IN-STENT RESTENOSIS AND DRUG-ELUTING STENTS

OSMAN KARAKAYA,
ALI METIN ESEN,
IRFAN BARUTCU,
MUSTAFA SAGLAM,
NIHAL ÖZDEMİR,
CIHANGIR KAYMAZ,

The introduction of intracoronary stents into clinical practice has dramatically changed treatment of obstructive coronary artery disease. Unfortunately, the procedure's utility is limited by a frequent complication: restenosis At the moment, repeat balloon angioplasty is considered to be the first line treatment option, especially in focal lesions. The recent introduction of drug-eluting stents (DESs) may help prevent ISR. However, DESs have not been universally successful, and they may introduce new complications that require further refinement. This review summarizes the current understanding of the pathogenesis of ISR and provides an objective overview of DESs.

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From:
Kosuyolu Heart Education and Research Hospital, Department of Cardiology, Istanbul,Turkey.

Address for reprints:
Osman KARAKAYA, MD
19 mayıs mahallesi sarıkanarya sok.
Muhsinbey Apt. No:25/17-Kozyatağı
Istanbul/TURKEY
Tel.:+90 216 384 64 13
Fax:+90 216 339 04 41
e-mail:drkarakaya@yahoo.com

Percutaneous transluminal coronary angioplasty has revolutionized the management of patients with coronary artery disease. The introduction of intracoronary stents into clinical practice has dramatically changed treatment of obstructive coronary artery disease. Unfortunately, the procedure's utility is limited by a frequent complication: restenosis. Coronary stenting prevents the elastic recoil and negative remodeling that can occur after angioplasty. Since having been shown to significantly reduce restenosis as compared to PTCA in selected lesions,1,2 the indication for stent implantation has been widened substantially. But, by inciting varying degrees of intimal expansion, it can also produce arterial renarrowing, known as in-stent restenosis (ISR). Restenosis is an iatrogenic novel "disease". As a result of a dramatic increase in implantation numbers worldwide in less selected and more complex lesions (bypass grafts, restenostic lesions, unstable angina, myocardial infarction), in-stent restenosis has been disclosed as a new entity with significant clinical and socioeconomic implications.

The initially favourable outcome data in "ideal", benestent/stress-type lesions (i.e. focal lesions <15mm in length in native vessels (3mm diameter)1,2 accounts for <25% of those lesions treated in a 'realworld' setting. Results of stenting in more complex coronary lesion subtypes (for example ostial, bifurcation, thrombotic or long lesions) have proved

less impressive, with angiographic and clinical restenosis rates ranging between 30% and 60%.3,4

With more than 1 000 000 stent implantations per year and an estimated overall clinical restenosis rate of 15–25%, between 150 000 and 250 000 patients were expected to present with in-stent restenosis in the year 2002 and require treatment.5,6 The precise mechanisms involved in the pathogenesis of ISR are incompletely understood. Despite a variety of different therapeutic options, the most effective treatment modality for 'in-stent restenosis' has as yet not been identified. This is, in part, due to a lack of randomized, controlled trials for most of the existing treatment modalities.

At the moment, repeat balloon angioplasty is considered to be the first line treatment option, especially in focal lesions. The recent introduction of drug-eluting stents (DESs) may help prevent ISR. However, DESs have not been universally successful, and they may introduce new complications that require further refinement. This review summarizes the current understanding of the pathogenesis of ISR and provides an objective overview of DESs.

IN-STENT RESTENOSIS

The first percutaneous transluminal coronary angioplasty (PTCA) was performed in 1977 by Andreas Gruentzig.7 This procedure resulted in significant objective improvement in myocardial ischemia and thus became increasingly popular.8 However, PTCA soon proved to be limited by an important complication: 25 to 45% of patients experienced restenosis of the dilated lesion, defined as a renarrowing of the dilated lesion of greater than 50% of vessel diameter.9 The processes resulting in postangioplasty restenosis are now understood and include mechanical collapse of the artery wall due to elastic recoil, negative remodeling, as well as variable amounts of intimal expansion secondary to cell proliferation, migration and abundant matrix production .10

The concept of endoluminal splinting was first proposed in 1964, however it was more than 20 years before the first human coronary stent was implanted.12,13 Coronary stents act as luminal scaffolds that are permanently inserted into diseased arteries to enlarge the lumen and improve blood flow downstream, thereby eliminating arterial recoil and constrictive remodeling.14 Indeed, numerous randomized clinical trials have demonstrated a 30-50% decrease in the rate of restenosis with stents compared to balloon angioplasty alone.1,2 But the problem of lesion renarrowing post-stenting is by no means solved, for the frequency of stent renarrowing (or in-stent restenosis, ISR) remains in the range of 10-40%. As described below, the pathogenesis and hence the therapeutic challenges associated with ISR are currently evolving.

Many studies report the incidence of ISR to be low, afflicting only 10-20% of lesions.1,2 But in some instances, complex lesions(bypass grafts, restenostic lesions, unstable angina, myocardial infarction) with unfavourable characteristics for long term success are being intervened upon, and these particular interventions drive the frequency of ISR into the 30-40% range or higher.3

With this widespread practice of stent insertion, a recent estimate suggested that over 100,000 cases of ISR will develop worldwide annually.7 Hence, there is an acute need to develop effective treatment strategies for the expanding problem of ISR. Like post-PTCA restenosis, ISR is usually defined angiographically as a binary event with greater than 50% diameter

renarrowing. It is important to note that not all patients with ISR will be symptomatic (e.g., due to collateral supply or medical therapy) and therefore, to accurately ascertain the frequency of ISR in a patient population, repeat angiography must routinely be performed. With the exception of patients enrolled in clinical studies, follow-up angiography is neither cost effective nor is it practical for many patients. Hence, clinical estimates of the frequency of ISR may be lower than those reported in angiographic studies.

THE CLINICAL AND ECONOMIC IMPORTANCE OF IN-STENT RESTENOSIS

The majority of studies to date have failed to demonstrate a convincing link between restenosis and short or long-term mortality. In contrast to de novo lesions, where plaque rupture and local thrombus formation can lead to acute myocardial infarction (MI) and death, restenosis tends to present as a gradual recurrence of anginal symptoms rather than an acute event.

Weintraub et al.15 reported that restenosis was a predictor of MI, but not of long-term mortality. Their data mostly reflected the outcome following balloon angioplasty without stenting. In a later study, Schuhlen, et al.16 analysed results from nearly 2,000 patients undergoing coronary stenting and routine follow-up angiography. They found a significantly greater mortality rate at four years among patients with angiographic restenosis compared with and those without (9% versus 6%, respectively).

It is notable that a substantial proportion of patients with angiographic restenosis are entirely asymptomatic.17 Nevertheless, when ISR does occur in symptomatic patients, it is difficult to treat and has a high recurrence rate.3 Despite the lack of differences in long-term survival between surgical and percutaneous coronary revascularisation, the rates of reintervention following PCI is five to tenfold higher than that following CABG.18 This in itself has major economic implications. In addition, restenosis has an adverse impact on quality of life (QOL), as demonstrated in the Optimum Percutaneous Transluminal Coronary Angioplasty versus Routine Stenting (OPUS-1) trial where patients without restenosis had less frequent angina, fewer physical limitations and improved QOL compared with patients with restenosis.19 The Stent Primary Angioplasty in Myocardial Infarction (Stent- PAMI) trial comparing balloon angioplasty with stenting found that stenting was associated with lower rates of angiographic and clinical restenosis and a significantly better QOL at six months.20 These factors, taken together, have led to considerable efforts towards the development of new strategies to treat and reduce the rate of ISR.

PATHOPHYSIOLOGY AND MORPHOLOGICAL PREDICTORS OF IN-STENT RESTENOSIS

Stent characteristics may also play a role in the pathogenesis of ISR, as there are variations in the number of struts and the amount of metal surface area that is in contact with the artery wall.21 Currently, most stents are made of a stainless steel alloy with either a slotted tube or modular design. However, as platelet adhesion and the potential release of oxidized heavy metal ions from the steel struts is a concern, other materials such as platinum and titanium alloys, including nitinol, a mixture of nickel and titanium, have been investigated.22 Unfortunately, most of these other alloys fail to match the necessary mechanical characteristics of stainless steel (e.g., recoil of self-expanding nitinol stents is a concern).23,24 Alternate stent coatings (e.g., gold, carbon, silicon carbide)

have also been used but with variable results.25,26 Nevertheless, recent registry data with a cobalt chromium stent are encouraging.27

There is a triphasic temporal distribution pattern for stent occlusion. Acute and subacute stent closure is different from ISR and typically occurs within the first 24 hours and 2 weeks post-stent deployment, respectively. While acute and subacute stent closure occurs in <1% of patients receiving stents, the usual causes are thrombosis within a stent that is mal-apposed to the vessel wall due to under-expansion of the balloon deploying the stent or dissection with thrombus accumulation in the artery segment immediately adjacent to the stent. In rare instances, acute and subacute stent closure may be due to an underlying hypercoagulable state or inadequate anti-platelet therapy. In contrast, ISR refers to stent renarrowing or closure that typically occurs within 3-12 months after stent implantation. Patients with ISR often note an insidious recurrence of the cardiac symptoms they experienced prior to stenting and infrequently suffer an acute event (e.g., myocardial infarction).

Once formed, not all ISR lesions are alike. Mehran and colleagues classified ISR into focal and diffuse patterns (Table 1).3 Focal ISR may occur at gaps or articulation sites in stents, at the stent margins, or at one or more sites within the body of the stent. In contrast, diffuse ISR may either be limited to within the stented segment or extend beyond the margins of the stent. While it is often difficult to predict which stented lesions will develop ISR, a number of clinical and angiographic predictors of ISR have been identified. Several studies have consistently identified a number of predictors of both angiographic and clinical restenosis following stent implantation. These include a small (< 2.5mm) reference vessel diameter, occlusions, ostial lesions, lesions within vein grafts, a longer lesion length, use of multiple stents, a history of previous restenosis and the presence of diabetes.28,29

Table 1. Classification of In-Stent Restenosis

	Macroscopic Description
Class I: Focal	• lesions 10mm in length • at unscaffolded segment • at body of stent • proximal OR distal margin
Class I: Multi-focal	• lesions at combination of 'focal'sites
Class II: Diffuse intra-stent	• lesions >10mm in length • confined within stent(s) • no extension outside stent margins
Class III: Diffuse proliferative	• lesions >10mm in length • extends beyond stent margins
Class IV: Total occlusion	• lesions with TIMI 0 flow

TIMI = thrombolysis in myocardial infarction.
Adapted from Mehran, et al.3

TREATMENT STRATEGIES IN IN-STENT RESTENOSİS PTCA

The treatment of ISR with conventional PTCA is still the prevailing therapy. Although technically straightforward, a number of studies have shown rates of angiographic and clinical restenosis ranging between 30% and 80% following this strategy.31,32 It is thought that the majority of luminal enlargement is achieved through additional stent expansion, with the rest being due to compression of neointimal tissue. Neointimal tissue may undergo re-intrusion through the stent struts soon after initial balloon expansion, with an acute loss of benefit.

a."Cutting" Balloon Angioplasty

The 'cutting' balloon (Boston Scientific Corp., Interventional Technologies Europe Ltd, Letter Kerry, Ireland), a balloon catheter with three or four microsurgical blades bounded longitudinally to its surface, was introduced as a potential tool to incise and facilitate redistribution of ISR plaque. However, a large multicentre, prospective, randomised trial showed no significant benefit in reducing recurrence of ISR (target lesion revascularisation (TLR) of 14% versus 13%) or major adverse cardiac events (16% versus 15%) compared with conventional PTCA.33

b. Directional Coronary Atherectomy

The 'debulking' technique of directional coronary atherectomy (DCA) involves removal of neointimal tissue from within stents, resulting in acute gain in luminal diameter. Despite reports from small series of patients of relatively low (25%) rates of TLR at 12 months, concerns over increased morbidity have limited the use of this technique.34

c. High-speed Rotational Atherectomy (HSRA-Rotablation)

Theoretically, mechanical debulking of neointimal with rotablation prior to PTCA should minimise vessel trauma and thus result in less subsequent recurrent neointimal proliferation compared with PTCA alone. This was demonstrated in an animal model of ISR.35 A single-centre study of 100 cases reported favourable outcomes with rotablation compared with historical controls of PTCA.36 However, the multicentre Angioplasty versus Rotational Atherectomy for Treatment of Diffuse In- Stent Restenosis Trial (ARTIST) of randomised patients with ISR to either conventional PTCA or rotablation showed a better six-month event-free survival after PTCA compared with rotablation (91% versus 80%, respectively; p=0.005). Both treatment strategies resulted in high restenosis rates (51% in PTCA group versus 65% in rotablation group).37 The single-centre randomised trial of Rotational Atherectomy Versus Balloon Angioplasty for Diffuse In-stent Restenosis (ROSTER) reported less residual intimal hyperplasia and lower TLR rates with HSRA compared with PTCA alone.38 It is important to note that the ARTIST and ROSTER trials are not directly comparable, as the latter study excluded a third of patients after baseline intravascular ultrasound (IVUS) assessment and significantly more patients underwent additional stenting in the ROSTER PTCA arm compared with the rotablation arm.

d. Excimer Laser Coronary Angioplasty

Another atheroablative tool is the excimer laser and this has been shown to ablate in-stent neointimal tissue safely and effectively, with a trend towards lower TLR at six months follow-up compared with PTCA alone (21% versus 38%, respectively; p=0.05).39 However, a randomised trial comparing the excimer laser and rotablation found no significant difference between TLR rates for both strategies at one year.40

e. Intravascular Brachytherapy

Brachytherapy has been shown to reduce the incidence of angiographic and clinical restenosis in trials of both de novo disease and ISR.41-43 The landmark Scripps Coronary Radiation to Inhibit Proliferation Post-Stenting (SCRIPPS) study reported favourable results following intravascular-radiation to treat restenosis (two-thirds was within stents) in humans.44 The six-month angiographic restenosis rates were significantly lower in the treatment group compared with placebo (17% versus 54%, p=0.01) and this difference was sustained at three years. The composite clinical endpoint of death, MI or TLR was also lower in the treated group compared with placebo (23% versus 55%, p=0.01).

The efficacy of Á-brachytherapy for the treatment of ISR was later confirmed by the Washington Radiation for In-Stent Restenosis Trial (WRIST), Gamma-1 and the Angiorad Radiation Technology for In-Stent Restenosis Trial in Native Coronaries (ARTISTIC).45,46 ß-radiation has advantages over Á -radiation in that it involves lower total body dose exposure and shorter (three to six minutes versus 15–20 minutes) intracoronary dwell times. Thus, ß-brachytherapy can be carried out within catheter laboratories in the presence of clinical staff and without the need for extra radiation protection. The theoretical disadvantages of ß-radiation compared with Á-radiation include lower vessel wall penetration and hence a less homogenous delivery of radiation. However, the Beta-WRIST trial, a single-centre registry using a yttrium ß- radiation source, showed similar results to the original Á-trial,47 thereby suggesting that the mechanism of action and clinical results of Á and ß-radiation are broadly similar.

The use of ß-emitting P-32 stents was evaluated by the IRIS-1 registry and was found to be safe and feasible, but with a high angiographic restenosis rate of 39%.48 Subsequent European dose-ranging studies have been equally disappointing, with IRIS-2 showing a 44% restenosis rate, predominantly at the stent edges. This so-called 'edge effect' is related to radiation dose, where the length of the radiation source does not fully cover the injured artery segment; hence, a segment of injured endothelium receives a low dose of radiation at the edges of the source.

An additional application for brachytherapy was suggested more recently with vein graft restenosis.49 Thus, brachytherapy has been demonstrated to be a safe and relatively effective strategy for the treatment of ISR, albeit with some limitations such as edge restenosis and late thrombotic occlusions. The latter phenomenon, reported in up to 9% of patients receiving brachytherapy to treat ISR, is postulated to be as a result of failure of re-endothelialisation of the 'bare' stent struts, leading to a prolonged thrombotic risk. Therefore, long-term (>6 months) therapy with clopidogrel is recommended in addition to acetylsalicylic acid.50

The issue of dosimetry has been clarified by several studies, whereby too little radiation appears to be, at best, ineffective and may have a proproliferative effect. Other concerns regarding the long-term safety of this technology include questions on late vessel wall degeneration (leading to aneurysm formation), late fibrosis (leading to delayed restenosis) and the development of radiation-induced tumours, either locally or at distant sites. Finally, overall, only about a 10% absolute reduction of restenosis was achieved by brachytherapy. This means that 10 patients have to be irradiated in order to prevent one of them from having a repeat intervention. Mortality and infarction rates are not reduced. In real terms, brachytherapy is not an entirely economical strategy.

f. Drug Eluting Stents

The evolution of drug eluting coronary stents has followed a remarkably rational course. For example, as organizing thrombus is considered an important initiating event in the development of ISR, therapies directed against both platelets and thrombin were early candidates for stent-based delivery. Unfortunately, stents dipped in the glycoprotein-IIbIIIa receptor antagonist abciximab failed to reduce the incidence of ISR.51 A similar lack of success was encountered with heparin. While variable benefit was exhibited in several animal studies with heparin-coated stents, non-randomized human

trials involving a broad range of patients demonstrated ISR rates that were comparable to those of trials of uncoated stents in similar patient populations.52, 53-58

Moreover, it should be noted that several of the early landmark clinical trials that established the superiority of stents to angioplasty alone used heparin coated stents. 30,59,60 The incidence of ISR in these studies varied from 16% in a low risk population to 55% in a population at high risk. Finally, a randomized clinical trial comparing a heparin-coated stent with an uncoated stent failed to demonstrate a difference in binary ISR rates (e.g., 33% and 30%, respectively).61

Inflammation in the peri-strut vascular tissue is thought to play a key role in the genesis of ISR. Therefore, corticosteroids, because of their potent anti-inflammatory properties, have also been investigated in porcine models of stenting. While one study using methylprednisolone did reveal less neointimal thickening with the drug-coated stent, two others with dexamethasone showed no such benefit.62-64

A third target for the prevention of ISR is smooth muscle cell proliferation. While it has been demonstrated that smooth muscle cell proliferation is exceedingly rare in tissue specimens removed from established human ISR lesions, little is known about the proliferation profile in the vessel segment early after stent implantation .65,66

If one extrapolates from animal models of stenting, peak proliferative activity is observed 7 days after stent insertion.67 Hence, several agents with anti-mitotic properties have been studied. Currently, two agents, sirolimus and paclitaxel, have shown remarkable efficacy in clinical trials, and will be discussed separately.

The concept of local drug delivery via coated stents is attractive, in that it combines biological and mechanical strategies in order to maximise the final angiographic result and also moderate the reaction of the vessel to the injury caused by stent implantation. The development of stents coated with antimitotic drugs, in particular sirolimus (rapamycin) and paclitaxel, has had a significant impact on the outcome of coronary stenting of non-complex de novo lesions in native coronary arteries, with a marked reduction in the incidence of angiographic restenosis.

There are several key factors involved in the construction of a coated stent. These include the compatibility of the stent coating with the artery wall, the means by which the therapeutic agent is initially retained and then released in vivo, the release kinetics (especially duration), the local distribution of the agent into the artery wall vs. the blood, the potential and relative toxicity of the agent to various cells in the artery wall (e.g., endothelial cells, SMCs, mononuclear cells), and finally the stent design, since the number of struts and the metallic surface area of the stent are important in determining the dose of therapeutic agent that will be available for delivery.

Sirolimus is a naturally occurring macrolide antibiotic produced by Streptomyces hygroscopicus and originally identified in 1975 from a soil sample from Rapa Nui (Easter Island). Initially, the drug was developed as an antifungal (rapamycin), but its clinical utility as such was undermined by its potent immune-suppressing effects. In 1999, sirolimus was approved by the FDA for the prevention of renal allograft rejection. Sirolimus is lipophilic with low aqueous solubility, thereby allowing for minimal drug loss in the blood and likely enhanced resident time in cell membrane lipids when delivered using a stent-based platform. The net effect of sirolimus is a cytostatic arrest of cell cycle progression from G1 phase to S phase. Studies in vitro and in vivo support the

concept that sirolimus inhibits SMC proliferation and neointimal formation .68-70

"First In Man" (FIM) was the first human study of a coronary stent eluting an anti-proliferative agent (sirolimus). Forty-five patients with stable coronary artery disease from two different centers were treated with a single sirolimus-coated BX Velocity stent, and the results were reported in two separate manuscripts. Using quantitative coronary angiography and 3D volumetric IVUS measurements obtained immediately post-procedure and 4 months later, there was minimal neointimal area formation in both groups (11.0 ± 3.0% and 10.4 ± 3.0% of lumen area for the slow and fast release formulations, respectively), and no in-stent or edge restenosis was detected. Furthermore, there were no major clinical events through 8 months of follow-up, including stent thrombosis, repeat revascularization, myocardial infarction or death. Angiographic follow-up revealed an absence of ISR at 12 months.71

The Study of Sirolimus Eluting Stent in De Novo Native Coronary Lesions (SIRIUS) study aimed to assess the usefulness of DESs in a more "real-life" population.72 De novo coronary artery stenoses in 1058 patients were randomized to receive either a sirolimus-coated or an uncoated BX Velocity stent. Compared with previous study populations, the patients in SIRIUS were at significantly higher risk for ISR: 25% were diabetic, over 40% had multivessel disease and the lesions were at least 15 mm in length. The SIRIUS study showed a 12-month TLR of 5% with sirolimus eluting stents compared with 20% in the control 'bare metal' stent group ($p<0.001$).73

Understandably, less favourable outcomes were observed in more complex subgroups such as long lesions, bifurcations, small (<2.5mm diameter) vessels, diabetics (especially insulin-dependent diabetics) and in vein graft interventions.

Finally, it should be noted that while these sirolimus DES data are very encouraging, oral sirolimus therapy has also been tested in patients undergoing PCI. Preliminary results from ORBIT, an open-label trial of intracoronary stenting with a 30-day treatment of oral sirolimus in 22 patients at high risk for ISR, demonstrated that oral sirolimus was ineffective in preventing ISR.74

The second drug to be delivered on a stent and prevent ISR is paclitaxel. This agent, produced in the bark of the Pacific yew tree, has potent anti-neoplastic properties and is FDA-approved for the treatment of ovarian cancer.75 The drug acts by interfering with cell microtubule function, causing the formation of abnormally long and stable microtubules that serve to inhibit cell division and migration, as well as intracellular signaling and protein secretion. Thus, like sirolimus, paclitaxel inhibits SMC proliferation ostensibly via a cytostatic mechanism. As well, similar to sirolimus, paclitaxel is lipophilic and insoluble in water, and therefore, well suited for stent-based delivery.

The ASPECT trial compared the safety and efficacy of a low dose (1.3 µg/mm2) and high dose (3.1 µg/mm2) paclitaxel eluting nonpolymeric stent with a control stent in 177 patients.76,77 The ELUTES trial (European EvaLUation of PacliTaxel-Eluting Stent) assigned 192 patients in a random manner to one of five groups: four paclitaxel-eluting stent groups receiving four different doses and an uncoated stent group.78 Finally, the TAXUS I trial randomized 61 patients to receive either a slow-release coated stent with paclitaxel embedded in a polymer or a conventional stent.79 Similarly, the TAXUS II study of two paclitaxel formulations (slow release, SR, and

moderate release, MR; each with 1 µg/mm2 of drug per stent) randomized 536 patients to a drug-coated vs. a bare NIR conformer 15 mm stent (Boston Scientific Corp., Natick, Mass.). The TAXUS II study reported a 6 month angiographic restenosis rate of 8% in paclitaxel eluting stents compared with 23% in the control 'bare metal' stent group ($p<0.0001$).80

POTENTIAL DISADVANTAGES OF DESs

There are several theoretical problems associated with the use of DESs. Potential drawbacks of DESs can be classified into two general categories: suboptimal efficacy and overwhelming efficacy (or toxicity). While these potential pitfalls continue to be carefully evaluated and DESs have for the most part been demonstrated to be safe.

There are several problems with DESs that relate to their possible lack of efficacy in preventing ISR. Obviously, the first factor to consider is the drug itself.

The drugs that are currently being explored are logical choices, and some have multiple modes of action (e.g., anti-proliferative and anti-inflammatory). Therefore, until more biological and molecular information is available regarding the processes involved in stent renarrowing, relatively broad spectrum therapeutic strategies will continue to be tested.

The second factor of vital importance is the dose of the anti-ISR drug. The ASPECT and ELUTES trials with paclitaxel-coated coronary stents clearly demonstrate a dose-response relationship between drug and ISR prevention.76,81 However, this issue is not as simple as the amount of drug per unit of stent surface area. Therapeutic success relates rather to the amount of drug per area of vessel wall. Thus, the relationship between stent and vessel wall is critical. Unfortunately, this relationship is highly variable and is determined by several factors including the configuration and topography of the involved blood vessel.

The third theoretical problem of DESs is "edge effect." Edge effect was a common complication of brachytherapy and refers to restenosis immediately adjacent to the proximal and distal margins of the stent.82 Angiographically, the appearance is similar to that of a candy wrapper. Edge restenosis has been attributed to geographic miss, (i.e. balloon-mediated injury with insufficient administration of radiation to the artery wall at the edges of a lesion).83,84 This same complication could conceivably affect DESs: injury to coronary artery segments not covered by DES. In clinical trials, this specific issue is being addressed by assessing not only the incidence of ISR, but also insegment restenosis (in-segment restenosis is commonly defined as binary restenosis within the stent plus the region 5 mm proximal or distal to the stent). In RAVEL, IVUS follow-up in a subset of 95 patients did not demonstrate a significant difference between the 2 groups in either lumen or plaque volume at the proximal and distal edges.85

A fourth concern regarding the long-term success rate of DESs is the so-called "catch-up phenomenon." Specifically, if a drug is eluted from the stent over a period of 14 to 30 days, what happens thereafter? In other words, is ISR significantly reduced by DESs or just postponed? Farb et al. demonstrated that intimal hyperplasia was inhibited at 4 weeks in their rabbit study of paclitaxel-eluting stents, but the effect was not sustained at 90 days.86 The longest available human follow-up of DESs comes from the FIM study. After 3 years, 92% of patients remained free of any major adverse cardiac events, and none occurred between years 2 and 3.87 While the human evidence accumulated thus far has failed to demonstrate

a catch-up phenomenon, longer follow-up of larger numbers of patients is required.

Important questions about the outcomes of DESs do not stem solely from their possible lack of efficacy, as problems may also arise from their potency. Specifically, if ISR is a form of arterial repair, what are the consequences when this tissue response is inhibited? Perhaps thrombosis may occur due to delayed endothelial regrowth, or aneurysm formation and stent malapposition may develop in response to medial and adventitial atrophy? Incomplete healing along with intimal hemorrhage has been observed in animal studies of paclitaxel-eluting coronary stents.88

In humans, DESs do appear to possess a propensity for late thrombotic complications. The SCORE trial compared a coronary stent eluting the taxane derivative 7-hexanoyltaxol, also known as QP2, to a bare stent.89 Although ISR rates were 0% in the coated stent group vs. 52% in the control group, the trial was terminated prematurely because of a high incidence (8%) of late stent thrombosis in the coated stent group.

Aneurysm formation, a potential complication related to the toxicity of anti-proliferative agents delivered to the coronary artery wall, may result in late stent malapposition. In their studies of paclitaxel-coated stents in pigs, Heldman and colleagues noted a reduction in medial thickness along with focal neointimal and medial wall hemorrhage and cell necrosis.90 While there are scattered unpublished reports of stent malapposition in the various DES trials, these have yet to be conclusively linked to clinical adverse events but will require careful long-term scrutiny.

DES TREATMENT OF IN-STENT RESTENOSİS

As noted repeatedly, the treatment of in-stent restenosis remains one of the most vexing shortcomings in interventional cardiology.

Finally, DESs have been evaluated as a possible treatment for ISR, and the results have been mixed. Sousa et al. reported the results of the Brazilian cohort of the ISR trial investigating the sirolimus-eluting BX Velocity stent as a treatment for ISR.91 After 12-month follow-up, only one patient developed ISR, and there were no major adverse cardiac events (MACEs). In the European cohort of the same study, however, results were less favourable.92 Angiographic follow-up at four months revealed that 3/16 patients (19%) had developed ISR, and after 9 months of clinical follow-up 3 patients experienced a MACE, including two deaths. Finally, TAXUS-III evaluated another paclitaxel coated stent in patients with established ISR.93 The 6- month ISR rate after insertion of a DES was 16%. MACE occurred in 29%, and most events were due to target vessel revascularization. Thus, the efficacy and safety of DESs in the treatment of ISR remain to be established.

CONCLUSION

In-stent restenosis is a pathophysiological process that occurs principally as a result of aggressive neointimal hyperplasia following stent implantation. This iatrogenic phenomenon has proved to be a problematic and stubborn entity. Deploying a stent in a human coronary artery lesion causes arterial injury and sets into motion a sequence of events that can result in clinically important renarrowing. These events include thrombus formation, inflammation, smooth muscle cell infiltration, and perhaps the

involvement of blood-borne precursor cells, followed by the generation of an abundant extracellular matrix. Stents that elute drugs such as sirolimus and paclitaxel significantly decrease the incidence of both angiographic and clinically relevant ISR compared to uncoated stents. However, follow-up of patients has been relatively short, and more data are needed regarding potential complications including edge effect, late thrombosis and late malapposition. The next several years will be exciting as the role of DES in daily practice is clearly defined.

For now, the high cost of DES will also contribute to the continued existence of ISR as it is difficult to imagine the use of DES in all patients, and like before bare metal stents will still be used in the majority of patients.

ABBREVIATIONS

DES = Drug-eluting stent
FIM = First in man
ISR = In-stent restenosis
IVUS = Intravascular ultrasound
MACE = Major adverse cardiac events
PCI = Percutaneous coronary intervention
PTCA = Percutaneous transluminal coronary angioplasty
TVF = Target vessel failure

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