thereby inhibiting mitosis of smooth muscle cell and inhibiting cell migration.¹⁷

Pharmacokinetics of DES

Pharmacokinetics is the mechanism through which a drug is absorbed, distributed, metabolized, and eliminated from the body. The pharmacokinetics of DES are determined by the drug's intrinsic properties and by the coating technique used in applying it on the stent platform. The physiochemical properties of the pharmacological agent used in a DES such as diffusivity, hydrophilic or hydrophobic nature, and presence or absence of protein binding are important considerations as these have an effect on the biological action of these agents.^{21,22}

The drug reservoir (polymer and drug mixture) is covered with a thin polymer membrane which functions as a rate-controlling membrane allowing a constant amount of drug to be released over time resulting in zero-order kinetics (Figure 3).²³ An example is the Cypher stent. The Cypher stent is designed to release 80% of total dose in 4 weeks and the rest over the course of the next 2 weeks.¹⁸ In a matrix design, a drug is usually dispersed inside the polymer matrix, and the drug is released into the environment without any rate-controlling barrier layer. Therefore, the amount of drug released over time varies, resulting in nonzero-order kinetics.²³ An example is TAXUS® Express²⁸ Coronary Stent System (Boston Scientific Corporation, Natick, MA). Although, there are three paclitaxel drug-release formulations (fast, moderate, and slow), only the moderate- and slow-release formulations have been tested in clinical trials. The moderate-release form of Taxus stent allows for an initial bolus release over the first 48 hours after stenting followed by a low-level release over the next 10 days. In these 10 days the slow-release formulation of Taxus stent has a drug release concentration of 8–10 times lower than that of the moderate-release formulation.²⁴ Only the slow-release formulation is marketed for clinical use.

By making small changes in formulation, such as increasing drug dose, coating thickness, or drug-to polymer ratio,

Figure 3 A cross-section through a stent strut.¹¹⁷

the release kinetics can be varied over a period of time.²⁵ A few characteristics of Food and Drug Administration-approved stents are listed in Table 1. Parameters used in assessing a DES include stent size, total amount of drug loaded, dose of drug per unit area, duration of release, residual drug within stent, and thickness of coating material.²⁶ The goal being to optimize drug release in order to achieve desired efficacy and minimize local vascular toxicity.

Efficacy of stents

First generation DES

The first in-man placement of a sirolimus-eluting stent (SES) occurred in 1999 as a part of a study of 30 patients with angina.²⁷ At 8-month follow-up, there was no evidence of restenosis with minimal neointimal proliferation detected by intravascular ultrasound and quantitative coronary angiography.²⁷ To compare the outcomes of the newly developed Cypher SES to conventional BMS, the Initial Double-Blind DES versus BMS Study (RAVEL) study was performed.²⁸ RAVEL randomized 238 patients with low-risk lesions to receive BMS or SES. At 1-year follow-up; SES had a restenosis rate of 0% while BMS had a restenosis rate of 27%.²⁸ A subsequent larger study, Study of Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in Treatment of de Novo Native Coronary Lesions (SIRIUS), enrolled 1058 patients with more complex lesions and showed that target lesion revascularization (TLR) occurred in 4.9% of the SES patients vs 20% in the BMS patients at 12 months ($P < 0.001$).²⁹ This significant difference persisted through 5 years of follow-up (Figure 4).³⁰ Single center and multi-center registries, the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital registry and the Arterial Revascularization Therapies Study registry also illustrated similar benefits for SES in the “real world setting.”^{31,32} Other subsets including diabetics, ST segment elevation myocardial infarctions, chronic total occlusions, saphenous vein grafts showed significantly better outcomes for in-stent restenosis, TLR, and major adverse cardiovascular events for SES.^{33–46}

Primary Stenting of Totally Occluded Native Coronary Arteries II (PRISON II) study enrolled 200 patients with chronic total occlusions and randomized 100 to SES and 100 to BMS and found significantly better outcomes in the SES arm (Table 2). The Gruppo Italiano di Studio sullo Stent nelle Occlusioni Coronariche (GISSOC) trial looked at 152 chronic total occlusions with 78 receiving SES and 74 receiving BMS; it showed SES to have significantly greater minimal

Table 1 Specifications of the Food and Drug Administration-approved drug-eluting stents

Stent	Drug (μm)	Polymer	Polymer thickness (μm)	Release kinetics 28 days	Metal	Strut thickness (μm)
Cypher® Stent (Cordis Corporation, Minneapolis, MN)	Sirolimus (140)	Polyethylene co-vinyl acetate and poly-n-butyl methacrylate	12.6	80%	SS	140
Taxus® Express ²⁰ Coronary Stent System (Boston Scientific Corporation, Natick, MA)	Paclitaxel (100)	Poly (styrene-b-isobutylene-b-styrene)	16.0	<10%	SS	132
Taxus® Liberté® Paclitaxel-Eluting Coronary Stent System (Boston Scientific Corporation)	Paclitaxel (100)	Poly (styrene-b-isobutylene-b-styrene)	16.0	<10%	SS	97
Endeavor® Sprint Zotarolimus-Eluting Coronary Stent System (Medtronic, Inc)	Zotarolimus (100)	Phosphorylcholine	4.1	95%	CoCr	91
Xience V® Everolimus Eluting Coronary Stent (Abbott Laboratories, Abbott Park, IL)	Everolimus (100)	Polyvinylidene fluoride co-hexafluoropropylene and poly-n-butyl methacrylate	7.6	80%	CoCr	81

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Abbreviations: SS, stainless steel; CoCr, cobalt chromium.

luminal diameter at 8-month follow-up (1.98 ± 0.57 mm vs 0.98 ± 0.80 mm, $P < 0.001$).⁴⁷ One small nonrandomized study of 38 patients with SES vs 37 patients with BMS in saphenous vein graft lesions demonstrated less in-stent late loss (0.38 mm vs 0.79 mm, $P < 0.05$), binary in-stent restenosis (11.3% vs 30.5% , $P < 0.05$), and TLR (5.3% vs 21.6% , $P < 0.05$) in the SES group at 6 months. However, at long-term follow-up of this small cohort, there was increased mortality in the SES arm (29% vs 0% , $P < 0.001$) with loss of benefit of SES in TLR (34% vs 38% , $P = 0.15$).^{48,49} But a more recent meta-analysis of DES compared to BMS in 7994 confirmed the benefits of DES and did not find any increased mortality or morbidity related to DES in saphenous vein grafts.⁵⁰ In the just reported Is DESing Associated With

Improved Results in Coronary Artery Bypass Grafts (ISAR CABG) trial, 610 patients from four centers received either a DES or BMS in their saphenous vein grafts and showed that there were significant reductions of TLR in the DES group (7.2% vs 12.9% , $P = 0.020$).⁵¹

The Taxus paclitaxel-eluting stent (PES) was developed at the same time SES was being tested. The Taxus PES showed significant improvements in minimal luminal diameter (2.60 ± 0.49 mm vs 2.19 ± 0.65 mm, $P < 0.01$), diameter stenosis (13.56 ± 11.77 mm vs 27.23 ± 16.69 mm, $P < 0.01$), and late lumen loss (0.36 ± 0.48 mm vs 0.71 ± 0.48 mm, $P < 0.01$) when compared to BMS in de novo coronary lesions with 6- and 12-month follow-up.⁵² Larger randomized trials including patients with ST segment elevation myocardial infarctions and more complex lesions also confirmed the benefits of PES over BMS.^{39,40,52–61} In the Taxus Stent Evaluated at Rotterdam Cardiology Hospital report of 2-year

Figure 4 Results of the Sirolimus-Eluting Stent in De Novo Native Coronary Lesions (SIRIUS) trial showing sirolimus-eluting stent (SES) vs base metal stent (BMS) at 12-month and 60-month follow-up.^{30,118}

Table 2 Results of PRImary Stenting of totally Occluded Native coronary arteries II (PRISON II) trial¹¹⁹

	SES	BMS	P value
Binary in-stent restenosis	7%	36%	$P < 0.001$
In-segment restenosis	11%	41%	$P < 0.0001$
Target lesion revascularization	4%	19%	$P < 0.001$

Abbreviations: BMS, bare metal stent; SES, sirolimus-eluting stent.

follow-up, it was reported that PES had similar efficacy to SES for restenosis.⁶²

Several studies have compared the outcomes of unselected patients with SES vs PES.^{63,64} The Sirolimus-Eluting Versus PES for Coronary Revascularization study (SIRTAX) looked at 1012 patients with 503 receiving SES and 509 receiving PES. Initial follow-up at 8 months showed superiority of SES with significantly lower rates of in-stent late loss and binary in-stent restenosis with seemingly fewer TLR and major adverse cardiovascular events. However, after 5 years of follow-up, there were no significant differences in any of the measured outcomes.

A meta-analysis of 16 randomized trials with over 8000 patients comparing SES and PES showed that patients who had SES had lower TLR (hazard ratio [HR]: 0.74, 95% confidence interval [CI]: 0.63–1.03, $P < 0.001$) and significantly less incidence of stent thrombosis (HR: 0.66, 95% CI: 0.46–0.94, $P = 0.02$).⁶⁵ However, there were no significant differences for the risk of death (HR: 0.92, 95% CI: 0.74–1.13, $P = 0.43$) or myocardial infarction (HR: 0.84, 95% CI: 0.69–1.03, $P = 0.10$). A more recent, but smaller meta-analysis of 810 patients showed similar outcomes with significantly less TLR (HR: 0.61, 95% CI: 0.44–0.85, $P = 0.004$) in patients who received SES when compared to PES.⁶⁶

Two studies compared SES vs PES in diabetics: DES in Patients with DIABETES Mellitus (DES-DIABETES) trial and the Intracoronary Stenting and Angiographic Results: Do Diabetic Patients Derive Similar Benefits from Paclitaxel-Eluting and SES (ISAR-DIABETES) trial. DES-DIABETES showed significantly less in-stent late loss (0.13 mm vs 0.53 mm, $P < 0.001$) and a lower rate of binary in-stent restenosis (3.4% vs 18.2%, $P < 0.001$) in patients who received SES.^{67–69} ISAR-DIABETES also showed significantly better outcomes with less in-stent late loss (0.19 mm vs 0.46 mm, $P < 0.001$) and binary in-stent restenosis (4.9% vs 13.6%, $P < 0.001$) in patients who received SES when compared to patients who received PES. No significant differences were seen in death or myocardial infarction but there was significantly less TLR in SES patients (3.5% vs 11.0% at 24 months) in the DES-DIABETES study.⁶⁸ In the ST segment elevation myocardial infarctions population, SES had lower in-stent restenosis (5.9% vs 14.8%, $P = 0.03$) and in-stent late lumen loss (0.09 ± 0.45 mm vs 0.33 ± 0.68 mm, $P = 0.002$) than PES.⁷⁰ Like other SES vs PES studies, there were no significant differences in major adverse cardiovascular events between the two types of DES. At 3-year follow-up there continued to be no significant differences in major adverse cardiovascular events.⁷¹

For unprotected left main stenting, there were no significant differences between SES and PES for death, myocardial infarction, or TLR. There was no difference in angiographic restenosis at 1 year.⁷² In a study of 360 nondiabetic patients with small vessels, SES had significantly less in-stent late loss with a difference of 0.32 mm ($P < 0.001$) when compared to PES and binary in-stent restenosis (relative risk [RR]: 1.67, 95% CI: 1.00–2.79, $P = 0.047$) as well as less TLR (RR: 2.24, 95% CI: 1.20–4.17, $P = 0.008$) when compared to PES.⁷³ While many smaller studies with unselected patients with diabetes, left main coronary artery disease, and acute infarctions show SES superiority over PES at short-term follow-up, at 5 years the SIRTAX trial demonstrated no difference in outcomes between SES vs PES.^{63,64,67–70,72,73}

Second generation DES

While first generation coronary stents utilized stainless steel for their metal backbone, second generation coronary stents are made with cobalt chromium struts. Cobalt chromium has an advantage over its predecessor, stainless steel, in that it is more radiopaque, it has more radial force, and it is thinner.

The first of the two approved second generation DES is the Endeavor stent which utilizes a phosphorylcholine polymer to deliver a sirolimus analog, zotarolimus. Imaging studies with angioscopy and optical coherence tomography have demonstrated the zotarolimus-eluting stent (ZES) have better neointimal coverage than SES (comparable to BMS).^{74,75} The Medtronic Endeavor Drug Eluting Coronary Stent System in Coronary Artery Lesions (Endeavor II) trial, the first randomized controlled trial comparing ZES to BMS, showed that ZES had significantly lower in-stent late loss, binary restenosis, and TLR in 1197 patients at 9-month follow-up (Figure 5).⁷⁶ At 5-year follow-up, ZES continued to have significantly lower major adverse cardiovascular events, target vessel revascularization, and TLR.⁷⁷ Stent thrombosis was low at 0.2% with ZES and 0.3% with BMS.⁷⁷

Comparing ZES to SES demonstrated ZES had more in-stent late loss (0.34 ± 0.44 mm vs 0.13 ± 0.32 mm, $P < 0.001$), binary in-stent restenosis (11.7% vs 4.3%, $P = 0.04$), and TLR (9.8% vs 3.5%, $P = 0.04$) at 9 months.⁷⁸ However, after 5 years ZES vs SES patients had lower all-cause mortality (5.2% vs 13.0%, $P = 0.02$), myocardial infarction (1.0% vs 4.6%, $P = 0.03$), and major adverse cardiovascular events (14.0% vs 22.2%, $P = 0.05$) compared to patients who received SES.⁷⁹ There was no difference between ZES and SES for target vessel revascularization or stent thrombosis at 5 years.⁷⁹ The Endeavor IV trial compared ZES to PES and showed no significant differences in target

Figure 5 Results of the Endeavor II Clinical Trial: The Medtronic Endeavor Drug Eluting Coronary Stent System in Coronary Artery Lesions showing zotarolimus-eluting stent (ZES) versus bare metal stent (BMS) at **(A)** 9-month follow-up and **(B)** 60-month follow-up.^{76,77}

Abbreviations: ISR, in-stent restenosis; MACE, major adverse cardiovascular events; TLR, target lesion revascularization; TVF, target vessel failure.

vessel revascularization, cardiac death, myocardial infarction, or stent thrombosis at 12 months.⁸⁰

The other approved second generation DES is the Xience V[®] Everolimus Eluting Coronary Stent (Abbott Laboratories, Abbott Park, IL), an everolimus-eluting stent (EES) with a biocompatible polymer and a synthetic derivative of

sirolimus, everolimus. The first randomized control trial looking at the safety and efficacy of EES, Clinical Evaluation of the Xience V Everolimus Eluting Coronary Stent Systems (SPIRIT) I, was conducted in 60 patients with 28 receiving EES and 32 receiving a BMS in native coronary lesions which showed significantly lower in-stent

late loss (0.10 mm vs 0.87 mm, $P < 0.001$) and binary in-stent restenosis (0% vs 25.9%, $P = 0.01$) in the EES patients, suggesting effective suppression of neointimal growth at 6 months.⁸¹ In SPIRIT II, which compared 223 patients who received EES with 77 patients who received PES, there was significantly less in-stent late loss in the EES patients when compared to the PES patients (0.11 ± 0.27 mm vs 0.36 ± 0.39 mm, $P < 0.0001$) at 6 months, but no significant differences in death, myocardial infarction, and TLR.⁸² This same cohort of patients showed a nonsignificant trend towards benefit of EES when compared to PES in respect to death, myocardial infarction, and TLR at 4 years.⁸²

The SPIRIT III trial enrolled over 1000 patients and also showed that in-stent late lumen loss was significantly less in the patients who received EES when compared to patients who received PES (0.14 mm vs 0.28 mm, $P \leq 0.004$) as well as having fewer major adverse cardiac events at 9 months (6.0% vs 10.3%, $P = 0.02$).⁸³ Subsequent studies have shown an advantage for EES compared to PES in a large population of patients (SPIRIT IV and the Second Generation Everolimus-Eluting and PES in Real-Life Practice [COMPARE] study) with significantly lower rates of myocardial infarction, TLR, as well as stent thrombosis.^{84,85} There has been criticism that EES has yet to be compared to SES which is regarded as the most efficacious first generation DES. This should be addressed in the currently ongoing Efficacy of Xience/Promus versus Cypher in Reducing Late Loss After Stenting (EXCELLENT) trial.⁸⁶

Newer coronary stents include those that have a novel polymer coating, are biodegradable, or are completely polymer free. The Endeavor® Resolute Zotarolimus Eluting Coronary Stent (Medtronic, Inc) is the next version of the Endeavor ZES undergoing clinical evaluation. This ZES consists of the Driver cobalt chromium stent platform and a polymeric coating which is a blend of three different polymers allowing for a delayed drug release, such that at least 85% of the zotarolimus is released within 60 days, with the remainder being released within 180 days. The Endeavor Resolute stent has been compared to the Xience V stent in the Resolute All-Comers trial.⁸⁷ This trial enrolled 2300 patients who were randomized in a 1:1 ratio to treatment with either the Resolute ZES or the Xience V EES. At 12-month follow-up the Resolute ZES was noninferior to EES with respect to the primary clinical end point of target lesion failure, a composite of cardiac death, target vessel myocardial infarction, and clinically indicated TLR (ZES 8.2% vs EES 8.3%, noninferiority $P < 0.001$).⁸⁷ This is

the beginning of a wealth of new stent technology. Further results are awaited.

Safety of DES

DES constitutes the vast majority of stents used to treat coronary lesions due to their low rates of restenosis when compared to BMS.⁸⁸ In 2006, safety concerns were raised regarding the risk of stent thrombosis with DES.⁸⁹ A meta-analysis published in 2006 comparing first generation DES with BMS concluded that there was increased noncardiac mortality at 2–3 years following stent placement.⁸⁹ The cause of the increased noncardiac mortality was not clear, nor was there any relationship with stent thrombosis.⁸⁹ Subsequently, the Basel Stent Cost-effectiveness Trial – Late Thrombotic Events (BASKET-LATE) trial prospectively randomized 746 patients undergoing PCI to DES or BMS to determine the rate of late cardiac events after discontinuation of dual antiplatelet therapy. The study demonstrated a 3.6% increased risk of cardiac death ($P < 0.01$) and a 3.8% increased risk of nonfatal myocardial infarction ($P < 0.04$) 7–18 months in the DES group. There was no significant difference in rates of angiographically-confirmed stent thrombosis; however, any late death or myocardial infarction was assumed to represent a “thrombosis-related event.”⁹⁰ Two major studies published in 2007, the combined analysis of the Cypher SES trials (RAVEL, SIRIUS, European SIRIUS, and Canadian SIRIUS)⁹¹ and the Swedish Coronary Angiography and Angioplasty Registry showed an increased risk of death or Q wave myocardial infarction with DES compared to BMS, which seemed to corroborate these findings.⁹²

These early studies questioning DES safety prompted two important steps: (1) a better definition of stent thrombosis was applied in a standardized fashion across all clinical trials and (2) larger meta-analyses were performed that were powered to detect differences in stent thrombosis rates. In 2007, the Academic Research Consortium defined stent thrombosis as definite, probable, or possible (Table 3).⁹³ Most experts believe that the Academic Research Consortium definitions of “definite and probable” stent thrombosis are the most precise methodology to estimate the occurrence of this event.

Using these new Academic Research Consortium criteria, four large meta-analyses found no difference in the rates of death, myocardial infarction, or stent thrombosis between DES and BMS (Figure 6).^{94–97} The largest of these studies examined 8646 patients undergoing DES and BMS implantation followed for 4 years and saw no difference in death or myocardial infarction.⁹⁴ This reassuring data was followed by a pooled analysis of four randomized controlled trials

Table 3 Academic Research Consortium definitions of stent thrombosis¹¹⁶

Category	Definition
Definite ST	<ul style="list-style-type: none"> • Angiographic or pathologic confirmation of partial or total thrombotic occlusion within the persistent region AND at least ONE of the following, additional criteria: <ul style="list-style-type: none"> – Acute ischemic symptoms – Ischemic electrocardiogram changes – Elevated cardiac biomarkers
Probable ST	<ul style="list-style-type: none"> • Any unexplained death within 30 days of stent implantation • Any myocardial infarction, which is related to documented acute ischemia in the territory of the implanted stent without angiographic confirmation of stent thrombosis and in the absence of any other obvious cause
Possible ST	<ul style="list-style-type: none"> • Any unexplained death beyond 30 days

Abbreviation: ST, stent thrombosis.

with 1748 patients undergoing PCI with DES or BMS. The DES group had a mortality of 6.7% compared to 5.3% in the BMS group this was not statistically significant.⁹⁵ Finally, two meta-analyses performed similar comparisons, which actually found the overall event rate to be significantly lower in the DES group. There were no increased rates of death or probable/definite stent thrombosis.^{96,97} These studies demonstrated that appropriate dual antiplatelet therapy for 1 year was necessary to preclude the risk of stent thrombosis and ensure the safety of DES.

Second generation DES theoretically have a lower risk of stent thrombosis due to earlier intimal coverage (Table 4).^{74,98} Angioscopy studies with ZES have shown neointimal stent coverage similar to BMS at 3-month follow-up.⁷⁴ Because the rate of stent thrombosis is very low, no study comparing ZES to BMS has been powered to

detect differences in stent thrombosis.⁹⁹ There is evidence of noninferiority for ZES when compared to first generation DES. The Danish Organization for Randomized Trials with Clinical Outcome (SORT-OUT) trial and Comparison of the Efficacy and Safety of ZES with Sirolimus-Eluting and PES for Coronary Lesions (ZEST) trials comparing ZES to first generation DES, showed no difference in the rate of stent thrombosis.¹⁰⁰ The ongoing Patient Related Outcomes with Endeavor versus Cypher Stenting Trial (PROTECT) will enroll 8800 patients and will report a primary endpoint of definite/probable stent thrombosis at 3-year follow-up. This will be the first larger scale data regarding the long-term safety of ZES.¹⁰¹

EES have consistently shown lower rates of probable/definite stent thrombosis compared to first generation DES in a series of clinical trials. Two trials, SPIRIT IV and COMPARE, showed statistically significant lower rates of stent thrombosis with everolimus stents when compared to PES. The ongoing EXCELLENT trial will be the first trial to compare the safety and efficacy of EES to SES.⁸⁶

Quality of life, patient satisfaction, and acceptability

Clinical trials in stable patients with coronary artery disease have failed to show a reduction in mortality or recurrent myocardial infarction with PCI.¹⁰² The primary benefit of PCI is relief of angina.^{103,104} Patient quality of life and outcomes are significantly improved by a reduction in their angina frequency and severity.¹⁰⁵ Recently the utilization of PCI in patients with stable coronary disease has come into question. A substudy of the Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation (COURAGE) trial published in 2007 compared the use of

Figure 6 (A) Relative rates of stent thrombosis in drug-eluting stent (DES) and bare metal stent (BMS) from three large meta-analyses. **(B)** Overall mortality in DES and BMS.^{94,95,97}

Table 4 First and second generation drug-eluting stents (DES)

First generation DES	Second generation DES
Sirolimus-eluting stents Cypher® Stent (Medtronic, Inc, Minneapolis, MN)	Zotarolimus-eluting stents Endeavor®
Paclitaxel-eluting stents Taxus®	Everolimus-eluting stents Xience V® Everolimus Eluting Coronary Stent (Abbott Laboratories, Abbott Park, IL) Promus® Everolimus-Eluting Coronary Stent System (Boston Scientific Corporation, Natick, MA)

optimal medical therapy to PCI and found that PCI led to improvements in angina frequency, quality of life, and patient satisfaction but that these differences disappeared at 3-year follow-up.¹⁰⁶ It is important to understand that the COURAGE trial suffered from serious limitations including the requirement that therapy was directed by angiography, the patient population was highly selected, there was very low rate of DES utilization, and a high crossover rate from medical therapy to PCI was permitted which weakens conclusions regarding late outcomes. A number of trials have demonstrated significant improvement in angina and quality of life with PCI in certain subgroups including the elderly,¹⁰⁷ those with severe angina,¹⁰⁸ and diabetics.¹⁰⁵ An integrated approach

to the management of angina including revascularization, medical therapy, and cardiac rehabilitation can improve quality of life and patient focused outcomes.

The symptom of angina pectoris results in significant impairment of several health-related quality of life measures. Exercise performance and overall physical activity declines dramatically with exertional angina. Psychologically, patients with angina have a higher risk of depression, poor disease related perception, and overall self-reported quality of life.¹⁰⁹ Proper management of angina leads to improvement in emotional wellbeing, physical activity, and patient perception of general health.¹¹⁰

The challenge of the past several years has been to determine the role of PCI in the management of angina. Several landmark studies demonstrated improvement in anginal symptoms with PCI (Figure 7). The Angioplasty Compared to Medicine trial randomized 212 veterans with single vessel coronary artery disease and inducible ischemia on stress testing to medical management or PTCA. In this study at 6-month follow-up, 62% of patients in the PTCA group were angina free compared with 47% of patients in the medical group ($P < 0.05$).¹⁰³ The Medicine, Angioplasty or Surgery Study trial randomized 214 patients with stable angina, isolated proximal left anterior descending coronary artery disease, and normal left ventricular function to

Figure 7 Freedom from angina in trials comparing medical therapy to percutaneous coronary intervention (PCI).

Abbreviations: ACME, Angioplasty Compared to Medicine trial; RITA-2, Second Randomized Intervention Treatment of Angina trial; COURAGE, Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation trial; BARI-2D, Bypass Angioplasty Revascularization Investigation 2 Diabetes trial; MASS, Medicine, Angioplasty, or Surgery Study.

coronary artery bypass graft, PTCA, or medical therapy. Both revascularization groups, coronary artery bypass graft and PTCA, showed improvements in angina. The PTCA group was superior to medical therapy for control of angina at 3-year follow-up.¹¹¹ Finally, the Second Randomized Intervention Treatment of Angina (RITA-2) trial randomized 1018 patients with single or multivessel coronary artery disease to PTCA or medical therapy. At 6-month follow-up, the PTCA group showed improvements in Canadian Cardiovascular Society angina class and exercise performance when compared to the medical therapy arm.¹⁰⁴ Outcomes analysis showed improvement in quality of life factors including overall vitality and tolerance of physical activity in the PTCA group that lasted 1 year. At 3-year follow-up, the difference between the two groups became negligible, but in the interim, there was 27% crossover from the medical therapy to the PTCA arm.¹¹²

The COURAGE trial included several quality of life endpoints.¹⁰⁶ The investigators assessed angina related specific health status with the Seattle Angina Questionnaire and overall physical and mental function with the RAND-36 health survey.¹⁰⁶ The PCI group showed significant improvement in freedom from angina up to 2-year follow-up. The vast majority of stents were BMS, and the rates of restenosis were not published. In the five domains assessed by the RAND-36 survey (physical functioning, physical limitation, vitality, pain, and general health), there were significant benefits in the PCI group at 6-month follow-up, but again these benefits were lost at 2-year follow-up.¹⁰⁶

The time-limited benefits with PCI are likely due to a significant number of medical therapy patients crossing over to PCI. COURAGE had a highly selected patient population. Patients were enrolled only after coronary angiography was performed. COURAGE excluded over 90% patients screened for unclear reasons. The data defining the reasons for exclusion has not been published. The observed annual rate of cardiac mortality in COURAGE was approximately 0.4%, which represents an extremely low risk cohort and suggests that high-risk patients were excluded. COURAGE enrolled 70% of patients with two- or three-vessel disease.¹¹³ Yet only 36% of patients received more than one stent. This suggests that revascularization was incomplete in a significant proportion of the PCI arm. Moreover, 42% of patients in the study had no or minimal angina (Canadian Cardiovascular Society class 0 or 1), as such it would be difficult to detect differences in anginal severity or frequency.¹¹³ A significant proportion of the medical therapy arm crossed over to PCI which may account for the loss of difference between the

two groups at long-term follow-up. Of the symptomatic group in the medical therapy arm, 32% were subsequently revascularized for severe or worsening symptoms. Finally, only 2.7% of patients in COURAGE received a DES and the late loss of anginal benefit may be due in part to BMS in-stent restenosis.¹¹³

The Trial of Invasive Versus Medical Therapy in Elderly Patients (TIME) examined the use of PCI in the elderly. TIME randomized 301 patients over the age of 75 with stable angina to invasive assessment with medical therapy or medical therapy alone.¹¹⁴ Patients randomized to the invasive strategy had a lower rate of major adverse cardiovascular events (death, myocardial infarction, or repeat hospitalization) when compared to medical therapy (49% vs 19%, $P < 0.0001$).¹¹⁴ Other similar studies have found benefits in quality of life measures for elderly patients undergoing PCI. The Alberta Provincial Project for Outcomes Assessment in Coronary Heart Disease (APPROACH) trial included two cohorts of about 1600 elderly patients. One cohort had patients undergoing PCI or coronary artery bypass graft, and the other cohort was treated with medical therapy. At 4-year follow-up, all measures of the Seattle Angina Questionnaire including angina frequency and severity were improved in the revascularization arm.¹¹⁵

The baseline severity of angina before PCI appears to predict improvement in angina after revascularization. In a multivariate analysis of 1020 patients undergoing PCI for nonacute myocardial infarction, the best predictors of improvement in angina was physical limitation prior to PCI and severity of angina as assessed by the Seattle Angina Questionnaire.¹⁰² In fact, the Seattle Angina Questionnaire predicted improvement in angina better than the number of vessels involved, ejection fraction, or age. Similarly, subsequent studies have demonstrated that patients with angina who report overall poor quality of life see the greatest benefit in angina and quality of life following PCI.¹⁰²

Diabetics often present with atypical symptoms of angina. However, diabetics who do present with stable angina appear to have significant symptom relief with revascularization. The Bypass Angioplasty Revascularization Investigation 2 Diabetes (BARI 2D) trial randomized 2364 patients with diabetes, coronary artery disease, and inducible ischemia on stress testing to medical therapy or revascularization.¹⁰⁵ Only 59% of patients exhibited typical angina. The 796 patients randomized to PCI showed improvements in worsening angina, new angina, subsequent coronary revascularization, and total rates of freedom from angina at 3-year follow-up.¹⁰⁵

The bulk of evidence supports a combined approach to the management of patients with angina. Coronary revascularization with stent placement should be complemented with exercise training and medical therapy. Certain patients such as the elderly, diabetics, and those with severe angina see clear benefits in quality of life and overall health after PCI for stable angina. Due to the limitations of COURAGE, it is still unclear what the role of PCI will be in other categories of patients. Further studies examining complete revascularization with DES in patients with stable angina will be needed to clarify this question.

Summary

It is clear from the data gathered among thousands of patients studied in clinical trials that the development of DES was a major step forward in the advancement of PCI. Multiple risk benefit analyses have demonstrated the cost-effective use of DES in patients with coronary artery disease. Concerns over the risk of subacute stent thrombosis rates with DES have been mitigated with prolonged use of dual antiplatelet therapy and with the newer generation of DES. Currently, patients who cannot be or who are unwilling to be compliant with prolonged dual antiplatelet therapy should receive BMS. The goals of the next generation of DES will be increased deliverability, will address difficult subsets of patients such as those with bifurcation disease, and will continue to have an improved safety profile with lower risks of stent thrombosis.

Disclosure

The authors report no conflicts of interest in this work.

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