CHAPTER

8

Drug Eluting Stents – Do They Address the Problem of Restenosis?

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Introduction

Percutaneous coronary intervention (PCI) has revolutionised the treatment of coronary artery disease, which remains one of the major causes of mortality in developed nations throughout the world. It is used to treat patients with both stable angina and acute coronary syndromes, and is also the treatment of choice in acute ST-elevation myocardial infarction. PCI is popular with patients when compared with coronary artery bypass grafting (CABG), as major surgery can be avoided, a shorter hospitalisation is involved, and return to active lifestyle is earlier. Furthermore, the immediate technical success rate is high, and the procedural mortality and morbidity rate is low.

Percutaneous transluminal coronary angioplasty (PTCA), first preformed in 1977 by Andreas Gruentzig, has revolutionized therapy for CAD. Since then, the field of interventional cardiology has witnessed vast improvement in techniques and an increase in research designed to eliminate some of the limitations associated with PTCA.[1,2] Restenosis, historically occurring in approximately 30% of patients within the first 6 months, is the Achilles heel of PTCA.[3-5] Restenosis is defined as an arterial healing response after injury involving vascular elastic recoil, neointimal proliferation, and negative remodeling.[1,2,6] Postangioplasty restenosis primarily results from negative remodeling with neointimal formation, which accounts for more than 60% of late luminal loss.[3,6,7] Stenting has effectively reduced the restenosis rates to approximately 15% to 30% by functioning as a mechanical scaffold that eliminates elastic recoil and negative remodeling.[3,4,8] The drastic rise in the use of stents identified a new problem with PTCA: restenosis occurring within the stent. In-stent restenosis (ISR) is defined as lumen diameter loss of greater than 50% within the stent. Abnormal coronary flow reserve can be demonstrated in the vessel once the diameter stenosis exceeds 50%.[9]

Pathophysiology of Restenosis

The pathophysiology of restenosis is complex and incompletely understood. Current evidence suggests that restenosis is a maladaptive response of the coronary artery to trauma induced during angioplasty consisting of thrombosis, inflammation, cellular proliferation, and extracellular matrix production that together contribute to postprocedural lumen loss over approximately 6 months (Figure 1).[10] Lumen loss after balloon angioplasty can be separated into 3 distinct stages: early loss associated with elastic recoil, late loss due to negative remodeling, and neointimal hyperplasia (Figure 2).[11]

Figure 1 : Restenosis timeline

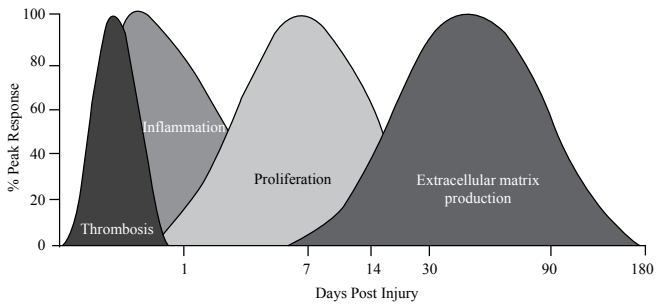
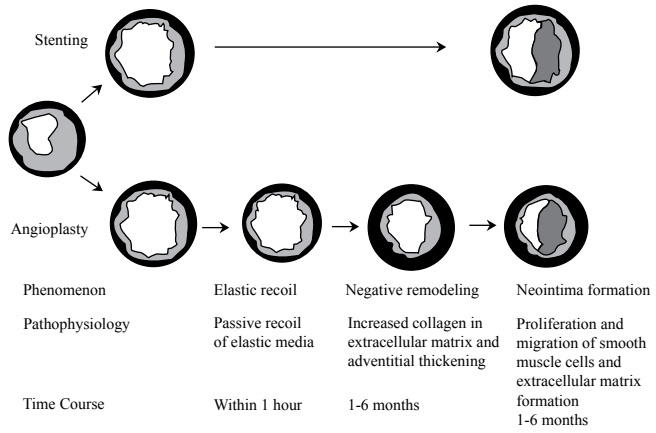


Figure 2 : Progression of restenosis



Endovascular stents reduce restenosis by providing a rigid luminal scaffolding for the vessel. Although bare-metal stents (BMS) reduce early elastic recoil and lumen loss due to remodeling, they do not decrease neointimal hyperplasia and may, in fact, amplify the proliferative component of restenosis. Inflammation and subsequent neointimal hyperplasia is proportional to the degree of penetration of the vessel wall by stent struts, suggesting that the inflammatory response has a critical role in the development of in-stent restenosis. In a study conducted by Farb and colleagues[12] in 56 patients receiving 116 stents, neointimal thickness, inflammatory cell density, and neointimal vascular channel density were significantly greater when struts were in contact with ruptured arterial media compared with fibrous plaque or an intact fibrous cap.[12] Penetration of stent struts into the plaque lipid core was also associated with significantly greater neointimal thickness and increased numbers of inflammatory cells. These data are supported by clinical trials in which low rates of in-stent restenosis have been observed in patients receiving stents coated with various antiproliferative and/or immunosuppressive agents.[13,14]

Drug-Eluting Stents' Focus on the Prevention of In-Stent Restenosis

The ability of the stent to deliver an agent locally to the site of injury reduces proliferation of vascular smooth muscle cells without causing systemic toxicity. The drug can be delivered by the stent through a variety of mechanisms. The first approach used dipping or spraying the drug on to the BMS.[15] This approach lacks the gradual drug and instead delivers a large bolus immediately into the local area. A second approach coats the metal stent with degradable or nondegradable biopolymers, which are loaded with the drug and delivers a sustained release of the agent. A drug-free coated polymer layer can be added to function as a diffusion barrier, further controlling the elution kinetics of the agent.[16]

The compatibility of the coated polymer with the vessel wall determines the degree of inflammation that is generated on contact. The majority of polymers used for stent coating have induced a substantial amount of inflammation in animal models. The major concerns that arise from the use of polymers include chronic inflammation specifically after the elution is complete, direct local toxicity to the vascular tissue, polymer incompatibility with circulating humoral factors, and polymer breakdown and erosion.[16] An ideal polymer effectively delivers antirestenotic therapy over an appropriate time course and remains biologically inert, tolerates mechanical stress, and is not thrombogenic.[16]

Many agents have been used in the preclinical trials for preventing Instent restenosis. The 2 agents that have repeatedly shown the most success in preclinical and clinical trials are sirolimus and paclitaxel.

Table 1 : Major RCTs comparing DES with BMS

	E-SIRUS	C-SIRUS	SIRUS	RAVEL
No. patients	352	100	1058	238
Lesion length (mm)	15.0	13.6	14.4	9.58
RVD (mm)	2.55	2.63	2.80	2.62
DM %	23	24	26	19
Follow up (months)	9	9	9	12
LLL (mm)				
BMS	1.05	1.02	1.00	0.88
SES	0.20	0.12	0.17	-88
P	< 0.0001	< 0.001	< 0.001	< 0.001
ISR (%)				
BMS	41.7	45.5	35.4	28.8
SES	3.9	0.0	3.2	0.0
P	< 0.0001	< 0.001	< 0.001	< 0.001
TLR				
BMS	20.9	18.0	23.2	25.7
SES	8.0	4.0	6.8	6.1
P	< 0.0001	0.05	< 0.0001	< 0.001
MACE(%)				
BMS	22.6	18.0	27.4	28.8
SES	4.0	4.0	12.6	5.8
P	< 0.0002	0.05	< 0.0001	0.002

Evidence on Efficacy of DES

Sirolimus-Eluting Stents

Sirolimus (Rapamycin) is a natural macrocyclic lactone with potent immunosuppressive and antimitotic action produced by a fungus, *Streptomyces hygroscopicus*. In 1999, the U.S. Food and Drug Administration (FDA) approved sirolimus for antirejection in renal transplants.[17] The agent binds intracellularly to FK binding protein-12 (FKBP-12) forming the immunosuppressive complex that inhibits the mammalian target of Rapamycin (mTOR), a key regulatory kinase that leads to an increase in the levels of p27kip1. The rise in p27kip1 inhibits the cyclin– cyclin-dependent kinase complex, blocking the G1-S transition and therefore restricting proliferation of VSMC.[18] When bonded to a stent, the effects are achieved locally without any systemic effects. The sirolimus-eluting stent generates essentially undetectable levels in peripheral blood.[19] There are 4 pivotal trials (Table 1) conducted with sirolimus-eluting stents (SES) that have generated impressive results that led to their approval by the FDA in April 2004.[20-30] The studies used the Bx-Velocity stent, which is a balloon-expandable tubular design made of tubular grade 316L stainless steel. The platform was coated with 5 µm of coating that consisted of a blend of 33% sirolimus and 67% of nonerodable polymer. The drug–polymer matrix contained 140 µg/ cm^2 of sirolimus. A drug-free polymer coat served as a diffusion barrier to control drug release such that 80% was released in the first 30 days postimplantation and no residual drug was detected beyond 90 days. [20-30]

The trials used similar methodology, inclusion and exclusion criteria, and protocols. Patients underwent quantitative angiographic analysis to determine late luminal loss (luminal diameter after procedure minus the luminal diameter at follow up), per cent diameter stenosis, and ISR, defined as diameter stenosis (DS) within the stent of greater than 50%. Major adverse cardiac events (MACE) were defined as death, acute myocardial infarction (MI), total vessel failure (TVF), and target lesion revascularization (TLR). TLR was defined as a repeat PTCA or coronary artery bypass grafting (CABG) involving the stented lesion driven by clinical signs of ischemia in the presence of angiographic restenosis.

RAVEL Trial

The RAVEL trial randomized 238 patients to compare the safety and efficacy of BMS (n = 118) and SES (n = 120). The 2 groups were similar with respect to all clinical variables except for a larger percentage of men in the BMS group. At 6 months follow up, 211 of 238 (89%) patients underwent angiography. There was a significant decrease in

late lumen loss, restenosis, TLR (0.8% vs. 23.7%) and MACE (5.8% vs. 28.8%) in SES compared to BMS.[25] The 3-year follow-up data were recently published demonstrating the continued clinical benefit of SES patients. The frequency of TLR was 25.7% in BMS and 6.1% in SES ($P < 0.001$). The incidence of MACE was 33.1% in the BMS and 15.8% in the sirolimus cohort ($P = 0.002$). There was no significant difference with regard to death or MI at 9 months and 3 years in the two groups. [26]

SIRIUS Trial

The SIRIUS trial enrolled 1058 patients in a randomized, double-blind multicenter trial to determine the clinical benefit of SES (n = 533) in comparison to BMS (n = 525). Each patient received 75 mg of clopidogrel daily for 3 months to reduce the risk of subacute thrombosis. Angiographic follow up was done 8 months postprocedure in 703 (66%) patients and demonstrated a significant decrease in late luminal loss in in-stent and in-lesion per cent DS in the SES group compared to controls. There was a significant reduction in the rate of ISR and in-lesion restenosis in SES. There was a significantly lower TLR (4.1% vs. 16.6%) and MACE (7.1% vs. 18.9%) in SES versus BMS at 9 months.[27] The 3-year clinical follow-up data in 985 (93%) patients showed persistent benefit of SES. The rate of TLR was 23.2% in BMS and 6.8% in SES. The frequency of MACE was 27.4% in BMS and 12.6% in the sirolimus group ($P < 0.0001$). There was no significant difference between the 2 groups in terms of death, MI, or stent thrombosis at 9 months and 3 years.[28]

E-SIRIUS/C-SIRIUS

The E-SIRIUS and the C-SIRIUS trials enrolled 352 and 100 patients, respectively, to confirm the successful results found in the RAVEL and SIRIUS trials. Angiographic analysis at 8 months was done on 308 (88%) patients in the E-SIRIUS and 88 (88%) in the C-SIRIUS, and demonstrated a significant reduction in the amount of late luminal loss in the in-stent and in-lesion per cent DS, TLR and MACE in SES. There was no significant difference in the frequency of death or MI between the 2 groups in either of the 2 trials.[29,30]

A Indian study (SERIES1) on sirolimus stent (supralimus), at 24 months of followup showed death in 3% , TLR in 4% and restenosis in 7% of patients.

In summary, the sirolimus trials repeatedly demonstrated higher efficacy of SES in the prevention of ISR and future requirement for revascularization.

Paclitaxel-Eluting Stents

Paclitaxel is a compound isolated from the bark of the Pacific yew tree in northwestern America (*Taxus brevifolia*). Today, the synthetic form of paclitaxel, Taxol, is used in oncology as treatment of breast and ovarian malignancies.[31] Paclitaxel exerts its pharmacologic effect by inhibiting microtubule depolymerization resulting in the formation of numerous decentralized and unorganized microtubules. This results in inhibition of cellular replication at the G0/G1 and G1/M phase, and stops cytokine-mediated induction of cell proliferation and migration.[31] The dosage of paclitaxel that is exposed to the vessel wall also determines the type of response that is generated. At high doses, paclitaxel has been shown to cause inflammatory cell loss, medial thinning, and increase in stent thrombosis.[32]

Analyzing and comparing the different trials that evaluated the efficacy of paclitaxel-eluting stents (PES) is a challenge as a result of the variation in the stent platforms used, protocols, dose densities, and techniques. The best approach is to evaluate the trials in subsets that used similar protocols and, more importantly, stent platform, coating, and polymer carrier if one was used.[33-40]

TAXUS Trials (Table 2)

The first trial in the TAXUS series, TAXUS I, was the first experience in humans with PES. The TAXUS trials I–V used either the NIRx or

Table 2 : RCTs involving paclitaxel eluting stents in comparison to their matched controls

	TAXUS I	TAXUS II-MR	TAXUS II –SR	TAXUS IV	TAXUS V
No. patients	61	269	267	1314	1156
Lesion length (mm)	11.3	10.5	10.6	13.4	17.3
RVD (mm)	2.97	2.70	2.80	2.75	2.69
DM %	18.1	15.5	13.5	32.3	30.8
Follow up (months)	12	12	12	9	9
LLL (mm)					
BMS	0.71	0.77	0.79	0.92	0.90
PES	0.36	0.30	0.31	0.39	0.49
P	0.008	<0.0001	<0.0001	<0.92	<0.0001
ISR (%)					
BMS	10.0	20.2	17.9	24.4	31.9
PES	0.0	4.7	2.3	5.5	13.7
P	NS	0.0002	0.0002	<0.001	<0.0001
TLR(%)					
BMS	13.3	14.6	12.0	17.4*	15.7
PES	0.0	3.1	4.6	5.6	8.6
P	NS	0.002	0.04	<0.0001	<0.0003
MACE(%)					
BMS	10.0	21.4	22.0	24.9*	21.2
PES	3.0	9.9	10.9	14.7	15.0
P	NS	0.017	0.02	<0.0001	0.008

the Express stent platform (TAXUS IV, TAXUS V) that was coated with a Translute coating and contained a polymer carrier on the surface. The copolymer system provides homogenous coverage of stent on deployment and assures predictable pharmacokinetics of drug delivery. The Translute coating forms a biphasic release of paclitaxel with an initial burst in the first few days and a second release that probably continues indefinitely. The dose used was 1 µg/mm^2.

TAXUS I was a prospective, double-blind, multicenter trial that randomized 61 patients into either the TAXUS or the BMS group. Angiography at 6 months showed a significant decrease in the late luminal loss and per cent DS in TAXUS arm. However, as a result of insufficient power of the study, the incidence of ISR, TLR, and MACE was not significantly different.[33]

The TAXUS II trial randomized patients into 2 separate PES groups. Both the slow-release and the moderate-release paclitaxel formulations had their respective controls that were matched for clinical and angiographic variables. At 6 months follow up, there was a significant decrease in the late luminal loss and in-stent per cent DS in both the slow-release and moderate-release groups when compared with their respective controls. The rate of ISR and in-lesion restenosis was significantly lower in both PES groups compared with their respective controls. The 12-month incidence of MACE was significantly lower in the TAXUS groups versus their matched controls. There was no significant difference in the rate of MI or death between either of the PES formulations with their respective BMS groups.[34]

Table 3 : Major RCTs using non polymer coated Paclitaxel eluting stents in comparison to bare metal controls

	Deliver	Elutes	Aspect
Dose mcg/mm^2	3.0	2.7	3.1
No. patients	1041	190	177
Lesion length (mm)	11.4	10.8	10.9
RVD (mm)	2.81	2.96	2.92
DM %	28.8	15.8	20
Follow up (months)	9	12	6
LLL (mm)			
BMS	0.98	0.73	1.04
PES	0.81	0.11	0.29
P	0.0025	0.002	<0.001
ISR (%)			
BMS	20.6	20.6	27.0
PES	14.9	3.2	4.0
P	0.02	0.056	<0.001
TLR(%)			
BMS	11.3	15.8	3.4
PES	8.1	5.4	3.4
P	NS	NS	NS
MACE(%)	NR		
BMS		18.4	5.2
PES		13.5	11.9
P		NS	NS

TAXUS IV was a large randomized, double-blind, multicenter trial that enrolled 1314 patients with similar clinical and angiographic variables to determine the efficacy and safety of PES (n = 662) versus BMS (n = 652). Clopidogrel was administered for 6 months after the procedure. Five hundred fifty-nine (43%) patients underwent follow-up angiography that demonstrated a significant reduction in the amount of late lumen loss, in-stent per cent DS, and the rate of ISR in PES compared with BMS. The incidence of TLR (3% vs. 11.3%) and MACE (8.5% vs. 15%) was significantly lower in PES versus BMS. There was no significant difference in the frequency of death from cardiac causes, MI, or stent thrombosis between the 2 groups.[35] The 2-year follow-up clinical data in 1238 (94%) patients demonstrated continued benefit of PES. The rate of TLR was 17.4% in BMS and 5.6% in PES ($P < 0.0001$). The incidence of MACE was 24.9% in BMS and 14.7% in PES ($P < 0.0001$). There was no difference in the incidence of cardiac death, MI, or stent thrombosis between the 2 groups.[36]

TAXUS V randomized 1172 patients with more complex lesions. In the 990 (75%) patients who underwent angiographic follow up at 9 months, there was a significantly lower rate of ISR and in-lesion restenosis, frequency of and MACE in PES in comparison to BMS. MI and cardiac death were even in the 2 arms. However, there was higher incidence of MI (8.3% vs. 3.3%) at 30 days in the PES versus BMS in the subgroup that received multiple stents. Although the subset analysis was underpowered, the data prompted further studies involving more complex lesions.[37]

Aspect Trial (Table 3)

The ASPECT trial was a randomized, multicenter, controlled, double-blind study that evaluated the use of PES to reduce ISR. The trial also attempted to show a dose-dependent reduction in restenosis by using 2 groups of PES with a dosage of 3.1 µg/mm^2 and 1.3 µg/mm^2 with the same control arm. One hundred seventy-seven patients were randomized into 3 groups, 60 into the 3.1-PES, 58 into the 1.3-PES, and 59 had BMS. Unlike the TAXUS trial, the ASPECT trial did not use a polymer carrier, but used a proprietary process to bond paclitaxel onto the abluminal surface of the Supra-G stent. Antiplatelet therapy was not standardized with some patients receiving cilostazol in place of clopidogrel. Angiographic analysis conducted in 172 (97%) patients demonstrated a significant dose-dependent reduction in late lumen loss and per cent DS. The incidence of ISR was 4% in the 3.1-PES group, 12% in the 1.3-PES group, and 27% in the BMS group The rate of TLR was 3.4% in all 3 groups, and the frequency of MACE at 6 months was 5.2% in the BMS and 1.3-PES groups and 11.9% in the 3.1-PES group. The increase in MACE was attributed to

an increase in subacute thrombosis in the 3.1-PES group, specifically in the patients who received cilostazol and did not receive clopidogrel.[38]

Elutes Trial

The ELUTES trial was a randomized, double-blind, controlled trial that evaluated the efficacy and safety of PES without a polymer coating. The cohort of patients was randomized into 5 groups (BMS 0.2 μg/mm^2, 0.7 μg/mm^2, 1.4 μg/mm^2, 2.7 μg/mm^2) with similar clinical variables except for a significant difference in age between the 0.2 and the 2.7-PES groups. The V-Flex Plus stent was prepared similarly to the method used in the ASPECT trial. Angiography at 6 months showed a significant reduction in late loss, per cent DS and the rate of ISR only in the 2.7 μg/mm^2-PES arm compared with BMS. The lower dosage PES had no significant difference in any end point compared to BMS. The rates of TLR and MACE were not significantly different between the 5 groups.[39]

Deliver Trial

The DELIVER trial was a prospective, randomized, placebo-control trial that randomized 1043 patients with similar clinical variables into the paclitaxel-coated (3.0 μg/mm^2) ACHIEVE stent (n = 522) versus the Rx ML PENTA stainless steel stent (n = 519). Angiography at 8 months in 442 (42%) patients demonstrated a significant decrease in the late lumen loss, in-stent and in-lesion percent DS in PES in comparison to BMS. There was no significant difference in the incidence of ISR, inlesion restenosis, or TLR between the 2 groups.[40]

Trials comparing Sirolimus versus Paclitaxel-Eluting Stents

The TAXi trial was the first prospective, randomized trial that compared the efficacy of SES (CYPHER) versus PES (TAXUS). Two hundred two patients with similar demographics were randomized to either SES (n = 102) or PES (n = 100). Although the data showed no significant difference in MACE between SES and PES at 6 months, the trial was limited in its sample size to determine any clinical superiority between the 2 DES.[41]

Reality Trial (Table 4)

The REALITY trial was a large prospective, randomized trial that compared the polymer-coated SES against the polymer-coated PES in terms of safety and efficacy. The study randomized 1353 patients with similar angiographic and clinical variables into SES (n = 684) and PES (n = 669) groups with the primary end point of in-lesion restenosis rate at 8 months. The trial demonstrated a significant decrease in the late luminal loss in patients treated with SES in comparison to PES. However, the incidence of in-lesion and ISR, TLR, MACE, MI, or cardiac death were even between the 2 groups at 9 months. Interestingly, the rate of vessel thrombosis at 30 days was significantly lower (0.4% vs. 1.8%, $P = 0.02$) in SES versus PES. The decrease in 30-day vessel thrombosis with SES raised concern about the safety of PES. Nevertheless this could have been an aberrancy in the statistical methodology[43]

Sirtax Trial

SIRTAX compared the efficacy of SES against PES. The study randomized 1012 patients with similar clinical and angiographic variables into SES (n = 503) and PES (n = 509) with the primary end point of MACE at 9 months. Follow-up angiography in 540 (53.4%) patients showed a significantly lower late lumen loss in the SES group. The rate of ISR and in-lesion restenosis was significantly lower in the SES group at 9 months. The incidence of TLR was 4.8% in SES and 8.3% in PES, and the frequency of MACE was 6.2% in the sirolimus and 10.8% in the paclitaxel group. Not unexpectedly, there was no difference in the rates of death, cardiac death, MI, or stent thrombosis between the 2 groups.[43]

ISAR-Desire Trial

ISAR-DESIRE was a unique prospective, randomized, controlled trial that assessed the efficacy of DES in the treatment of ISR in

comparison to conventional balloon angioplasty. Three hundred patients with similar clinical variables and documented angiographic ISR were randomized to receive SES (n = 100), PES (n = 100), or balloon angioplasty (n = 100). Angiographic analysis preformed in 275 (92%) patients showed a significant decrease in rates of restenosis in both DES cohorts in comparison to balloon angioplasty at 9 months. A secondary analysis comparing the 2 DES showed a significant decrease in late lumen loss and in-stent per cent DS in SES versus PES. There were lower rates of in-stent, in-lesion restenosis and MACE that did not reach significance in the SES group. There was no significant difference in the incidence of death or MI across all 3 groups.[44]

ISAR-Diabetes Trial

ISAR-DIABETES was a randomized trial that evaluated whether PES showed similar efficacy as SES in the management of patients with diabetes. Two hundred fifty patients were randomized 1:1 to receive either SES or PES. The trial showed a significant decrease in late lumen loss, per cent DS in the SES group. There was a significant decrease in the incidence of ISR and in-lesion restenosis in SES versus PES. The frequency of TLR was 6.4% in the SES and 12% in the PES group, but failed to reach statistical significance at 9 months. There was no difference in death or MI.[45]

Next generation of DES

Four other antiproliferative agents have been evaluated in a randomized setting: ABT-578, actinomycin, everolimus, and 7-hexanoyltaxol.[46-50] Of these 4, only ABT-578 and everolimus have shown promise for further clinical evaluation. The ENDEAVOR I, II and III trial (n =1,197) was the first RCT to evaluate ABT-578 DESs.[46] Compared with BMSs, ABT-578 DES significantly reduced the incidence of restenosis and TLR. ABT- 578 DESs were also associated with a low rate of stent thrombosis (0.5%) and no events of late stent malapposition. The 3-armed ACTION trial (n = 360) showed actinomycin to be a poor antirestenotic agent.[47] Despite actinomycin's positive preclinical findings, adverse angiographic and clinical results were observed with the drug doses evaluated.

Everolimus (XIENCE V) has been evaluated in 2 RCTs: FUTURE I and II.[48,49] FUTURE I (n = 42) was a feasibility trial, which in addition to demonstrating the safety of the stent system also showed reduced restenosis compared with patients assigned BMSs.[48] FUTURE II (n = 64) demonstrated reductions in the incidence of restenosis and TLR (RRRs 84% and 68%, respectively), although only the former finding was significant.[49] In the 2 studies, the everolimus coated DES was well tolerated, which in conjunction with its demonstrated angiographic improvements has prompted additional FUTURE studies to be initiated. The SCORE trial (n = 266) tested the 7-hexanoyltaxol-based QuaDDS DES (Quanam Medical Corp., Santa Clara, California/Boston Scientific Corp., Natick, Massachusetts) against BMSs.[50] The trial was stopped early because of markedly higher rates of stent thrombosis and MI in patients in the QuaDDS arm. Despite its poor safety profile, the QuaDDS DES effectively reduced the incidence of restenosis, which as a result minimized the difference observed between the 2 groups with respect to TLR. Thus, whereas ABT-578 and everolimus DESs have been shown to be well tolerated and offer promise for improving angiographic and clinical outcomes actinomycin and 7- hexanoyltaxol DESs have failed to establish sufficient safety profiles for further evaluation.

SPIRIT III : Ischemia-driven TLR Through 284 Days

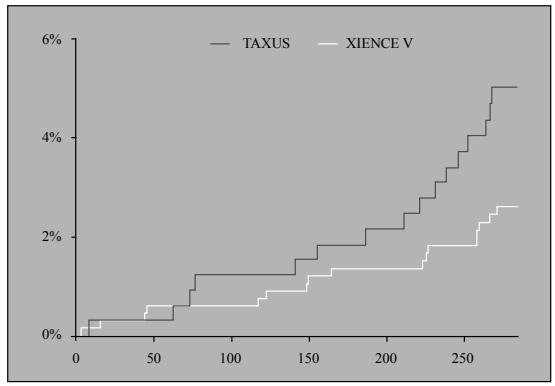


Table 4 : RCTs comparing efficacy of sirolimus with paclitaxel eluting stents

	ISAR Diabetes	ISAR-Desire	SIRTAX	Reality
No. patients	250	200	1012	1353
Lesion length (mm)	13.1	11.95	12.9	17.1
RVD (mm)	2.73	2.60	2.83	2.40
DM %	100	21.5	19.9	27.9
Follow up (months)	9	12	9	8
LLL (mm)				
SES	0.19	0.10	0.12	0.09
PES	0.46	0.26	0.25	0.31
P	<0.001	0.009	<0.001	<0.001
ISR (%)				
SES	4.9	11.0	3.2	7.0
PES	13.6	18.5	7.5	8.3
P	0.02	NS	0.013	NS
TLR(%)				
SES	6.4	8.0*	4.8*	5.0
PES	12.0	19.0	8.3	5.4
P	NS	NS	0.025	NS
MACE(%)	NR			
SES		11.0	6.2	9.2
PES		22.0	10.8	10.6
P		NS	0.009	NS

Spirit I and II showed low rates of restenosis, TLR and MACE with Xcience V evorilimus coated stents compared to the BMS arm. This was associated with the least late loss compared to all other DES so far. Spirit III compared TAXUS with Xcience V and at 9 months the latter had a lower ischemia driven TLR.

Discussion

Restenosis has been a limiting factor to the clinical success of percutaneous coronary intervention. The introduction of stents significantly reduced rates of restenosis by eliminating elastic recoil and negative remodeling. However, the augmented inflammatory response that leads to an increase in neointimal hyperplasia associated with stenting initiated a new challenge in interventional cardiology: ISR. Understanding the pathophysiology of restenosis, and specifically ISR, on a cellular and molecular level allows for the development of targeted therapy. DES deliver antiproliferative agents at effective doses to an area that experiences intense inflammation, thus reducing neointimal formation without reaching toxic levels in the blood.[19]

Table 5 : Summary of the Randomized Clinical Trials Comparing the Efficacy of sirolimus with Paclitaxel-Eluting Stents

	Reality	SIRTAX	ISAR-Desire	ISAR-Diabetes
No. patients	1353	1012	200	250
Lesion length (mm)	17.1	12.9	11.95	13.1
RVD (mm)	2.40	2.83	2.60	2.73
DM (%)	27.9	19.9	21.5	100
Follow up (months)	8	9	12	9
LLL (mm)				
SES	0.09	0.12	0.10	0.19
PES	0.31	0.25	0.26	0.46
P	<0.001	<0.001	0.009	<0.001
ISR (%)				
SES	7.0	3.2	11.0	4.9
PES	8.3	7.5	18.5	13.6
P	NS	0.013	NS	0.02
TLR (%)				
SES	5.0	4.8	8.0*	6.4
PES	5.4	8.3	19.0	12.0
P	NS	0.025	NS	NS
MACE (%)				
SES	9.2	6.2	11.0	
PES	10.6	10.8	22.0	
P	NS	0.009	NS	

*Target Vessel revascularization

DM indicates diabetes mellitus; ISR, in-stent restenosis; LLL, late lumen loss; MACE, major adverse cardiac events; NR, not reported; PES, paclitaxel-eluting stents; RVD, reference vessel diameter; SES, sirolimus-eluting stents; TLR, target lesion revascularization

The wide use of DES has brought forth another concern of subacute stent thrombosis that may result in a catastrophic cardiac event. The use of aspirin and clopidogrel is crucial in preventing subacute stent thrombosis.[51] The major clinical trials involving sirolimus and paclitaxel demonstrated a total thrombosis rate of 0.4% and 0.6%, respectively.[27,35] However, the majority of the patients in these trials presented with relatively simple lesions. With the increased use of DES in patients with acute MI, bifurcation lesions, treatment of ISR, the rate of subacute stent thrombosis may increase. A recent prospective, observational study that enrolled a total of 2229 consecutive patients who underwent stenting with either SES or PES attempted to provide more accurate data by evaluating patients with complicated lesions.[52] At 9 months, 29 (1.3%) patients had stent thrombosis and 14 (0.6%) patients developed subacute thrombosis with a case-fatality rate of 45%. The most common predictor of stent thrombosis was premature discontinuation of antiplatelet therapy. Early discontinuation of antiplatelet therapy is associated with a 30-fold increase in incidence of stent thrombosis.[53] Other independent predictors included renal failure, bifurcation lesions, diabetes, low ejection fraction, and stent length.[52] Although the rate of stent thrombosis in this observational study was significantly higher, the absolute number of cases is still low. Given the consequences that result from stent thrombosis, it is critical that patients and their physicians are educated regarding continuing their antiplatelet therapy with aspirin and clopidogrel. The duration of therapy may need to be increased in patients with more complicated lesions, although that conclusion will have to be drawn from further randomized, controlled trials.

In reviewing the data from major randomized trials involving SES and PES, one can appreciate the potential of DES. Approximately 3160 patients were evaluated in the Bx-Velocity SES and 4201 were evaluated in studies involving the TAXUS stent. SES produces a remarkable reduction in late luminal loss, diameter stenosis, and neointimal hyperplasia demonstrating the effectiveness of sirolimus in inhibiting rapidly proliferating vascular smooth muscle cells. The reduction in ISR to less than 5% of the lesions underlines the success sirolimus stents have at keeping the vessel patent. Clinically, SES was successful in significantly reducing MACE by decreasing the requirement for revascularization. In none of the sirolimus trials was there a mortality benefit or a significant reduction in the incidence of MI. The efficacy and safety of sirolimus up to 4 years of follow up indicates that the coated polymer stent loaded with 1 $\mu g/mm^2$ of sirolimus serves as an effective agent in the prevention of ISR. The coated polymer controls the release kinetics to provide an initial burst of sirolimus at the time of a high rate of proliferation and a basal elution for inhibition of neointimal formation within the critical window of the first month.

The paclitaxel trials can be divided into 2 groups. The first is the TAXUS trials,[33-37] which used a coated polymer and repeatedly demonstrated significant reduction in late loss, diameter stenosis, and neointimal hyperplasia. The reduction in the incidence of ISR is not as dramatic as observed in the sirolimus trials but is significant. The rate of MACE at 1 year was again reduced significantly by decreasing the need for revascularization; however, there was no reduction in the incidence of MI or cardiac mortality. The second group of trials (ASPECT, ELUTES, DELIVER)[38-40] did not use a polymer-coated stent and failed to demonstrate a clinical benefit in terms of MACE or prevention of future revascularization. The trials also showed that an increased paclitaxel dose was required to produce a significant angiographic benefit that was comparable to the TAXUS or sirolimus groups. The controlled release of the drug with the coated polymer generates a greater angiographic benefit and more favorable clinical outcomes. The lack of polymer requires the use of higher doses of antiproliferative agents that perhaps induce injury to the vessel wall, reducing the benefit of PES, and thus does not show improvement in clinical outcomes.

The lack of mortality benefit may be a concern for practitioners in the community. However, the absence of a mortality benefit in drug-eluting stent clinical trials is consistent with the fact that angioplasty has repeatedly failed to show improvement in mortality in patients with stable CAD. This is attributed to the high crossover of medically treated patients to PTCA once they become unstable. Angioplasty, as an extension of medical therapy, reduces angina, limitation of activities of daily living, decreases hospitalization, and provides a less invasive alternative to surgical revascularization.

Conclusions

- DES has reduced the incidence of restenosis and TLR to less than 10% for "on label" use
- The recent concern of late stent thrombosis (0.6% per year with DES) seems to be offset by the lower rates of restenosis and TLR by DES.

Abbreviations

BMS- Bare metal stent, DES- Drug eluting stent, LLL- Late lumen loss, DS- Diameter stenosis, TLR- Target lesion revascularisation, MACE- Major adverse cardiac events, TVR- Target vessel revascularisation, TVF- Target vessel failure, MI- Myocardial infarction, RVD- Reference vessel diameter, ISR- Instent restenosis, PTCA- Percutaneous transluminal coronary angioplasty

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