

Drug-eluting Stents: The End of Restenosis?

A Wong,¹FAMS, MBBS, MRCP (UK), C Chan,¹FAMS, MBChB (Hons), FRCP

Abstract

One of the major advancements in interventional cardiology has been the introduction of drug-eluting stents (DES). By incorporating anti-proliferative agents onto the surface of the stent, neointimal hyperplasia occurring within the stent, which is the main cause of in-stent restenosis (ISR), is markedly reduced. Stents coated with agents, like sirolimus or paclitaxel, when compared to bare metal stents (BMS), had shown remarkable reduction in binary restenosis and target vessel revascularisation (TVR) rates in large randomised clinical trials. The final hurdle of percutaneous coronary intervention (PCI) seems to have been overcome. However, there are still many uncertainties that need to be clarified. The long-term safety of DES remains a major concern; in particular, stent thrombosis and incomplete stent apposition. In the real world, there is a tendency to implant DES in smaller vessels, longer lesions, and complex lesions, as these are high risk for ISR and would yield the greatest benefit. Whether the excellent results of clinical trials of DES can be replicated in these more complex lesions is still unknown and awaits further studies. Although early experience with DES in complex lesions had shown improved results, a higher number of ISR were seen. Finally, the high cost of these devices has precluded their use in all patients undergoing PCI and deliberation among healthcare policy-makers on who should receive DES has centred not only on financial, but also legal and ethical issues. As DES has not completely eliminated ISR and not all patients can afford DES, ISR may survive the initial assault of DES, albeit considerably less in number, for now.

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Introduction

Percutaneous coronary intervention (PCI) is the preferred revascularisation approach for most patients with coronary artery disease because, with comparable clinical outcomes in selected patients, PCI is less invasive and offers shorter hospital stay and faster recovery as compared to coronary artery bypass grafting (CABG).¹ The acceptance of PCI as an alternative to CABG is further enhanced by the adjunct use of coronary stent, which makes PCI a safer procedure and with less repeat procedures in the long-term compared to balloon angioplasty alone.² Sudden occlusion of vessel due to thrombus formation on the stent (subacute stent thrombosis or SAT) and re-narrowing of vessel lumen by neointimal growth within the stent lumen (in-stent restenosis or ISR) are 2 complications initially encountered with the use of coronary stents. Whereas the former complication has been reduced to <1% with adequate antiplatelets regime, ISR can occur up to 50% in high-risk patients undergoing

coronary stenting. Therefore, the major limitation of PCI is the need for repeat target vessel revascularisation (TVR) due to restenosis. In patients with high risk of restenosis, especially in patients with diabetes mellitus with small vessel and long diffuse disease, CABG actually yield more favourable results.^{3,4}

Many drugs and devices have failed to limit restenosis and it has become, and been accepted, as an intrinsic part of PCI.⁵ It is, therefore, not surprising that results of several recently published pivotal trials of drug-eluting stents (DES),^{6,7} which showed remarkable reduction of ISR and TVR in the treatment arm, have generated great euphoria in the interventional cardiology and belief that the Achilles' heel of coronary stenting has finally been conquered. DES is heralded as one of the greatest advancements in interventional cardiology, no less important than the development of balloon angioplasty and coronary stent.

¹ Department of Cardiology
National Heart Centre, Singapore

Address for Reprints: Associate Professor Charles Chan, Director of Cardiovascular Laboratory, Department of Cardiology, National Heart Centre, Singapore 168752.

However, we believed that although the battle seems to have been won, the war against ISR, and atherosclerosis in general, is far from over. They are still too many uncertainties and questions regarding DES that need to be better defined and answered before we can claim victory over ISR. In this review article, we briefly look into the effects of DES on the pathophysiology of restenosis, the available clinical trials data and real world clinical experience of DES, and finally, the uncertainties of this new device and the question of whether restenosis can indeed be abolished with DES.

Pathophysiology of In-Stent Restenosis

There are 3 important components of the pathophysiology of ISR which are identified to be involved in restenosis at different time frames after PCI: elastic recoil, negative arterial remodelling and neointimal hyperplasia.^{8,9} Elastic recoil is the immediate shrinkage of vessel after PCI due to the elastic properties of the arterial wall. Negative remodelling and neointimal hyperplasia occur more gradually at the injured segment due to contraction of arterial wall during healing and growth of the smooth muscle cells (SMC) within the arterial lumen, respectively, after PCI. These changes on the arterial wall are normal healing responses to injury and the severity of these responses determines the likelihood of restenosis.

In balloon angioplasty, elastic recoil and negative arterial remodelling are the main components of restenosis, and both have been eliminated by coronary stenting, which provides permanent mechanical scaffolding within the artery. Neointimal hyperplasia plays a part in restenosis after balloon angioplasty but is the main mechanism of restenosis in ISR.¹⁰ Metallic stents, which cause deeper vessel wall injury, stimulate higher degree of neointimal hyperplasia than balloon injury. Even in large vessels (>3.0 mm) with discrete lesions, ISR still occurs between 20% and 30% of patients and in complex lesions, the figure is much higher.^{2,11}

The pathogenesis of neointimal hyperplasia after stenting is related to activation of SMC in the media, which leads to its proliferation and migration into the vessel lumen.¹² Immediately after stenting, there is denudation of endothelial cells of the arterial wall due to mechanical trauma and this leads to platelet adhesion, activation and aggregation, and subsequent fibrin deposition and thrombus formation within the stent (*thrombotic phase: day 0 to 3*). Although these thrombi are usually minute and do not impede coronary flow, they attract inflammatory cells, like macrophages and lymphocytes, which demarginate from the bloodstream (*recruitment phase: day 3 to 8*). The infiltration of these cells in these thrombi stimulates the production of various growth factors and cytokines locally, which activate the dormant (G₀ phase) vascular SMC in the media to re-enter

into cell cycle and replicate. The SMC thus proliferate in the media and subsequently migrate into the thrombus in the stent lumen. The thrombus is eventually replaced by SMC, which form the neointimal within the stent lumen (*proliferative phase: day 8 to healing*).

ISR occurs in those with the most neointimal growth. Binary restenosis, which is used commonly to describe failure of devices to maintain patency of the target lesion, is usually defined as more than 50% diameter stenosis of the target lesion at follow-up angiography 6 to 9 months after index procedure.

Effects of Drug-eluting Stents on Neointimal Hyperplasia

The understanding of the roles of SMC in the process of ISR has resulted in novel therapeutic approaches to prevent ISR. Since the process of SMC activation and replication occurs locally at site of injury, one of the approaches is to deliver a high concentration of an effective anti-proliferative agent locally to stop this process without systemic toxicity. In fact, intracoronary radiation was the first anti-proliferative treatment found to be effective in inhibiting neointimal hyperplasia.¹³ However, its side effects, including the risk of late stent thrombosis (due to delayed re-endothelialisation of stent), edge effects (restenosis occurring at the edges of radiated segment) and the requirement of multi-disciplinary approach (involving radiation physicist and oncologist) have hampered its acceptance into routine clinical practice. Conceptually, coronary stent coated with anti-proliferative agent is an ideal local drug delivery system, as it can potentially limit all 3 components of ISR; not only can the stent prevent vessel elastic recoil and negative arterial remodelling, it also deliver the drug to the target lesion site to prevent neointimal hyperplasia. The development of DES technology has made this approach possible and this can be achieved without major modification of interventional techniques.

Various classes of agents, incorporated on the stent surface, targeting specific sites of restenotic process are available and are under investigation. These include the immunosuppressive (sirolimus, rapamycin analogues and mycophenolic acid), anti-inflammatory (corticosteroid and tranilast), anti-proliferative (paclitaxel, angiopeptin and actinomycin), antithrombotic (hirudin and iloprost), extracellular matrix modulator (batimastat) and pro-healing (oestradiol) agents. To date, only 2 anti-proliferative agents, sirolimus and paclitaxel, have been found to be effective in preventing neointimal hyperplasia in clinical trials.^{6,7}

Sirolimus (rapamycin) is a natural fermentation product of *Streptomyces hygroscopicus* and is a macrolide antibiotic with potent immunosuppressant properties. Its cellular actions are mediated by its binding to a specific intracellular

protein (FKBP12), and the resultant complex inhibits a regulatory enzyme, called TOR (target of rapamycin). The inhibition of TOR prevents cell cycle progression from G₁ phase to S phase, and therefore limiting SMC replication and proliferation (Fig. 1).¹⁴ Paclitaxel is anti-neoplastic agent originally isolated from the bark of the Pacific yew tree, *Taxus brevifolia*. It is a microtubule-stabilising agent and prevents reorganisation of the microtubules network, which is vital for mitotic function. The cell cycle is arrested at M phase and SMC proliferation and migration are inhibited (Fig. 1).^{15,16} Preliminary results of several rapamycin analogues, in particular ABT-578 (methyl rapamycin) and everolimus [40-O-(2-hydroxyethyl)-rapamycin], were very promising and DES coated with these agents are expected to be available soon for clinical use.

The eluting kinetics, which is the timing and dose of release of the drugs on the DES, are important. Rapid bolus release of high concentration of drugs can cause local vessel toxicity and sufficient amount of drugs is required at the site to prevent SMC replication. For controlled bolus and extended release, these drugs are coated onto stent together with polymers, which act as drug reservoirs. Polymers are synthetic biomaterials that are supposedly biocompatible. One example of polymers is phosphorylcholine, which is a synthetic copy of the outer membrane of red blood cells. Types, compositions and designs of the polymers coated on the stent dictate the eluting kinetic of the DES.

In the commercially available sirolimus DES (CYPHERTM), the BX VelocityTM coronary stent system (Cordis, Johnson and Johnson) is coated with a layer of non-erodable polymer of 5 to 10 µm thick, which is incorporated with sirolimus (140 µg sirolimus/cm² of stent), and an additional topcoat as a diffusion barrier for controlled release of the drug. It is designed to release approximately 80% of the total dose of sirolimus in 30 days. Although

there are a variety of methods of incorporating paclitaxel and dosages onto coronary stents, only the polymer-based paclitaxel eluting stents have been found to be safe and efficacious. In the TAXUSTM stent (Boston Scientific Corp), a proprietary polymer (Translute) loaded with 1 µg of paclitaxel/mm² of stent is coated on the ExpressTM stent (Boston Scientific Corp) platform, to allow an initial bolus release phase over the first 48 hours after stenting followed by a low-level release phase for approximately 10 days. The slow-release (SR) formulation of TAXUSTM stent, which has a lower 10-day drug release compared to the moderate-release (MR) formulation, is currently used in clinical practice.

Available Clinical Data

The first published non-randomised study of DES in human was the *First In Man* (FIM) study,¹⁷ where sirolimus coated stent was implanted in 45 patients in Brazil and Europe. In this pioneer study, there were no major adverse cardiac events (MACE) at 1-year clinical follow-up and neointimal thickening within the stent was minimal on angiographic and intravascular ultrasound follow-up. In the RAVEL (*Randomised study with sirolimus-eluting Velocity balloon-expandable stent in the treatment of patients with de novo native coronary artery lesion*) trial conducted in Europe,¹⁸ nicknamed the '0% restenosis trial', had literally no restenosis in patients treated with sirolimus DES as compared to 26% in the bare metal stent (BMS) arm. This remarkable effect of sirolimus DES was subsequently confirmed, although not with zero restenosis, in the larger SIRIUS (*Sirolimus-coated BX Velocity stent in the treatment of patients with de novo coronary artery lesions*) trial,⁶ which included patients with longer lesions, with restenosis rate of 8.9% vs. 36.3% in the BMS arm. The E- and C-SIRIUS (*European and Canadian SIRIUS*)^{19,20} included a total of 452 patients and had restenosis rates of 5.9% and 2.3%, respectively, in the DES arm. Results of these clinical trials are summarised in Table 1. The TVR rates were consistently reduced to single digit and the effectiveness of sirolimus DES in preventing ISR was proven beyond doubt.

Unlike sirolimus DES, a variety of techniques of coating, dosages and stent designs were available for paclitaxel DES. Results of some of the published and presented randomised controlled trials utilising paclitaxel DES are listed in Table 2.^{7,21-24} In TAXUS II and IV trials,^{7,22} which used polymer-based paclitaxel stents, the ISR was only 7% and 7.9%, respectively, in patients receiving DES. The benefit of paclitaxel DES extended across all subgroups, including patients with small vessels and diabetes mellitus, who had greatest relative reduction in ISR. All other non-polymer-based paclitaxel study stents, however, had not shown acceptable safety and efficacy levels to be accepted

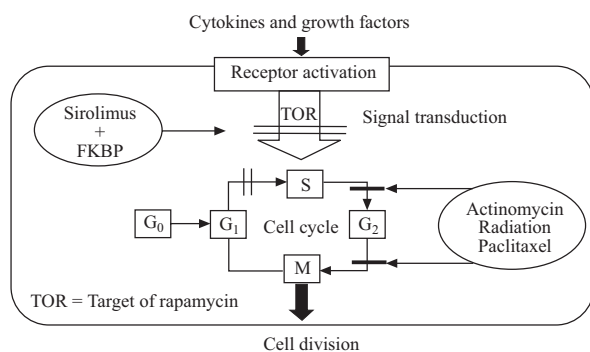


Fig. 1. The mechanism of actions of various anti-proliferative agents on specific targets in smooth muscle cell.

Table 1. Summary of Randomised Controlled Trial Comparing Sirolimus DES and Bare Metal Stent

	RAVEL		SIRIUS		E-SIRIUS		C-SIRIUS	
	Sirolimus (n=120)	Control (n=118)	Sirolimus (n=553)	Control (n=525)	Sirolimus (n=175)	Control (n=177)	Sirolimus (n=50)	Control (n=50)
Baseline data								
Age, y	61.8	59.7	62.1	62.4	62.0	62.6	60.3	60.7
Male, %	70	81	73	70	70	71	70	68
Diabetes mellitus, %	16	21	25	28	19	27	24	24
Hypertension, %	62	61	68	68	63	64	56	48
Hyperlipidaemia, %	38	43	73	75	77	71	84	86
Unstable angina, %	48	52	53	54	30	36	48	54
Prior MI, %	38	34	28	33	41	43	48	42
Lesion length (mean), mm	9.56	9.61	14.4	14.4	14.9	15.1	14.5	12.6
RVD (mean), mm	2.60	2.64	2.79	2.81	2.6	2.51	2.65	2.62
Outcomes*								
Late loss [†] (mean), mm	-0.01	0.80	0.24	0.81	0.19	0.80	0.12	0.79
Binary restenosis, %	0	26	8.9	36.3	5.9	42.3	2.3	52.3
Subacute stent thrombosis, %	0	0	0.4	0.8	1.1	0	2.0	2.0
Death, %	1.67	1.69	0.9	0.6	1.1	0.6	0	0
Myocardial infarction, %	0.8	1.69	2.8	3.2	4.6	2.3	2.0	4.0
TLR, %	0	23.7	4.1	16.6	4.0	20.9	4.0	18.0
Overall MACE, %	5.8	28.8	8.6	21.0	8.0	22.6	2.0	19.0

MACE: major adverse cardiac events; MI: myocardial infarction; RVD: reference vessel diameter; TLR: target lesion revascularisation

* Angiography follow-ups were performed at 6 months (RAVEL, SIRIUS) and 9 months (E- and C-SIRIUS), and clinical follow-up at 9 months for all except for RAVEL (1 year).

† All in-segment except for RAVEL which was in-stent.

for clinical use.^{21,23,24} Another paclitaxel DES trial,²⁵ which used multiple polyacrylate sleeves as platform for a paclitaxel drug to elute, was terminated prematurely because of excess subacute and delayed stent thrombosis in the treatment arm. Stent thrombosis and lack of clinical benefits were the major concerns for non-polymer-based paclitaxel.

Stents coated with rapamycin analogues, ABT-578 and everolimus, have completed phase II study in the ENDEAVOR I (Randomised controlled trial to evaluate the safety and efficacy of the Medtronic AVE ABT-578 eluting DriverTM coronary stent in de novo native coronary artery lesions) and FUTURE (First use to underscore reduction in restenosis with everolimus) I trial, respectively, and the results were not dissimilar to the early paclitaxel and sirolimus results, with extremely low in-stent luminal loss and MACE rates.^{26,27} Recruitment for phase III studies involving some of these DES have been completed and while the results are eagerly awaited, it is expected that these DES will be as impressive as their predecessors. On the other hand, anti-proliferative agent like actinomycin, although shown to be effective in animal models,²⁸ failed to show clinical efficacy in humans, and the ACTION (Actinomycin eluting stents improve outcomes by reducing neointimal hyperplasia) trial was prematurely terminated because of high rates of repeat revascularisation in the treated arm.²⁹

Several important lessons have been learned from these

trials, albeit some failed ones. Firstly, a safe and effective DES in reducing restenosis depends on all 3 components of a DES: the drug, the release mechanism or polymer, and the stent. An ideal anti-restenotic agent coated on the stent should possess potent anti-proliferative effects in humans but should also allow healing processes to occur. It should have a wide therapeutic window to avoid local toxicity to the vessel wall, which can incite thrombosis and inflammation at the site of DES implantation. The eluting kinetics of the drugs, and thus the designs of the carrier polymer, on the DES are crucial as evident in the paclitaxel trials, where the same agent incorporated differently on the stent yields contrasting clinical results. It seems that for paclitaxel, only the proprietary polymer-based release mechanism is effective and safe. The stent design for DES is theoretically important as the surface area of the stent struts dictates the amount of drug in contact with, and therefore delivers to, the vessel wall. There is currently no study comparing stent with different designs but coated with similar agent and polymer. Stent designs dedicated for drug delivery is being developed but we predict that the difference made by these changes will be small, as attempts to increase the surface area of the stents will compromise its deliverability to more complex lesions.

Secondly, although the implantation of DES does not differ from BMS, several important techniques to minimise operator-related failure of stents are advocated. The

Table 2. Summary of Randomised Controlled Trials Comparing Paclitaxel DES with Bare Metal Stent

	ASPECT			ELUTES*			DELIVER I		TAXUS II			TAXUS IV	
	Control (n = 60)	High (n = 58)	Low (n = 59)	Control (n = 39)	High (n = 37)	Low (n = 37)	Control (n = 519)	Achieve® (n = 522)	Control (n = 270)	SR (n = 131)	MR (n = 135)	Express® (n = 652)	TAXUS® (n = 662)
Dose, µg/mm²	0	3.1	1.3	0	2.7	0.2	0	3	0	1	1	0	1
Baseline data													
Age, y	58	60	58	61	56	64	62.7	61.8	59.9	61.5	59.3	62.1	62.8
Male, %	76	72	80	82	81	73	70.7	70.5	78	70	76	72.4	71.8
Diabetes mellitus, %	17	18	24	10	21	22	26.8	30.7	15	11	17	33.3	31.1
Hypertension, %	47	42	31	54	49	51	65.1	65.9	62	63	60	69.0	70.5
Hyperlipidaemia, %	19	13	7	44	59	49	60.1	59.0	NA	NA	NA	65.6	65.0
Prior MI, %	29	23	22	41	30	32	27.2	25.7	42.5	36	39	29.9	30.5
Target vessel LAD, %	51	53	50	38	41	38	46.4	42.2	48	40	42	41.1	40.0
Lesion length, mm	10.5	10.9	11.2	10.8	11.1	11.3	11.1	11.7	10.6	10.6	10.2	13.4	13.4
RVD, mm	2.88	2.94	2.93	2.99	2.95	3.03	2.77	2.85	2.75	2.8	2.7	2.75	2.75
Outcomes													
Late loss, mm	1.04	0.29	0.57	0.73	0.11	0.71	0.56	0.43	0.78	0.31	0.3	0.61	0.23
Binary restenosis, %	27	4	12	20.6	3.2	20.6	22.4	16.7	21.9	5.5	8.6	26.6	7.9
Stent thrombosis, %	0	5.1	1.7	2.5	2.7	0	0.4	0.4	0	1.5	0.7	0.8	0.6
Death, %	0	0	1.7	0	2.7	0	0.8	0.2	0.8	0	0	1.1	1.4
MI, %	1.7	3.3	1.7	0	2.7	0	1.0	1.4	5.3	2.4	2.3	3.7	3.5
TLR or TVR, %	3.4	8.5	5.2	15.8	5.4	5.4	7.6	6.0	17.5	10.1	6.9	12.0	4.7
Overall MACE, %	5	10	7	18	14	5	9.4	7.5	21.7	10.9	9.9	15.0	8.5

MACE: major adverse cardiac events; MI: myocardial infarction; MR: moderate release; RVD: reference vessel diameter; SR: slow release; TLR: target lesion revascularisation; TVR: target vessel revascularisation

* Only the highest and lowest doses were included in the table.

disturbing observation of increase restenosis at the stent edges (in-segment 8.9% versus in-stent 3.2%) in the SIRIUS trial⁵ was reminiscent of the candy wrapper effect of radioactive stents, where restenosis occurring at both edges of stents. However, this edge effect, which was thought to be due to unmasking of tissue growth in injured area or lesion not covered by the DES, was not seen in the E- and C-SIRIUS trials,^{19,20} which advocated the usage of longer stents to cover the entire lesion or injured segment, direct stenting and avoiding gaps between stents. Indeed, a great stent still needs a good interventionist for optimal outcomes.

Real World Experience of DES

Clinical trials are conducted under controlled conditions with strict inclusion and exclusion criteria, and their results may not be translated into real world clinical practice where indications of use of these DES are more liberal and usually include more complex lesions not normally included in clinical trials. Commercially available stents were first approved outside US after the RAVEL and TAXUS II trials and since then, large amount of real world clinical experience of DES were gathered from Europe and Asia Pacific cardiac centres.

The RESEARCH (Rapamycin-eluting stent evaluated at Rotterdam Cardiology Hospital) registry is a single-centre registry of unrestricted use of sirolimus DES in all patients with de novo lesion within a 6-month period to evaluate the

safety and efficacy in daily practice.³⁰ WISDOM registry (Web-based TAXUS inter-continental observational data transitional registry program), however, is a multicentre registry of patients who received approved paclitaxel DES stent in real world setting with no strict clinical and angiographic inclusion criteria.³¹ In the National Heart Centre (NHC) DES Registry, 514 patients received CYPHER™ and/or TAXUS™ stents within a 12-month period from May 2002 after DES were approved for clinical use in Singapore. Results of the RESEARCH and WISDOM registries are summarised in Table 3 in comparison with NHC's experience of DES.

The results of the RESEARCH and WISDOM registries were impressive considering the complexity of the lesions, with TVR and MACE rates between 3% to 5% and 4% to 10%, respectively. In our local experience with DES, the results are similar to the rest of the world with a TVR and MACE rate of 4% and 7%, respectively. Patients included in these real world registries were of high risk of restenosis, with 25% and 43% type C lesions in the WISDOM and RESEARCH registries, respectively. In the NHC DES registry, 20% of lesions treated were considered complex lesions, including bifurcation, ostial disease, ISR and chronic total occlusion lesions.

Even more radical applications of DES were seen in the Milan Complex Lesion Registry, where unprotected left main, bifurcation and multi-vessel stenting were also

Table 3. Summary of Published 'Real World' Experience of DES Compared to our Centre's DES Registry

	WISDOM (n = 778)	RESEARCH (n = 508)	NHC DES Registry (n = 514)
Demographic data			
Age, y	58.6	61.0	58.9
Male, %	84	68	79
Diabetes mellitus, %	33	18	34
Hypertension, %	59	41	67
Unstable angina, %	34	37	NA
Acute myocardial infarction, %	18	18	NA
Acute coronary syndromes, %	NA	NA	30
Prior myocardial infarction, %	28	30	26
Angiographic data			
LAD target vessel, %	57	59	62
AHA/ACC Type C lesion, %	25	43	NA
Lesion length (mean), mm	15.6	NA	NA
Stent length (mean), mm	22.1	38.7	20.2
RVD (mean), mm	2.9	NA	2.79
Total number of stent	983	1067	664
Number of stents/patient	1.2	2.1	1.3
Clinical outcomes			
Clinical follow-up, month	6*	12	10 [†]
Subacute stent thrombosis, %	0.4	0.4	0.8
Death, %	0.9	3.4	0.4
Myocardial infarction, %	0.4	NA	1.9 [‡]
TVR, %	3.0	5.1	4.2
Overall MACE, %	4.3	9.7	7.2

AHA/ACC: American Heart Association/American College of Cardiology; LAD: left anterior descending artery; NA: not available; NHC: National Heart Centre; RVD: reference vessel diameter; TVR: target vessel revascularisation

* Only n = 253 had completed 6-month follow-up in WISDOM.

† Mean follow-up period for NHC DES registry.

‡ All peri-procedural enzymes elevation.

included. In this registry, the MACE and TVR rate was 20.4% and 14.2%, respectively, in patients treated with sirolimus DES (n = 323 and lesion = 739). TLR rate of 19%, 15% and 14% was observed in patients treated for unprotected left main (n = 31), bifurcation lesion (n = 62) and multi-vessel stenting (n = 112), respectively.³²

These real world results of DES are comparable to randomised trials and considerably better than previous experience with BMS, especially in complex lesions. These results will further encourage some to use DES in lesions that are not included in the randomised studies. In some private institutions in Singapore, where there are no financial constraints, the penetration of DES has reached closed to 100% (personal communication). Whether the use of DES in *all* patients is economically and clinically justified will depend on the individual healthcare systems in different institutions and countries, and further evidence from clinical trials to show the benefits of DES in more complex lesions.

Potential Problems of DES

Although DES as a whole is efficacious and safe both in clinical trials and real world practice, there are still a few reservations for its widespread use in clinical practice. The major concerns are the safety of DES and economic burden imposed by DES on healthcare systems.

Late Thrombosis

The anti-proliferative effects of the agent delay endothelialisation of the stent and thus predispose patients treated with conventional 2 to 4 weeks of antiplatelets therapy to stent thrombosis.³³ The mandatory use of dual antiplatelet therapy for at least 3 months did not result in any increase in stent thrombosis in subsequent trials. However, the time required for the endothelial cells to fully cover the DES in certain individuals is unknown and may be as variable as those who develop ISR. By October 2003, the Food and Drug Administration (FDA) received more than 290 reported cases of SAT since CYPHER™ stent was launched in the US and 60 of these were associated with patient death.³⁴ Although there is no real increase in overall rate of SAT with sirolimus DES, the warning issued by the FDA may generate concern that we may be creating a rare but more 'malignant' disease (SAT) by eliminating a relatively more common but 'benign' one (ISR). There were also sporadic reports of late stent thrombosis even after 18 months post-DES implantation.³⁵ Should we extend the duration of antiplatelet therapy for patients receiving DES? Can patients, or even physicians, accept the risk of this unpredictable but catastrophic event long after the index procedure?

Incomplete Stent Apposition

This is defined as 1 or more stent struts not in contact with the vessel wall on intravascular ultrasound (IVUS) at any point of time after stent implantation. It was present in 10 (21%) patients receiving the sirolimus stent in the RAVEL trial who underwent IVUS investigation, significantly higher than 2 (4%) in the BMS arm at 6-month follow-up.³⁶ This may be due to either initial incomplete deployment of stent during implantation or positive remodelling (enlargement of vessel lumen) of the vessel wall due to DES. But other mechanisms like plaque regression, cell necrosis, apoptosis and allergic reaction to sirolimus have also been postulated. However, except for one case that develops coronary aneurysm, the severity of incomplete stent apposition (ISA) on IVUS did not change over time and, more importantly, ISA was not related to any adverse clinical outcomes at 1 year. However, in-view of its high occurrence, long-term follow-up is required to determine the effects of these abnormal findings.

Lacking Long-term Result

The remarkable efficacy of sirolimus DES in reducing

MACE in the FIM study, RAVEL and SIRIUS trials, still remain at 3-year, 2-year and 1-year follow-up, respectively.³⁷⁻³⁹ However, we should be cautious and not try to extrapolate these results to the longer term. The recently reported 5-year follow-up of the WRIST (Washington radiation for in-stent restenosis trial) study, which used the anti-proliferative effect of intracoronary gamma radiation for the treatment of ISR, has shown that the final result of the study at 5 years still showed significant benefits in the radiation arm (46.2% vs 69.2% in MACE rate; $P = 0.008$), but the magnitude of the benefit was significantly weakened by TVR rate of 21.6% in the radiation arm (vs 6.1% in placebo arm) between 6 and 60 months.⁴⁰ The authors concluded that radiation may delay the restenosis process in part and its long-term benefit was reduced by late catch-up phenomenon and late thrombosis. Are we just delaying the inevitable?

Economic Burden

The benefit of these new devices comes, literally, with a price. In a cost-effective analysis of SIRIUS trial based on the US healthcare system,⁴¹ it was found that the difference between the medical cost of the 2 groups were only about USD\$300 over a 1-year period, despite a USD\$3000 difference after the initial hospitalisation, and the cost for each TVR avoided was USD\$1650. Although this is considered cost effective in US standard in the population as a whole, it has no meaning to individual institutions which provide and generate revenue from revascularisation procedures.

With 2 available DES in the market, the incremental cost of each DES in Singapore is now around SGD\$2500 to \$3000. Taking into account the average stent usage of 1.3 stents per patient in NHC's DES Registry and an annual PCI number of approximately 2000 cases in NHC, the annual incremental cost of implanting DES in all patients in our centre will be close to SGD\$7 million. In healthcare systems that are based on diagnosis related grouping (DRG), pre-specified reimbursement from third-party payer is paid to hospitals for specific treatment provided to a patient. The incremental cost of DES will not be recovered without adequate readjustment of reimbursement and, in addition, hospitals will face further loss in revenue due to reduction in the need for repeat TVR because of the efficacy of DES, including CABG, which is a highly profitable procedure for many hospitals. In a study performed in the US,⁴² using a computer model from a perspective of a large tertiary hospital, the projected annual loss was USD\$5.4 million, even after taking into account the proposed adjustment of reimbursement, during the first 5 years after the introduction of DES and the largest driver of cash flow shift is the conversion of CABG to DES.

The deliberation of who should receive this costly device

is putting cardiologists in a dilemma in institutions worldwide. Are we morally and legally justified to withhold a proven and effective treatment from a patient in order to save cost? Where do we draw the line between altruism and self-preservation? For now, however, we can ease our conscience, as widespread adoption of DES is not justified yet because the long-term benefit of DES is still uncertain. Furthermore, in certain subgroups of patients (e.g. vessel size >3 mm and lesion length <15 mm), the benefit may be just marginal and therefore may not be cost-effective.⁴³ It is hoped that competitions in the DES market will eventually lower the cost so that every party, including the hospital and the reimbursement body, can afford DES.

The End of Restenosis?

Does the introduction of DES mean the end of restenosis? The answer is definitely no. To begin with, the lesions included in SIRIUS and TAXUS IV represented only a small proportion of daily practice. Even in these relatively simple lesions, there was still an overall 8% to 9% restenosis rate in the DES arm. Although subgroup analysis of published trials showed greatest benefit in patients with diabetes mellitus, smaller vessels and longer lesions, restenosis rates of these subgroups in clinical practice treated with DES are also expected to be higher.

In a recent publication, bifurcation stenting with DES, performed in well-known centres, was associated with ISR rates of 26%.⁴⁴ This, and the experience in the Milan registry,³³ reminds us that for complex lesions, even in experienced hands, the current generation of DES has not completely solved the problem of ISR. DES has, however, reduced the restenosis rate of these complex lesions to the level of that of simpler lesions treated with BMS. ISR of DES, if it occurred, is usually of focal type rather than diffuse or proliferative type, which is more recalcitrant to repeat treatments.⁴⁵

For now, the high cost of DES will also contribute to the continued existence of ISR as it is difficult to envisage the use of DES in all patients, and therefore BMS will still be used in the majority of patients.

Conclusions

DES represents one of the most innovative advancements in interventional cardiology. The combined mechanical and pharmacological anti-restenotic properties of DES target all 3 components of ISR, and have successfully dampened the amplitude of ISR in all subgroups of patients, particularly in high-risk groups, in both clinical trials and real world clinical practice. ISR, although drastically reduced, has not been eliminated completely, especially in more complex lesions. Although the incidence is low with adequate duration of antiplatelet regime, late stent thrombosis of DES is still a major concern. The durability

of the beneficial effects of DES in recent DES trials awaits the results of long-term follow-up. Currently, in view of its high cost, the use of DES in most institutions with inadequate reimbursement has been rationed to subgroups with high risk of ISR. These practices have been extrapolated from the results of subgroup analysis of randomised clinical trials, despite many being off-label use. On-going trials and registries may widen the indications for DES and confirm the rationale for this practice. Until there is a dramatic drop in cost price of these DES, only selected patients will benefit from this latest advancement in cardiology for now.

REFERENCES

- Pocock SJ, Henderson RA, Rickards AF, Hampton JR, King SB 3rd, Hamm CW, et al. Meta-analysis of randomised trials comparing coronary angioplasty with bypass surgery. *Lancet* 1995;346:1184-9.
- Serruys PW, de Jaegere P, Kiemeneij F, Macaya C, Rutsch W, Heyndrickx G, et al. A comparison of balloon-expandable-stent implantation with balloon angioplasty in patients with coronary artery disease. Benestent Study Group. *N Engl J Med* 1994;331:489-95.
- The Bypass Angioplasty Revascularization Investigation (BARI) Investigators. Comparison of coronary bypass surgery with angioplasty in patients with multivessel disease. *N Engl J Med* 1996;335:217-25.
- Legrand VM, Serruys PW, Unger F, Van Hout BA, Vrolix MC, Fransen GM, et al. Three-year outcome after coronary stenting versus bypass surgery for the treatment of multivessel disease. *Circulation* 2004;109:1114-20.
- Lim VY, Chan CN. Prevention of restenosis after percutaneous coronary intervention: the continuing challenge. *Ann Acad Med Singapore* 2002;31:102-6.
- Moses JW, Leon MB, Popma JJ, Fitzgerald PJ, Holmes DR, O'Shaughnessy C, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med* 2003;349:1315-23.
- Stone GW, Ellis SG, Cox DA, Hermiller J, O'Shaughnessy C, Mann JT, et al. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. *N Engl J Med* 2004;350:221-31.
- Mintz GS, Popma JJ, Pichard AD, Kent KM, Satler LF, Wong C, et al. Arterial remodeling after coronary angioplasty: a serial intravascular ultrasound study. *Circulation* 1996;94:35-43.
- Hoffmann R, Mintz GS, Dussaillant GR, Popma JJ, Pichard AD, Satler LF, et al. Patterns and mechanisms of in-stent restenosis. A serial intravascular ultrasound study. *Circulation* 1996;94:1247-54.
- Virmani R, Farb A. Pathology of in-stent restenosis. *Curr Opin Lipidol* 1999;10:499-506.
- Fischman DL, Leon MB, Baim DS, Schatz RA, Savage MP, Penn I, et al. A randomized comparison of coronary-stent placement and balloon angioplasty in the treatment of coronary artery disease. *N Engl J Med* 1994;331:496-501.
- Schwartz RS, Henry TD. Pathophysiology of coronary artery restenosis. *Rev Cardiovasc Med* 2003;3(suppl 5):S4-S9.
- Teirstein PS, Massullo V, Jani S, Popma JJ, Mintz GS, Russo RJ, et al. Catheter-based radiotherapy to inhibit restenosis after coronary stenting. *N Engl J Med* 1997;336:1697-703.
- Marx SO, Marks AR. Bench to bedside: the development of rapamycin and its application to stent restenosis. *Circulation* 2001;104:852-5.
- Schiff PB, Fant J, Horwitz SB. Promotion of microtubule assembly in vitro by taxol. *Nature* 1979;277:665-7.
- Sollott SJ, Cheng L, Pauly RR, Jenkins GM, Monticone RE, Kuzuya M, et al. Taxol inhibits neointimal smooth muscle cell accumulation after angioplasty in the rat. *J Clin Invest* 1995;95:1869-76.
- Sousa JE, Costa MA, Abizaid AC, Rensing BJ, Abizaid AS, Tanajura LF, et al. Sustained suppression of neointimal proliferation by sirolimus-eluting stents: one-year angiographic and intravascular ultrasound follow-up. *Circulation* 2001;104:2007-11.
- Morice MC, Serruys PW, Sousa JE, Fajadet J, Ban Hayashi E, Perin M, et al. A randomised comparison of a sirolimus-eluting stent with a standard stent for coronary revascularization. *N Engl J Med* 2002;346:1773-80.
- Schofer J, Schluter M, Gershlick AH, Wijns W, Garcia E, Schampaert E, et al. Sirolimus-eluting stents for treatment of patients with long atherosclerotic lesions in small coronary arteries: double-blind, randomised controlled trial (E-SIRIUS). *Lancet* 2003;362:1093-9.
- Schampaert E, Cohen EA, Schluter M, Reeves F, Traboulsi M, Title LM, et al. The Canadian study of the sirolimus-eluting stent in the treatment of patients with long de novo lesions in small native coronary arteries (C-SIRIUS). *J Am Coll Cardiol* 2004;43:1110-5.
- Park SJ, Shim WH, Ho DS, Raizner AE, Park SW, Hong MK, et al. A paclitaxel-eluting stent for the prevention of coronary restenosis. *N Engl J Med* 2003;348:1537-45.
- Colombo A, Drzewiecki J, Banning A, Grube E, Hauptmann K, Silber S, et al. Randomised study to assess the effectiveness of slow- and moderate-release polymer-based paclitaxel-eluting stents for coronary artery lesions. *Circulation* 2003;108:788-94.
- Knopf W. DELIVER I: A US multicenter, randomised, single-blind study of the ACHIEVE drug coated coronary system. Presented at: Transcatheter Cardiovascular Therapeutic; 2003 Sept 16-21; Washington DC. Available at: http://www.tctmd.com/expert-presentations/multi-slide.html?product_id=5302. Accessed July 14, 2004.
- Gershlick A, De Scheerder I, Chevalier B, Stephens-Lloyd A, Camenzind E, Vrints C, et al. Inhibition of restenosis with a paclitaxel-eluting, polymer-free coronary stent: the European evaluation of paclitaxel Eluting Stent (ELUTES) trial. *Circulation* 2004;109:487-93.
- Grube E, Hauptmann K, Colombo A, DiSciascio G, Silber S, Bach R, et al. SCORE trial interim safety results: despite efficacy, late stent thrombosis with the QuaDDS-QP2 stent [abstract]. *J Am Coll Cardiol* 2002;39(suppl A):38A.
- Costa R, Lansky A, Mehran R, Tsuchiya Y, Cristea E, Negoita M, et al. Everolimus-eluting stent for the treatment of de novo coronary lesion: An angiographic follow-up of the FUTURE trial [abstract]. *Am J Cardiol* 2003;92(suppl 1):61L.
- Meredith I. ENDEAVOR I: 4-month angiographic and IVUS result. Presented at: Transcatheter Cardiovascular Therapeutic; 2003 Sept 16-21; Washington DC. Available at: http://www.tctmd.com/expert-presentations/multi-slide.html?product_id=5356. Accessed July 14, 2004.
- Robinson K, Chronos N, Royal J, Suh L, Cipolla GD, Virmani R, et al. Actinomycin-D drug eluting stents preserve lumen size and inhibit fibrocellular neointima in pig coronary arteries [abstract]. *Circulation* 2001;104(suppl II):506.
- Serruys PW. Final ACTION results: Actinomycin Eluting stents improves outcomes by reducing neointimal hyperplasia. Presented at Transcatheter Cardiovascular Therapeutic; 2002 Sept 24-29; Washington DC. Available at: http://www.tctmd.com/expert-presentations/multi-slide.html?product_id=3801. Accessed July 14, 2004.
- Lemos PA, Serruys PW, van Domburg RT, Saia F, Arampatzis CA, Hoyer A, et al. Unrestricted utilization of sirolimus-eluting stents compared with conventional bare stent implantation in the "real world": the Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital (RESEARCH) registry. *Circulation* 2004;109:190-5.
- Abizaid AC. WISDOM Registry update. Presented at Transcatheter Cardiovascular Therapeutic; 2003 Sept 16-21; Washington DC. Available

- at: http://www.tctmd.com/expert-presentations/multi-slide.html?product_id=5206. Accessed July 14, 2004.
32. Colombo A. Updates from international registries: The Milan Complex Lesion Registry. Presented at Transcatheter Cardiovascular Therapeutic, 2003 September 16-21, Washington DC. Available at: http://www.tctmd.com/expert-presentations/multi-slide.html?product_id=6026. Accessed July 14, 2004.
 33. Kerner A, Gruberg L, Kapeliovich M, Grenadier E. Late stent thrombosis after implantation of a sirolimus-eluting stent. *Cathet Cardiovasc Interv* 2003;60:505-8.
 34. FDA public health web notification: Information for physicians on sub-acute thrombosis (SAT) and hypersensitivity reactions with the use of the Cordis CYPHER™ coronary stent. US: Food and Drug Administration. 2003. Available at: <http://www.fda.gov/cdrh/safety/cypher.html>. Accessed March 12, 2004.
 35. Virmani R, Guagliumi G, Farb A, Musumeci G, Grieco N, Motta T, et al. Localized hypersensitivity and late coronary thrombosis secondary to a sirolimus-eluting stent: should we be cautious? *Circulation* 2004;109:701-5.
 36. Serruys PW, Degertekin M, Tanabe K, Abizaid A, Sousa JE, Colombo A, et al. Intravascular ultrasound findings in the multicenter, randomised, double-blind RAVEL (RAnomised study with the sirolimus-eluting VElocity balloon-expandable stent in the treatment of patients with de novo native coronary artery Lesions) trial. *Circulation* 2002;106:798-803.
 37. Abizaid A. Updates from the FIM experience: Are the results durable? Presented at Transcatheter Cardiovascular Therapeutic; 2003 Sept 16-21; Washington DC. Available at: http://www.tctmd.com/expert-presentations/multi-slide.html?product_id=6014. Accessed July 14, 2004.
 38. Morice MC. RAVEL 2-year follow-up. Presented at Transcatheter Cardiovascular Therapeutic; 2003 Sept 16-21; Washington DC. Available at: http://www.tctmd.com/expert-presentations/multi-slide.html?product_id=6018. Accessed July 14, 2004.
 39. Holmes DR Jr, Leon MB, Moses JW, Popma JJ, Cutlip D, Fitzgerald PJ, et al. Analysis of 1-year clinical outcomes in the SIRIUS trial: a randomised trial of a sirolimus-eluting stent versus a standard stent in patients at high risk for coronary restenosis. *Circulation* 2004;109:634-40.
 40. Waksman R, Ajani AE, White RL, Chan R, Bass B, Pichard AD, et al. Five-year follow-up after intracoronary gamma radiation therapy for in-stent restenosis. *Circulation* 2004;109:340-4.
 41. Cohen DJ, Bakhai A, Shi C, Githiora L, Berezin RH, Caputo R, et al. Cost-effectiveness of sirolimus drug-eluting stents for the treatment of complex coronary stenosis: results from the randomised SIRIUS trial [abstract]. *J Am Coll Cardiol* 2003;41(suppl):32A.
 42. Kong DF, Eisenstein EL, Sketch MH Jr, Zidar JP, Ryan TJ, Harrington RA, et al. Economic impact of drug-eluting stents on hospital systems: a disease-state model. *Am Heart J* 2000;147:449-56.
 43. Greenberg D, Bakhai A, Cohen DJ. Can we afford to eliminate restenosis? Can we afford not to? *J Am Coll Cardiol* 2004;43:513-8.
 44. Colombo A, Moses JW, Morice MC, Ludwig J, Holmes DR Jr, Spanos V, et al. Randomised study to evaluate sirolimus-eluting stents implanted at coronary bifurcation lesions. *Circulation* 2004;109:1244-9.
 45. Colombo A, Orlic D, Stankovic G, Corvaja N, Spanos V, Montorfano M, et al. Preliminary observations regarding angiographic pattern of restenosis after rapamycin-eluting stent implantation. *Circulation* 2003;107:2178-80.