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Review Article

Preventing restenosis in early drug-eluting stent era: recent developments and future perspectives

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Abstract

Restenosis is the major limitation of the successful therapy of percutaneous coronary intervention (PCI) for patients with coronary artery disease. The problem was appreciated in the late 1970s to early 1980s. Only in recent years, anti-restenotic therapy has achieved a breakthrough with the development of drug-eluting stents. Here, we provide an overview about pathological mechanisms of restenosis after PCI. Present therapeutic approaches to overcome restenosis and recent clinical results are revisited, and some major concerns in the post-drug-eluting stent era are discussed.

Introduction

Coronary artery disease (CAD) is the major cause of death in the industrialized world. Pathogenesis of coronary artery disease is multifactorial involving a complex procedure, which finally leads to vascular narrowing or occlusion and subsequently myocardial ischaemia or infarction (Figure 1). Since the pioneering work by Andreas Grüntzig in 1977, who opened a narrowed coronary artery with a balloon catheter (Gruntzig 1978), percutaneous coronary intervention (PCI) such as percutaneous transluminal coronary angioplasty (PTCA), with or without stent implantation, evolved into successful therapeutic approaches for patients with symptomatic coronary artery disease. Over 1.5 million PCIs are performed annually worldwide (American Heart Association 2001); PCI has become the most common therapeutic intervention for treating coronary artery disease and outnumbers coronary bypass surgery (Smith 2001). The success of PCI is, however, moderated by a significant restenosis rate. Restenosis occurs in 30–50% of patients with balloon dilatation and in 22–32% of cases with stenting within 6 months after intervention (Serruys & Levendag 1997). Patients with restenosis have to be treated by re-interventions. In the year 2000 in Germany, 25 000 patients needed a second treatment, causing estimated overall expenses of €500 million (Silber 2002b). For clarification, notwithstanding the lack of a clear consensus, the most frequently used definition of *angiographic restenosis* is a stenosis of at least 50% of the lumen diameter and/or at least 50% late loss of the acute lumen gain after PCI (Wurdeman et al 1998). The term *binary restenosis* is used somewhat interchangeably with angiographic restenosis, although it is more strictly defined as a stenosis of at least 50% of the lumen diameter at follow-up. Another important restenosis definition is clinical restenosis, which is defined when repeat revascularization of the target lesion (TLR) is needed to relieve re-occurring signs and symptoms of myocardial ischaemia. Clinical studies involving stents coined the terms *in-stent restenosis* (ISR) (a restenosis developed within the stented area), *in-segment restenosis* (a restenosis developed within the area of the stent plus an additional 5 or 10 mm at the proximal and distal borders) and *target vessel revascularization* (TVR) (which extends the restenosis definition to the entire target vessel). Four patterns of ISR have been suggested (Mehran et al 1999): pattern I includes focal lesions; pattern II is diffuse within the stent; pattern III is diffuse outside the stent; pattern IV is a totally occluded ISR.

As a consequence of these previous considerations, reported restenosis rates in clinical studies depend on the cardiovascular risk factors, the characteristics of the coronary artery lesion and the applied restenosis definition. The risk factors encompass smoking, hypertension, hypercholesterolaemia, diabetes and age (Cuming et al

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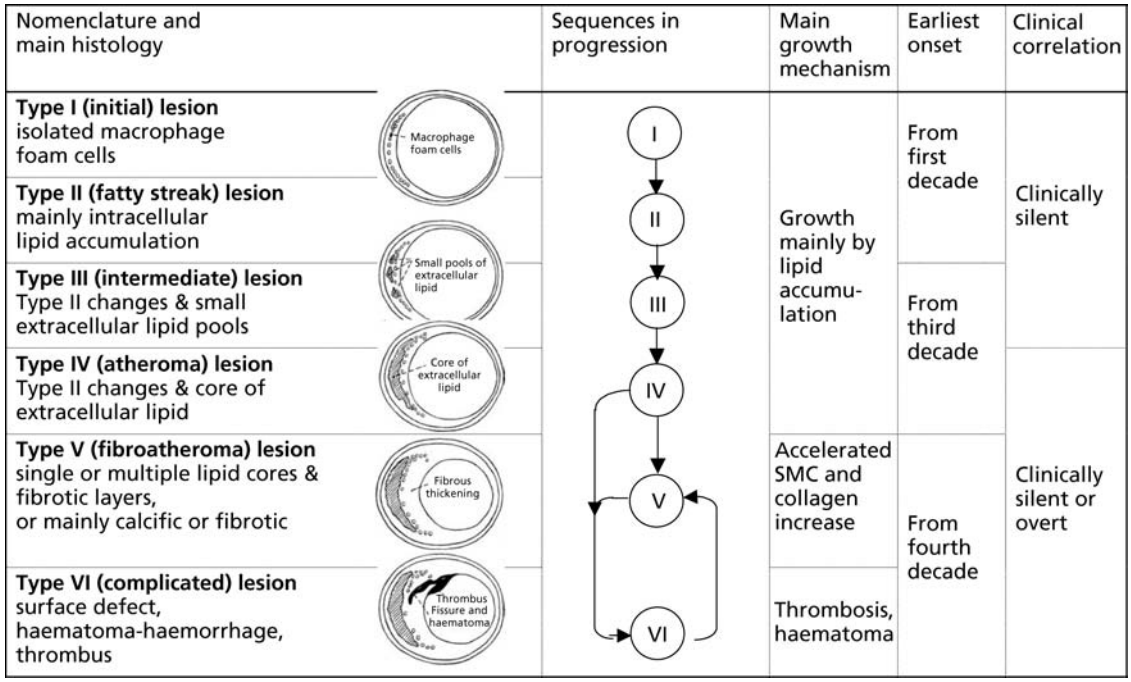

Figure 1 Evolution and progression of human arteriosclerotic lesions. Changes in lesion morphology from type I to type VI occur primarily because of increasing accumulation of lipid. The loop between V and VI illustrates how lesions increase in thickness when thrombotic deposits form on their surfaces. Thrombotic deposits may form repeatedly over varied time spans in the same location and may be the principal mechanism for gradual occlusion of medium-sized arteries (adapted from Stary et al (1995), with permission).

1993; Bach et al 1994). With regard to coronary artery lesion characteristics, there is increased incidence of restenosis in patients with complex lesions (i.e. long lesions, ostial lesions, calcification, lesions at bifurcations, side branch involvement, small vessel diameter or total occlusion) (Rensing et al 1993). Finally, it is debated whether infections with cytomegalovirus, *Chlamydia pneumoniae* or *Helicobacter pylori* increase the restenosis risk (Handa et al 1993; Radke et al 2001; Schiele et al 2001).

Mechanisms of restenosis

A normal coronary artery consists of the adventitia, media and intima, with the internal elastic lamina being located between the media and intima, and with the endothelial layer separating the intima from the circulating blood. Restenosis is considered a local vascular response to mechanical injury caused by the PCI procedure in the blood vessel wall. The vascular injury leads to local production of numerous vasoactive, thrombogenic and mitogenic factors (Table 1) causing vasoconstriction, thrombosis and structural changes of the vascular wall that lead either to acute or late restenosis after the procedure. Although the mechanism of restenosis after PCI is not yet fully understood, two major processes are considered to be crucial, namely vascular remodelling and neointima formation.

Arterial remodelling is defined as any enduring changes in size or composition of an adult blood vessel that enables the blood vessel to adapt to changes in local blood flow pattern (Galis & Khatri 2002). Inappropriate remodelling enhances the pathogenesis of major cardiovascular diseases such as atherosclerosis and restenosis. It was noted that human atherosclerotic arteries often enlarge in response to plaque formation, which is called positive vascular remodelling, a compensatory mechanism that limits further vascular lumen narrowing (Glagov et al 1987). Immediately after balloon dilatation, elastic recoil occurs, which is an initial response of the elastic fibres of the blood vessel wall to the overstretching by the balloon catheter; this contributes to the early loss of volume gain after the procedure. The so-called constrictive or negative vascular remodelling (Figure 2), a process resembling scar formation with subsequent scar tissue contraction, is the main mechanism causing loss of vascular lumen at later times after the intervention (Andersen et al 1996). Negative remodelling is believed to be mediated primarily by adventitial myofibroblasts, possibly also by smooth muscle cells (SMC), which re-organize extracellular matrix and change the vessel size without overall change in tissue volume (Mintz et al 1997; Schwartz et al 1998; Sangiorgi et al 1999). Early elastic recoil and negative arterial remodelling are both prevented by stent implantation, which may together with the higher initial luminal gain explain the lower restenosis rate after stenting than after balloon dilatation alone.

Neointima formation is caused by migration of SMC from the media, or of myofibroblasts from the adventitia,

Table 1 Factors involved in restenosis after PCI

Factor	Effect
Cells of the immune system (granulocytes, leucocytes)	
PDGF, bFGF, FGF-α	SMC proliferation
TGF-β	Stimulation of SMC excretion of extracellular matrix
Leucotrienes	Vessel spasm
PDGF	Blood platelet aggregation
Blood platelets/aggregated blood platelets (thrombus)	
TGF-β1	Stimulation of SMC excretion of extracellular matrix (collagen, proteoglycans) and migration
5-HT (serotonin)	SMC migration, proaggregatory effects
5-HT, ADP (co-factor thrombin)	Vessel spasm
PDGF	Blood platelet aggregation; SMC proliferation and migration
Thromboxane A2	Leucocyte activation, stimulation of leucotriene secretion, vasoconstriction, proaggregatory effects
Prostacyclin	Antiaggregatory effects, vasodilatation
Injured or proliferating endothelial cells	
bFGF	SMC proliferation
Lowered heparin proteoglycan	Lowered SMC inhibition
Lowered EDRF (NO)	Lowered vessel relaxation
SMC	
bFGF, PDGF-like (cofactor angiotensin II)	SMC proliferation
TGF-β	Stimulation of SMC that excrete extracellular matrix
Pressure and enlargement of vessel wall	SMC stimulation, elastic recoil, mediated by: increased DNA synthesis; release of growth factors; individualization leading to increased area available for stimulants

into the lumen and subsequent proliferation and excretion of extracellular matrix from these cells. It is interpreted as overshooting wound healing response or as an adaptation to the altered arterial flow after vessel dilatation (Leung et al 1976; Glagov et al 1988; Bassiouny et al 1992; Meyerson et al 2001). Animal experiments suggest that the incidence of restenosis depends on the severity of the injury and that neointimal formation is increased when arterial injury occurs concurrently with nonspecific systemic stimulation of the innate immune system, as typically caused by inflammation and a consequent cycle of injury and inflammation. Neointima formation is the primary mechanism causing ISR, whereas it plays a relatively minor role in restenosis after balloon dilatation. The stent struts cause endothelial denudation and deep injury of the vascular wall. This aggravates the vascular injury, results in platelet adhesion/aggregation at the injury site and triggers inflammatory responses within the blood vessel wall that boost neointima formation (Caramori et al 1999).

Recent research on cellular and molecular mechanisms of restenosis has mainly focused on neointima formation within the stent area rather than on negative vascular remodelling, which can be practically prevented by stents. Numerous growth factors and cytokines are released from aggregating platelets, inflammatory cells and vascular wall cells (Table 1, Figure 3). These factors are believed to be the major stimuli for SMC migration/proliferation after stenting. Thrombus formation can also act as scaffold providing a substratum for SMC migration, proliferation and matrix synthesis. Animal experiments suggest that adventitial fibroblasts may also respond to injury, starting migration and proliferation across the media into the intima (Okamoto et al 2001). The role of leucocytes in the neointima formation cascade has recently been highlighted, especially the importance of neutrophil infiltration after PTCA without stent placement and monocyte/macrophage infiltration after PTCA with stent placement (Welt et al 2000, 2003). In contrast to balloon injury, stent-induced injury resulted in sustained chemokine expression and leucocyte recruitment (Welt et al 2000, 2003).

The molecular mechanisms of vascular cell proliferation/migration are not fully understood yet. The commonly accepted model of SMC proliferation or migration suggests that numerous growth factors and cytokines activate cell surface receptors, thereby triggering activation of an array of signal transduction pathways leading to cell cycle progression. Earlier investigations have focused on individual growth factors and their specific receptors (Table 1). Targeting only a single growth factor at the receptor level is unlikely to be successful in restenosis prevention. Blocking downstream mechanisms of SMC proliferation, such as intracellular signal transduction pathways and cell cycle progression, which is commonly activated by multiple growth factors, proves more efficient in preventing restenosis as demonstrated by the results obtained with sirolimus or paclitaxel (see below). The detailed molecular mechanisms of SMC cell proliferation have recently been reviewed (Poon et al 2002; Indolfi et al 2003).

Therapeutic approaches

Much effort has been devoted in the past to developing mechanical devices and searching for drugs to prevent restenosis after PCI. Directional coronary atherectomy catheter, rotational atherectomy and laser-assisted angioplasty have been tested in clinical trials without success in lowering the restenosis rate, as compared with standard balloon dilatation (Appelman et al 1996; Bauters & Isner 1998; Dietz et al 2001). Conversely, the recent development of drug-eluting stents (DES) probably represents the most prominent breakthrough in restenosis prevention after PCI.

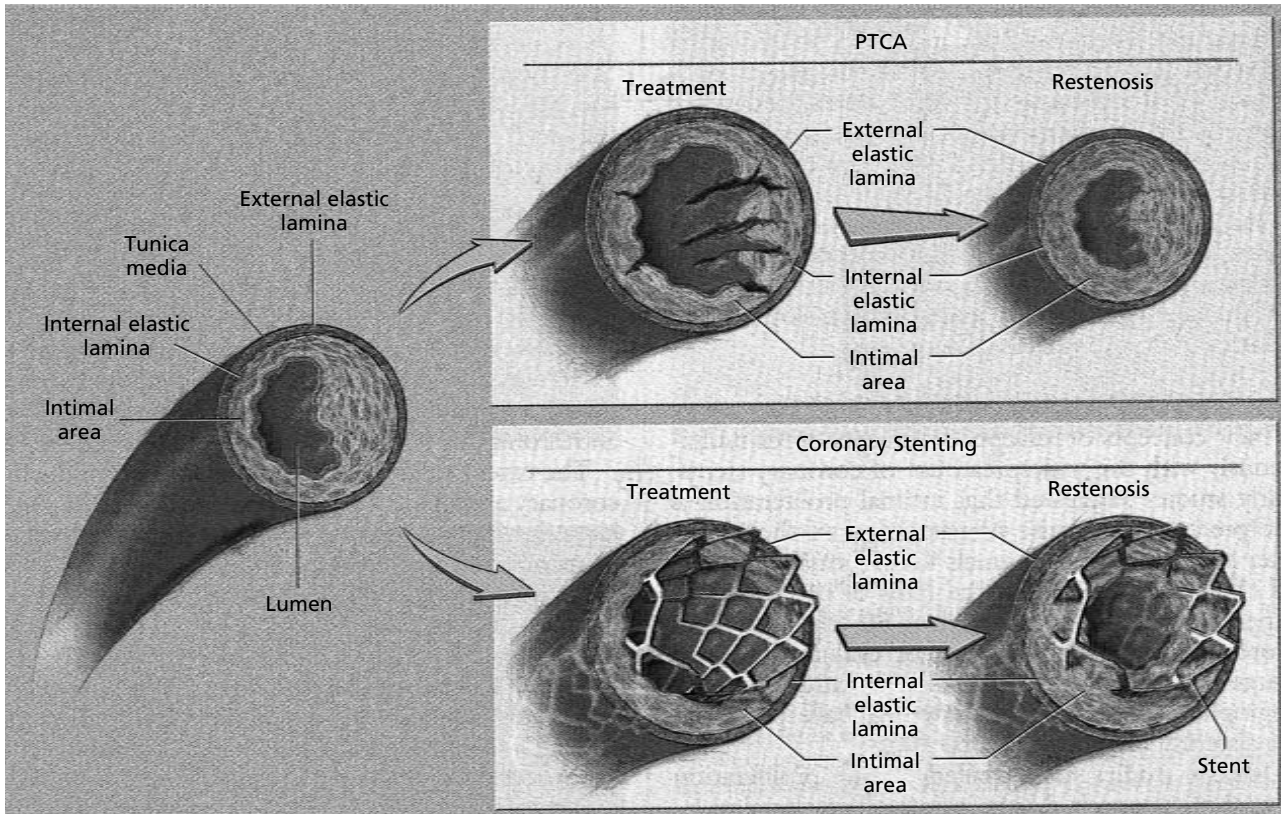

Figure 2 Pathophysiology of restenosis after balloon angioplasty and stenting (Bittl 1996, with permission).

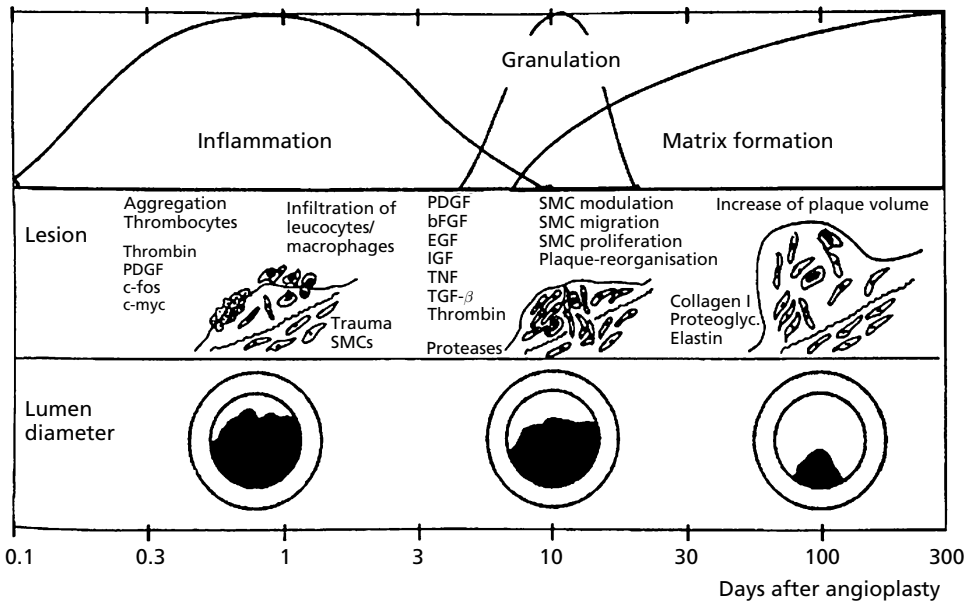

Figure 3 Overview of pathologic mechanism of restenosis formation. Selected stages of vascular lesion are shown together with relevant mechanisms and factors involved. The lesion stages are associated with specific restenosis phases and corresponding angiographic status (Bauriedel et al 1994, with permission).

Stents

Stents were introduced in 1986 and have so far proven to be the only effective mechanical means for reducing the restenosis rate after balloon dilatation. Stents are thin cylindrical wire meshes (diameter 3–5 mm; length 15–30 mm) made of medical-grade stainless steel (BMS, bare metal stent; Figure 4A). Over the past years, stents have been improved continuously in terms of ease of handling and flexibility. As steel offers a highly thrombogenic surface (Figure 4B, C), anti-thrombotic drug therapy is necessary after stent implantation to prevent thrombotic events. The undisputed superiority of stents over conventional balloon angioplasty has resulted in a plethora of stents in clinical use. Recent data, however, have indicated that not all stent models perform similarly. Nuances in stent design and construction have impacted significantly on the immediate and long-term clinical outcome. Stent design and stent surfaces have been, and continue to be, improved (Unverdorben et al 2003). Among the stainless-steel stents, those with multicellular or tubular designs have proven to be superior to coiled or hybrid stent models, and thin-strut stents perform better than thicker-strut stents (Hausleiter et al 2003; Lau et al 2004). Coating stainless-steel stents with gold, carbide, phosphorylcholine or heparin does not appear to confer any additional benefit compared with bare metal stents. In contrast, randomised trials have demonstrated that DES coated with various anti-proliferative drugs, with or without a carrier polymer, afford unparalleled restenosis rates compared with non-drug-eluting stents (see below).

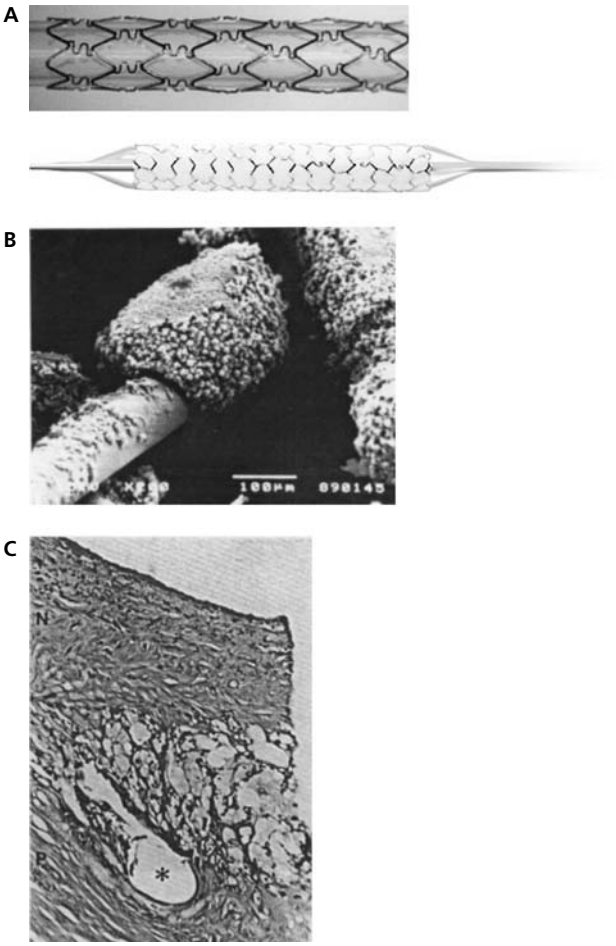

Figure 4 The JOMED JOSTENT Flexmaster (A). Micrograph of a stent three days post implantation; typical thrombotic disorder is visible, with platelet, leucocyte and fibrin adhesion (B). Light micrograph of a human saphenous vein bypass graft removed 10 months after stent implantation (C); a prominent neointima (N) has formed and borders on the old atherosclerotic plaque (P); at the junction between the old plaque and the recent neointima, abundant foam cells are found in the new neointima void* representing the site of a removed 70-μm diameter stent wire (Serruys et al 1991, with permission from American College of Cardiology Foundation).

The number of implanted stents increases steadily due to the lower restenosis rate as compared to balloon angioplasty. In Germany between 1999 and 2000, stent implantation increased from 57 to 68% of PTCA patients (Mannebach et al 2001), and in 2002 this number reached 75% (i.e. 148 853 stents placed after 207 937 PTCA (E. Bruckenberger, 15. Herzbericht 2002 mit Transplantationschirurgie, http://www.herzbericht.de/).

Cardiologists who recommend routine stent placement rather than restriction to patients at risk of immediate vessel closure emphasize the benefit of a larger immediate post-procedural lumen and inhibition of negative remodelling. The enlarged lumen, relative to that of non-stented arteries, persists for more than 6 months after PCI (Kuntz & Baim 1993; Kuntz et al 1993). The so-called bigger-is-better theory postulates a reduced restenosis rate for a larger post-procedural vessel lumen (Escaned et al 1999; Serruys et al 1999; Di Mario & Karvouni 2000; Faxon 2000). The outcome regarding restenosis development is most favourable in selected patient populations such as non-diabetics with short lesions and large vessel diameters. In general, stent implantation is limited by the diameter of small vessels and the actual location and size of the primary stenosis. Thanks to continuous handling improvements, major adverse cardiac events (MACE) are nowadays in the range of 12–15% after PCI with BMS placement (Unverdorben et al 2003; Lemos et al 2004c). Further progress is necessary regarding the smooth morphological transition between the proximal and distal ends of the stent and the adjacent arterial segments to avoid chronic (over)stretching and stressing of the vessel wall (Doriot et al 2003).

Drug-eluting stents (DES)

The recent development of DES represents a prominent advance in restenosis prevention (Table 2). Several drugs have been tested in animal models and human trials. The efficacy and safety of DES might differ depending on the drug and stent delivery systems used. Recent research has focused on the various constituents of DES, including stent backbone, materials used for drug delivery and the physico-chemical properties of the pharmacological agents themselves (Campbell & Rogers 2004).

Table 2 Successful recent and ongoing clinical trials with sirolimus- and paclitaxel-eluting stents

Trial name	No. of patients	Follow-up time (months)	Restenosis rate (%) DES vs control	Year of publication
Sirolimus				
RAVEL	238	6	0 vs 26	2002
SIRIUS	1058	8	9 vs 36	2003
E-SIRIUS	352	8	5.9 vs 42.3	2004
RESEARCH	508	12	3.7 vs 10.9	2004
DIABETES	ongoing			
3D	ongoing			
Paclitaxel				
TAXUS I	31	18	0 vs 10	2003
TAXUS II	538	6	2.3 vs 17.9 SR 4.7 vs 20.2 MR	2003
TAXUS IV	1314	9	7.9 vs 26.6	2004
ASEPCT	177	4–6	4 vs 27	2003
ELUTES	190	6	3.2 vs 20.6	2004
TAXUS III	28	Treating in-stent restenosis		2003

DES, drug-eluting stent.

Sirolimus-eluting stents

The most extensively studied drug for stent coating is sirolimus, also called rapamycin (Handa et al 1993), a natural fermentation product of *Streptomyces hygroscopicus* (Figure 5). In 1991, sirolimus was found to be an effective inhibitor of graft-vessel disease and accelerated arteriopathy (Meiser et al 1991). In later animal experiments, systemic administration of sirolimus inhibited not only the vascular response to injury caused by allograft rejection, but also the neointimal formation as a response to balloon catheter injury (Gregory et al 1993; Morris et al 1995). In animal and clinical studies, sirolimus was efficacious against in-stent neointimal formation after stent implantation (Burke et al 1999; Rensing et al 2001; Klugherz et al 2002; Morice et al 2002a). Its mechanism of action is via receptor inhibition of the mammalian target of rapamycin (mTOR), which controls protein synthesis through activation of the mitogen-stimulated serine/threonine kinase p70s6k and prevents down-regulation of cell cycle inhibitor p27KIP1, resulting in the cessation of cell-cycle progression in the late G_1 to S phases (Poon et al 2002). By this very same mechanism, which is commonly activated by multiple SMC growth factors (Table 1), the proliferation and migration of human SMC is inhibited by sirolimus (Marx et al 1995; Poon et al 1996, 2002; Marx & Marks 2001).

The first clinical study with sirolimus-eluting stents was reported in 2001 by Sousa and colleagues (Sousa et al 2001b), who treated 30 angina pectoris patients. No ISR and no MACE occurred within 8 months after stent implantation. The absence of ISR was maintained over 1 year, as demonstrated in another study involving 45 patients (Sousa et al 2001a), and up to 2 years in a

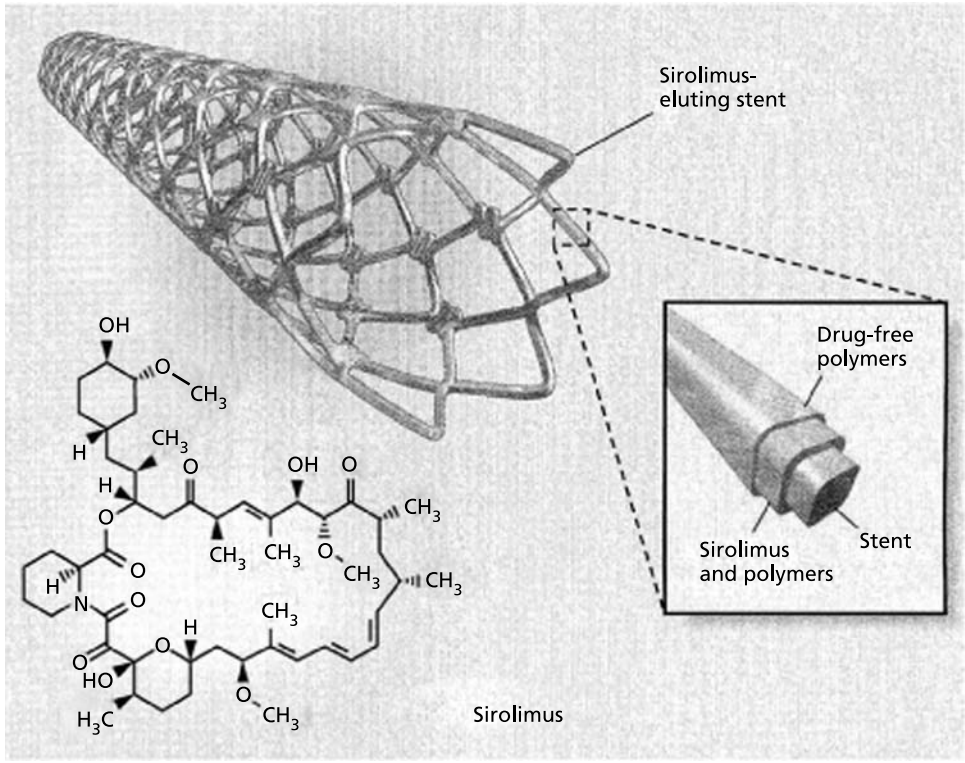

Figure 5 Sirolimus-eluting stent with the chemical structure of the drug molecule (Morice et al 2002b, with permission).

further study involving 15 patients (Degertekin et al 2002). In 2002, the results of the first randomized double-blind study with the sirolimus-eluting BX Velocity balloon-expandable stent (Cordis Corp.) in patients with de-novo native coronary lesions (RAVEL; Table 2) were published (Morice et al 2002a). This trial enrolled 238 patients, and none of the patients in the sirolimus stent group showed signs of restenosis at 6 months after intervention. It is worth noting that the control group, which had received the bare metal BX Velocity stent, exhibited after one year a MACE rate of 28.8%, which is remarkably higher than the 12–15% observed in other studies using conventional stents (Unverdorben et al 2003; Lemos et al 2004c). This difference in MACE in patients treated with BMS might be ascribed to the stent design, which is continuously improving (see above). In the RAVEL trial, only a relatively small number of patients with simple coronary artery lesions of less than 18 mm in length were enrolled. Another trial termed SIRIUS (SIRrolImUS-eluting BX Velocity balloon expandable stent trial) enrolled 1058 patients with more complex coronary diseases (i.e. longer lesions, smaller vessel diameters and patients suffering from diabetes (26%)); here, 9% in-segment restenosis (stent plus 5 mm proximal and distal borders) was noted in the sirolimus-eluting group as compared with 36% in the control group (Moses et al 2003), suggesting that restenosis after sirolimus-eluting stent implantation may be due to smaller vessel size, the higher percentage of diabetes patients or increased complexity of the lesions. Especially, restenosis at the proximal stent margin did not significantly differ between the sirolimus and control group (Aggarwal et al 2003). The SIRIUS results were further confirmed by the European (E)-SIRIUS trial (Schofer et al 2003). Because of the selection of patients in the randomised trials, experts have questioned whether the sirolimus-eluting devices are still effective in unrestricted patients. The latest results from the RESEARCH Registry (Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital) show that unbiased utilization of sirolimus-eluting stents in daily practice is safe and effective in reducing repeat revascularization and MACE during at least 1 year, as compared with bare stent implantation (Lemos et al 2004c). The registry enrolled 508 patients who received sirolimus-eluting stents and compared the outcome with data from 450 patients who had received BMS at a time before sirolimus-eluting stents came into use. At 1 year after implantation, clinical restenosis (i.e. need for revascularization in the target lesion, TLR) and MACE (combined TLR, death, myocardial infarction) occurred in, respectively, 3.7 and 9.7% of the sirolimus-eluting stent group and in, respectively, 10.9 and 14.8% of the BMS group. Since diabetes mellitus is an important risk factor for ISR, a randomized clinical trial with sirolimus-eluting stents to prevent restenosis in diabetic patients with de-novo coronary stenosis (DIABETES) is underway. The 3D (Diabetic Double Dose) Study is further assessing the effect of a higher sirolimus dose. These trials will demonstrate whether the sirolimus-eluting stent is effective in preventing restenosis in this group of high-risk patients. Sub-group analysis of SIRIUS trial data showed TLR was reduced in diabetic patients from 22.3% with BMS to 6.9% with Cypher stents at 270 days, and in non-diabetic patients from, respectively, 14.1 to 2.99%. Also MACE were reduced in diabetic patients from 25% with BMS to 9.2% with Cypher stents and from, respectively, 16.5 to 6.5% in non-diabetic patients. These results demonstrate remarkable benefits of Cypher stents in diabetic patients. However, a trend towards a higher rate of TLR and MACE still remains in this group of patients (Abizaid et al 2004a; Moussa et al 2004). Sub-group analysis of the multicentre RAVEL trial to examine the impact of the sirolimus-eluting stent on outcomes in diabetic patients (9 received sirolimus-eluting stents and 25 were treated with BMS) revealed, however, that patients treated with the sirolimus-eluting stent experienced a virtual abolition of neointimal proliferation and low event rates at long-term follow-up (Abizaid et al 2004a).

During the first nine months after marketing approval from the FDA (Food and Drug Administration of the USA), Cypher stent sales surpassed the expectations and were the key contributor to sales and net earnings growth of Cordis. At the end of the first quarter of 2004, some 600 000 patients around the world received a Cypher stent. Current studies are evaluating the benefit of the Cypher stent in preventing ISR (SISR, TROPICAL study) in patients with more complex lesions and using direct stenting without prior dilatation. In the ARTS II study, the benefit of the Cypher stent in patients with multivessel coronary disease amenable to stenting or CABG (Coronary Artery Bypass Graft) will be evaluated. Preliminary 1-month MACCE (Major Adverse Coronary and Cerebral Events) of the Cypher stented ARTS II population are as low as in the CABG-treated population of ARTS I. First (6 months) results of the TROPICAL study revealed a binary restenosis rate of 9.7% and a TLR of 2.5% (Johnson & Johnson 2004, http://www.jnj.com/news/jnj_news/20040525_134918.htm). Further, sub-group analysis of 459 patients with left anterior descending coronary artery (LAD) stenosis in the SIRIUS trial revealed that sirolimus-eluting stents significantly decreased revascularization rates in LAD lesions, as compared with BMS (i.e. after 1 year, revascularization rates were comparable with historic single vessel bypass surgery revascularization rates) (Sawhney et al 2004).

The remarkable anti-restenotic effect of sirolimus-eluting stents has attracted much interest to develop new or even better DES with sirolimus analogues, as outlined in the following.

Everolimus-eluting stents

Everolimus, a sirolimus analogue, was tested with a new stent type (Challenge stent) introduced by Biosensors International Inc., covered by a resorbable composite coating, that contains the immunosuppressive drug within a biodegradable poly(hydroxyacid) matrix. The FUTURE I + II feasibility trials revealed a 30-day MACE rate of 0%, as well as a restenosis rate of 0% at 6-month follow-up in a total of 32 patients. Based on these results, the FUTURE programme has now been expanded by Guidant with two large multicentre studies, FUTURE III and IV, which evaluate this stent design in a larger patient population. FUTURE IV should also prove the

non-inferiority of the everolimus-eluting challenge stent as compared with an approved DES (Cypher) (Grube & Buellesfeld 2004b).

Tacrolimus (FK506)-eluting stents

Tacrolimus is another structurally and functionally related analogue of sirolimus. It has been tested with two different stents, a Jomed stent and the Joflex stent, with the latter being coated with a nanoporous ceramic layer of aluminium oxide. However, the safety studies PRESENT I (low drug dose) and II (high drug dose), as well as EVIDENT (evaluating the stenting of bypasses), failed to prove clinical benefit. Whether tacrolimus proves to be beneficial will be further tested by the PRESET study, which applies the drug directly to the stent without any additional stent coating (Grube & Buellesfeld 2004a).

ABT-578-eluting stents

ABT-578 is a synthetic analogue of sirolimus, which was coated on the Driver stent. This new stent type has thinner struts, technically made feasible by the use of a stronger Co-Cr alloy, resulting in a lower profile and better deliverability in the vessel (Buellesfeld & Grube 2004). ENDEAVOR I is the first human trial, including 100 patients with native de-novo coronary lesions. The 4-month follow-up data demonstrated a MACE rate of 2.0%. A large multicentre trial, ENDEAVOR II, including a higher number of patients with more complex lesions, has been started. The US multicentre study ENDEAVOR III will provide head-to-head comparison between the ABT-578-eluting stent system and the sirolimus-eluting Cypher stent in 369 patients.

Paclitaxel-eluting stents

The second most extensively studied drug for stent coating is the anti-tumour agent paclitaxel, which inhibits cell proliferation and migration by disturbing cellular microtubule organisation. Whereas sirolimus has been clinically tested at a single dose only and with a single type of stent carrying a specific coating for controlled release, paclitaxel has been tested at various doses and with various stent types and release-controlling materials. Early studies showed promising results on restenosis inhibition in-vivo (Kolodgie et al 2002). Several clinical trials with paclitaxel-eluting stents are ongoing (Table 2). The first randomized, multicentre SCORE trial, using QuaDS stents coated with the paclitaxel derivative 7-hexanoyltaxol (QP2), enrolled 266 patients. At 6 months after intervention, the restenosis rate was low (6.4% vs 36.9% in the control group), but increased to 61.5% at 12 months (Virmani et al 2002). The trial had to be stopped due to important MACE at 30 days (10.2% vs 0% in the uncoated stent group). The atherectomy specimen analysis suggested that subacute and delayed stent thrombosis, which was possibly induced by excessive drug concentration, may have caused the increased incidence of MACE. The randomized TAXUS-I safety trial (BSC, NIRx, paclitaxel-coated) also demonstrated reduced restenotic lesions at 6 months (0% vs 10%); here, no thrombotic events were observed, presumably due to a lower drug dose. The positive effects persisted for up to 18 months, as reported from follow-up observations (Buellesfeld et al 2003). The TAXUS-II, -III and -IV trials have addressed further aspects of efficacy and safety of the TAXUS paclitaxel-eluting stent. TAXUS-II, a randomized double-blind trial with 536 patients, evaluated slow-release (SR) and moderate-release (MR) formulations of a polymer-based paclitaxel-eluting stent (TAXUS) for revascularization of single, primary lesions in native coronary arteries (Colombo et al 2003; Tanabe et al 2004). At 6 months, angiographic restenosis was reduced from 17.9 to 2.3% in the SR-cohort ($P < 0.0001$) and from 20.2 to 4.7% in the MR-cohort. The incidence of MACE at 12 months was also significantly lower in the TAXUS-SR (10.9%) and TAXUS-MR (9.9%) groups than in the controls (22.0 and 21.4%, respectively). The TAXUS-III trial was designed as a non-randomized trial enrolling 28 patients with ISR to evaluate the feasibility and safety of paclitaxel-eluting stent for treatment of ISR. The inclusion criteria were 30 mm lesion length, a stenosis amounting to 50–99% of vessel diameter and 3.0–3.5 mm vessel diameter. The patients were treated with one or more TAXUS NIRx SR paclitaxel-eluting stents. Stent implantation proved to be feasible and safe for the treatment of ISR (Tanabe et al 2003). No subacute thrombosis was observed, and angiographic restenosis occurred in 16% of the cases, mainly in the gap between two paclitaxel-eluting stents; the MACE rate was 29%. TAXUS-IV was a prospective, randomized, double-blind study involving 73 US medical centres and 1314 patients, who received a stent in a single, previously untreated coronary-artery stenosis (Stone et al 2004a). A total of 652 patients were randomly assigned to receive a BMS (EXPRESS) and 662 to receive an identically appearing, slow-release, polymer-based paclitaxel-eluting stent. The clinical and angiographic restenosis rates at 9 months were reduced from, respectively, 12.0 and 26.6% for the BMS-group to, respectively, 4.7 and 7.9% for the paclitaxel-eluting stent group. At 9 months, however, no differences were observed between the two groups in terms of death rates from cardiac causes or myocardial infarction (4.7 and 4.3%, respectively) and stent thrombosis (0.6 and 0.8%, respectively). Between 9 and 12 months, there were significantly fewer myocardial infarctions (0% vs 1.1%, $P = 0.007$), TVR (2.4% vs 5.8%, $P = 0.002$), and MACE (2.4% vs 6.3%, $P = 0.0009$) in the paclitaxel-eluting stent than in the control stent group. The authors concluded that the relative efficacy reported at 9 months for the polymer-based, paclitaxel-eluting TAXUS stent compared with the EXPRESS stent continued to increase at 1 year, with no evident safety problems (Stone et al 2004b). The consistent inhibition of restenosis by paclitaxel-eluting stents was further confirmed by the ASPECT and ELUTES trials (Table 2) (Hong et al 2003; Gershlick et al 2004). In the latter studies, no significant beneficial effect on 6-month MACE was observed. This may imply that the stents used in TAXUS-I, -II and -IV, where paclitaxel eluted from a polymer carrier, were superior to the stents without a polymeric paclitaxel release system, as used in the ASPECT and ELUTES trials (Silber 2003; Stone et al 2004b).

Other drug-eluting stents tested in clinical trials
In the following, we would like to highlight a number of animal and clinical studies on other selected drugs eluted from stents. In these studies, the stents have sometimes been combined with systemic or oral drug therapy. Most of the selected drugs have previously already been studied in systemic administration, an area which, per-se, is not covered in this review.

Heparin-eluting stents. Stents coated with heparin have originally been the most intensively tested devices in clinical settings. Although heparin per-se has shown strong anti-proliferative and anti-migratory action on SMC (Au et al 1993; Chajara & Capron 1993; Yang et al 1999) and despite initial encouraging results (Schmid et al 1993), multicentre clinical trials did not corroborate the anti-restenotic efficacy of systemically administered heparin (Brack et al 1995). Further studies showed that heparin-coated Jostent stents were not superior to uncoated premounted NIR stents (Medinol, Tel Aviv, Israel) with respect to initial efficacy, (sub)acute thrombosis, 6-month restenosis rates or 12-month clinical outcomes (Semiz et al 2003).

The negative results might be ascribed to different sensitivity of SMC to heparin (Herbert et al 1992; Geary et al 1995). It has been shown that venous and arterial SMC exhibited different heparin receptor density (Wilson et al 1994), although this latter finding is controversial (Varty et al 1994; Stohr et al 1995). Nonetheless, a reduced heparin sensitivity of SMC represents an increased atherosclerosis and restenosis risk (Chan et al 1993).

Corticosteroid-eluting stents. The anti-inflammatory dexamethasone significantly inhibited SMC proliferation both in-vitro and in-vivo (Voisard et al 1994). However, the high doses and long-term systemic administration necessary to prevent chronic-inflammatory processes associated with restenosis (Franklin & Faxon 1993) would likely cause unacceptable adverse effects. The results with various corticosteroid-eluting stents from animal experiments and clinical studies (STRIDE) are not too impressive (Muller et al 1994; De Scheerder et al 1996a; Lincoff et al 1997; Strecker et al 1998; Liu et al 2003). A pilot study with a highly dosed dexamethasone-eluting stent in 30 patients showed a restenosis rate of 31% at 6-month follow-up (Hoffmann et al 2004). Due to this pilot study, a large randomized study with dexamethasone-eluting stent (EMPEROR) was halted before patient inclusion.

Tranilast-eluting stents. Although tranilast showed an inhibitory effect on SMC proliferation, its oral administration or delivery from DES did not efficiently prevent restenosis (evaluated by angiography and intravascular ultrasound measurements) in a large clinical trial enrolling 11 484 patients (PRESTO) (Holmes et al 2002).

Cytotoxic and anti-cancer drugs. Antineoplastic and antimitogenic agents have been considered for prophylaxis and therapy of restenosis, because restenotic SMC exhibit mitotic rates similar to tumour cells (O'Brien et al 1993; Voisard et al 1993). SMC proliferation, controlled normally by the intact endothelium, is indeed inhibited quite effectively, in-vitro and in-vivo, by various antineoplastic and antimitogenic drugs (e.g. vincristine, cytarabine, doxorubicin (Voisard et al 1993) and colchicine (O'Keefe et al 1992)). When colchicine was encapsulated into nanospheres and tested for local delivery, neointimal proliferation was inhibited successfully in rats, but not in rabbits (Dev et al 1997; Mishaly et al 1997). So far, only colchicine has been tested clinically, possibly because of an unfavourable benefit-to-risk ratio of the other compounds upon systemic administration. A safer application causing fewer side effects (e.g., by using a localized delivery system) would be required for these compounds to enter clinical testing. However, the interruption of a recent clinical trial with an actinomycin D-eluting stent due to a high incidence of repeat revascularization in the treated vessels, possibly related to the drug's toxicity, raises great concern about the utilization of this class of drugs for future development of drug-eluting stents.

Tyrosine kinase inhibitors. Many growth factors such as platelet-derived growth factor (PDGF) and fibroblast growth factor (FGF) stimulate SMC proliferation by activation of the tyrosine kinases receptors. A study using a biodegradable stent made of poly(L-lactic acid) and coated with the tyrosine kinase inhibitor ST638 showed a significant inhibition of coronary artery restenosis in pigs (Yamawaki et al 1998). Tyrphostins are low-molecular-weight inhibitors of protein tyrosine kinases; a representative named AG-1295 was assessed for the anti-proliferative effects on SMC-proliferation in animal models. When embedded in biodegradable nanospheres and delivered locally, AG-1295 showed neointima-inhibiting potency after endothelial balloon denudation (without stent implantation) (Banai et al 1998). Local sustained delivery of AG-1295 from perivascularly implanted polymeric matrices resulted in a 35% reduction of neointimal formation on day 14 after balloon injury in the rat carotid model (Fishbein et al 2000). Recently, oral administration of the PDGF receptor tyrosine kinase inhibitor TKI963 also reduced stent-induced restenosis in the pig model, suggesting the possible clinical application of this drug in restenosis prevention (Bilder et al 2003).

Estrogen-eluting stents. Estrogen has been shown to reduce SMC proliferation and stimulate endothelial regeneration after angioplasty (Dai-Do et al 1996; Geraldes et al 2002), suggesting that estrogen may prevent ISR and delay the risk of late stent thrombosis. In a porcine ISR model, 17-β-estradiol-eluting stents were associated with reduced neointimal formation without affecting endothelial regeneration (New et al 2002). A human study (EASTER trial) with an estrogen-eluting stent is ongoing and the first data has shown low rates of restenosis and revascularization at 1 year follow-up in 30 patients (Abizaid et al 2004b). The anti-restenotic effect of estradiol warrants further investigation with a large randomized multicentre trial.

Anti-thrombotic and other bioactive agents. Nitric oxide (NO) is an important endothelium-derived vascular protective factor. NO not only reduces platelet aggregation, leucocyte adhesion and in-vitro SMC proliferation, but also affords a sustained vasorelaxation (Tarry & Makhoul 1994), suggesting the potential of NO-releasing agents in restenosis prevention. The NO-precursor L-arginine and NO-producing drugs (e.g., molsidomine) have been tested for anti-restenotic activity. Results from animal experiments are so far inconsistent (McNamara et al 1993; Watkins et al 1993; Davies et al 1994; Kalinowski et al 2001; Rolland et al 2002), and clinical studies with molsidomine produced contradictory data (Zimmer 1994; Lablanche et al 1997). Use of NO-eluting polymer-coated coronary stents, however, did not prevent restenosis in a pig model (Buergler et al 2000; Yoon et al 2002). This was attributed to inflammatory responses caused by the polymer in the coated stents. In sheep and pig restenosis models, neointima formation after experimental coronary artery stenting was inhibited with a biodegradable stent coated with anti-thrombotic recombinant pegylated (r-PEG)-hirudin and with the prostacyclin analogue iloprost (Alt et al 2000). For the latter, no clinical data on restenosis is available so far; the pilot study was stopped due to a lack of stents (Hofma et al 2001).

Angiopeptin. Angiopeptin released from stents or administered subcutaneously in a continuous regime produced beneficial anti-restenotic effects in animal models (De Scheerder et al 1996b; Hong et al 1997), which, however, could not be confirmed in a pig model and in man (Emanuelsson et al 1995; Eriksen et al 1995; Armstrong et al 2002). The negative results might be due to the fact that angiopeptin, as well as its analogues octreotide and lanreotide, inhibit effectively only SMC proliferation, but not cell migration. In addition, angiopeptin only reduced the PDGF-stimulated, but not the insulin-like growth factor (IGF) I- or b-FGF-stimulated proliferation of human SMC (Grant et al 1994; Howell et al 1994; Sakamoto et al 1998; Aavik et al 2002).

Other approaches. Inhibition of SMC proliferation has also been approached by coating stents with an antisense oligonucleotide against the proto-oncogene c-MYC, an important transcription factor for SMC proliferation, or by inhibiting SMC migration by means of the matrix metalloproteinase (MMP) inhibitor batimastat (BRILLIANT I trial). Thus far, these studies have not shown anti-restenotic effects in man (Kutryk et al 2002; Wood 2002).

Radiation therapy — catheter based or combined with stents

Besides drug-eluting stents, radiation therapy, also called brachytherapy, is the second approach showing some success in restenosis inhibition, especially in treating ISR. Radiation of cells results in DNA damage leading to cell death during cell division. For radiation therapy, special catheters for local irradiation are used. Alternatively, stents coated with radioactive compounds are implanted. When such coated stents were tested in more than 400 patients, overall restenosis rate was not reduced. This was ascribed to the so-called edge effect or candy-wrapper effect (Serruys & Kay 2000). The edge effect is caused by the lower radioactive dose at the stent endings, where SMC have been damaged through PTCA and thereby stimulated. Consequently, the low radioactive dose enhances SMC proliferation in the vessel wall adjacent to the stent and eventually leads to a slowly developing new stenosis that annuls the potential benefit of the treatment. These newly developing stenoses do not manifest after implantation of conventional stents or after conventional PCI. Self-expandable radioactive stents, which are not placed by an expanded balloon causing the additional injury of the vessel wall, showed a much more favourable outcome. Thus, the implantation of non-self-expanding radioactive stents with the usual procedure is not recommended for restenosis prevention (Hehrlein 2002).

In catheter-based brachytherapy, variable doses of γ-rays were applied in earlier studies, while low doses of β-rays are increasingly used to limit generalized radioactive exposure (Verin et al 1995; Waksman et al 1995) and because of handling convenience (Silber 2002a). Radiation therapy was successful in small animal and human studies (Bottcher 1994; Liermann et al 1994). A recent review summarizes the outcome of 41 brachytherapy studies enrolling a total of 4975 test and 1717 control patients (Silber 2002a). It was concluded that late stent thrombosis (4–15% in older trials) can be prevented by co-administration of clopidogrel and acetylsalicylic acid over 1 year, and that the edge effect can be avoided by a more precise radiation practice and the use of longer radiation sources to ascertain adequate irradiation of the entire PCI-damaged segment. Under such precautions, brachytherapy after PCI has been considered to be an effective therapeutic option for preventing ISR, which has until recently been the only evidence-based interventional therapy that had received both CE (Conformité Européenne) certification and FDA approval (Garas et al 2001; Ajani & Waksman 2002; Silber 2002a). Despite this success of brachytherapy, it remains unclear whether this treatment only delays or prevents (in-stent) restenosis and whether the sometimes-observed necrotic areas containing prothrombotic material, so-called black holes, will cause late problems (Lowe et al 2002; Virmani et al 2002). Nevertheless, with the advance of DES and the decreasing need to treat ISR, the number of centres still offering brachytherapy is decreasing. Moreover, a recent non-randomized clinical study demonstrated that sirolimus-eluting stent is as effective as vascular brachytherapy in treatment of ISR with a higher mortality rate in the brachytherapy group (7%) as compared with the sirolimus-eluting group (0%) (Saia et al 2004). Brachytherapy has also been reported to cause exercise-induced vasoconstriction in the proximal and distal vessel segments adjacent to implanted stents (Togni et al 2004). These results

may favour the use of DES rather than brachytherapy for treatment of ISR.

Major clinical concerns in early DES era and perspectives

The mid-term clinical results with sirolimus- and paclitaxel-eluting stents are very promising, as only up to 9% restenosis rates remain within one to two years. Despite the great success of the FDA-approved and CE-certified Cypher stent, some obstacles remain to be solved. Firstly, with the current DES, neointima-formation-related TLR is not completely abolished. Restenosis after DES implantation, so-called post-DES restenosis, remains a target for treatment. In the case of sirolimus-eluting stent treatment, up to 5% of the patients require repeated revascularization. In these patients, the overall recurrent restenosis rate was 42.9%. Although the recurrent restenosis rate of originally de-novo lesions, re-treated with DES, including sirolimus- and paclitaxel-eluting stents, is reasonably low, it still occurs at 18.2%, indicating that no optimal treatment for post-DES-restenosis is available (Lemos et al 2004a). Secondly, DES does not appear to remedy the problem of proximal stenosis at the target lesion so that the restenosis number is expected to increase with longer observation times and when higher percentages of patients with high risk factors such as diabetes are included (Liistro et al 2002; Virmani et al 2002). Thirdly, drug resistance to sirolimus and paclitaxel has been observed from studies in other areas (Huang & Houghton 2001; Yusuf et al 2003), but may also occur in the field of restenosis prevention. Fourthly, the FDA recently issued a warning of sub-acute thrombosis and hypersensitivity reactions to sirolimus-eluting stents and a report of aneurismal dilatation of the stented segment was published (Virmani et al 2004). With our steadily improving understanding of the mechanisms of restenosis and SMC proliferation and migration, new therapeutics with high potency and less toxic effects may be evaluated and included in new DES to overcome these remaining problems, which should also improve the cost-effectiveness of the currently available DES on the market.

In the present DES era, we may reconsider some of those drugs that had in the past been proven to be effective in inhibiting SMC proliferation and migration, but remained often inefficient upon systemic administration in clinical settings. It might be worthwhile to re-evaluate some of these drugs in combination with DES. Among these drugs, the statins would be our favourites for coating on DES. Statins, which are HMG-CoA reductase inhibitors and lower blood cholesterol, exert direct anti-proliferative activity on SMC both in-vitro and in-vivo, resulting in lower intimal thickening in arteriosclerosis models (Soma et al 1993; Corsini et al 1994; Munro et al 1994; Yang et al 2000). In clinical trials with PTCA-treated patients, orally administered statins prevented variably the occurrence of restenosis (Onaka et al 1994; Weintraub et al 1994; Mulder et al 2000). On the contrary, a recent clinical study showed significant reduction of restenosis in patients treated with stenting (Walter et al 2001), suggesting the possible application of statins for stent coating. Nowadays, statins are increasingly given orally to PCI patients, because they lower the overall (late) MACE rate (Unverdorben et al 2003) and exert a beneficial effect on further CAD progression.

Gene therapeutic approaches

Gene therapeutic approaches for restenosis prevention are at the early investigational stage. Major issues of these approaches relate to the selection of the correct gene, of an optimal vector and of an adequate administration procedure. Since NO is an important vascular protective factor, which causes vasodilatation, prevents SMC proliferation and blood clotting and acts as a scavenger of free radicals, the effects of NOS gene transfer on restenosis have been studied in various animal models. Gene transfer of endothelial nitric oxide synthase (eNOS) or inducible NOS (iNOS) has produced promising results in animal models of vascular injury. In Goettingen minipigs, liposome-based gene transfer of iNOS inhibited stent-induced neointimal formation in femoral and coronary arteries (Muhs et al 2003). These findings may have an important impact on the future implementation of NOS-based gene therapy in clinical practice. The first clinical trial (PREVENT I, a prospective, randomized, controlled trial) using genetic engineering techniques to inhibit cell-cycle activation in coronary venous bypass grafts with E2F decoy oligonucleotides was performed in high-risk patients with peripheral arterial occlusion (Mann et al 1999). The data demonstrated the safety and biologic efficacy of intraoperative gene transfection of human bypass vein grafts. The unpublished results of the randomized, double-blind, placebo-controlled PREVENT II trial confirmed the safety and feasibility of using this product and demonstrated increased patency and positive vascular remodelling (inhibition of neointimal size and volume) in the treated group at 12 months. Follow-up examination revealed an average of 40% reduction in critical stenosis (Dzau 2003). Yet another one-step gene therapeutic method used an angiogenic plasmid encoding the gene of the vascular endothelium growth factor (VEGF) (Losordo et al 2002). Upon localized delivery, this treatment was successful in a phase-I/II clinical trial to enhance myocardial perfusion through angiogenesis. However, this avenue to induce neovascularization may be delicate (Isner 1999, 2001; Moulton et al 1999; Celletti et al 2001a, b, 2002; Dake 2001; Ware 2001). Indeed, intimal neovascularization in the apolipoprotein-E-deficient mice model of atherosclerosis caused plaque growth, hence stenosis and possibly restenosis. Administration of VEGF enhanced plaque growth in two different animal models of arteriosclerosis, which questions the appropriateness of VEGF gene therapy. So, therapeutic angiogenesis is a complex problem that requires a sophisticated approach (Webster 2003). A biased mini-review on cardiovascular gene therapy (Kibbe et al 2000) highlighted only the successful studies, but masked out the drawbacks. Recently, AVI BioPharma reported a successful phase-II study of intramural delivery via a catheter of Resten-NG — a c-myc gene antisense drug; here angiographic restenosis was reduced from 33.3 to 8.3% following

angioplasty with stent placement. The initiation of a phase-III trial is planned, but with a stent as delivery platform of the antisense drug.

Conclusion

With the mid-term clinical success of sirolimus- and paclitaxel-eluting stents, utilization of DES became daily practice. The, thus far, promising clinical results will be further confirmed with the high number of implanted DES in daily practice and in larger clinical studies with longer follow-up periods, particularly in high-risk patients (complicated lesions, diabetics). Some remaining clinical situations in the DES era as discussed above, such as post-DES restenosis, subacute or late-stent thrombosis with hyperreactivity of the blood vessel wall occurring in certain patients, warrant further investigation. Unfortunately, DES implantation does presently not seem to lower interventional costs, as for routine DES implantation, additional DES material costs of €50 000–80 000 per each prevented re-intervention will occur (approx. 2 stents/patient, 5–7% re-intervention reduction, additional €2000 /stent) (Lemos et al 2004b, c). So, at present, it might be advisable to treat only those patients with DES who are at high risk of developing a restenosis (e.g., small vessel diameter, diabetes, complicated and long lesions) or who are principally candidates for CABG, but may become treatable by PCI combined with restenosis-preventing DES; low risk patients should be treated with BMS or without stent. If DES were implanted in 90% of the presently conducted PCI, total stent costs would amount to €500 million per year in Germany alone. For comparison, in 2001, the total costs for implanted metal stents amounted to €62 million; estimated material costs for brachytherapy of ISR would only add another €62 million (Silber 2002b). Nonetheless, we may expect that increased competition between several marketed DES will substantially decrease their costs. For some seminal stent coatings (everolimus, ABT-578 analogue of sirolimus, tacrolimus), large clinical studies are currently being conducted in a size sufficient to gain FDA approval. The new DES, if proven to be as successful as the sirolimus- or paclitaxel-eluting stents, will surely decrease the costs. Brachytherapy, on the other hand, may be limited to certain groups of patients or disease states (Kuchulakanti & Waksman 2003), or even fade away from clinical practice. Gene therapeutic approach is still at its premature stage, much effort on the bench-side should be made before it is translated to the bed-side. For the non-initiated readers who would like to follow the developments in the field, we recommend consulting various internet sites (http://www.theheart.org/; www.americanheart.org/; www.ptca.org/; www.ehendrick.org/heart/restenosis.htm; mivtherapeutics.com/education/restenosis/).

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