Innovative therapies for optimizing outcomes of coronary artery disease

Ahmed, T.A.H.N.

Chapter 6

Restenosis after PCI. Part 2: prevention and therapy

J. Wouter Jukema[1], Tarek A. N. Ahmed[1], Jeffrey J. W. Verschuren[1] and Paul H. A. Quax[2]

[1]Department of Cardiology,Leiden University Medical Center, Leiden, The Netherlands.

[2]Department of Vascular Surgery, Leiden University Medical Center, Leiden, The Netherlands.

Nat Rev Cardiol 2011 Oct 11 [Epub ahead of print]

ABSTRACT

The techniques and materials used during percutaneous coronary intervention have advanced considerably over the past 3 decades, yet restenosis remains one of the major drawbacks of this procedure. Many innovative technologies, including drug-eluting stents, with or without specific polymers, and fully biodegradable stents have been and continue to be developed in the search for a safe and effective antirestenosis therapy. Remarkable advances in stent design and nanoparticle delivery systems ('nanovehicles') have already fueled revolutionary changes in the prevention and treatment of in-stent restenosis. In this Review we provide an overview of the latest innovations for optimizing outcomes of coronary stenting, and up-to-date information about prevention and treatment of in-stent restenosis.

KEY POINTS

- Although drug-eluting stents decrease the incidence of restenosis, they do not yet fully prevent this problem; furthermore, long-term safety issues indicate that new technologies are still warranted
- New-generation polymer coatings, including biocompatible permanent polymers and biodegradable polymers, and stents without a polymer, represent innovative technologies that aim to preserve vascular biology in the long-term
- Biodegradable stents prevent the long-term problems associated with foreign material in the coronary arteries; the first human studies employing these stents show promising results
- Nanoparticle-mediated drug delivery systems are expected to revolutionize the development of innovative therapeutic devices, allowing local or targeted delivery of the drug with an excellent biocompatibility profile
- Drug-eluting balloons provide homogenous drug distribution in the vascular wall and represent a favorable option for the treatment of restenosis
- Gene-eluting stents are expected to play an important role in the prevention of in-stent restenosis, particularly in patients with a high genetic-risk profile

INTRODUCTION

Since its introduction in the late 1970s,[1] percutaneous coronary intervention (PCI) has become the most important and widely used treatment for patients with obstructive coronary disease. Although the technique and the materials used during the procedure have advanced tremendously, restenosis—the renarrowing of the treated obstruction—remains one of the major complications of PCI.[2] Intravascular stents were developed as an adjunct to primary angioplasty for the management of early complications, including arterial dissection, and for the treatment for early elastic recoil. Despite the beneficial effects of stenting, however, rates of restenosis remained persistently high, giving rise to a new problem—in-stent restenosis (ISR). The introduction of drug-eluting stents (DESs) was seen as a solution to this problem and, initially, DESs reduced the incidence of ISR considerably.[3] However, these promising results led to increased use of DESs in a diverse range of complex coronary lesions, and for off-label indications, leading to a resurge in the rates of ISR.[4,5]

In light of the increasing number of PCI procedures being performed, the difficulty of treating ISR, and the increasing cost of adjuvant medication and devices, defining subsets of patients at increased risk for restenosis would be useful. These patients could benefit from additional treatment modalities. Until now, identification of subgroups has been only partially successful, as was discussed in detail in Part 1 of this Review.[6] The ongoing efforts to better understand the underlying pathophysiological mechanisms of restenosis and vascular biology continuously fuel research on the prevention and treatment of ISR. Here, in Part 2 of the Review, we will assess the most important innovations for optimizing the outcomes of coronary stenting, and data on the prevention and treatment of restenosis in general, and ISR in particular, published in the 5-year period up to August 2011.

PREVENTION OF RESTENOSIS

In general, PCI with DESs is currently the best approach for the prevention of restenosis.[7] However, safety concerns about stent malapposition, late stent thrombosis, and delayed restenosis have arisen.[8,9] The main cause of these problems has, in addition to patient-related and lesion-related factors, been attributed to the stent polymer.[10] Additionally, the eluted antiproliferative agent and the stent platform (metal alloys and strut thickness) have been implicated in ISR. These concerns have fueled research in stent development, utilizing new antiproliferative agents, polymer technology, and metal stent platforms (Table 1).

Antiproliferative agents

Sirolimus (rapamycin)-eluting stents (SESs; Cypher®, Cordis Corporation, Bridgewater, NJ, USA) and paclitaxel-eluting stents (PESs; Taxus®, Boston Scientific, Maple Grove, MN, USA),

Table 1: Developments in preventive measures for restenosis

Target	Development	Status
Antiproliferative drug	Sirolimus derivatives (biolimus A9[18,19,22] and novolimus[23])	Clinical*
Polymer	Biolinx® (Medtronic Vascular, Inc., Santa Rosa, CA, USA)[25,26]	Clinical*; preliminary‡
Polymer	PolyzeneF[27–29]	Clinical*; preliminary‡
Polymer	Biodegradable (polylactic acid, polylactic-co-glycolic acid,[30–32] SynBiosys® [InnoCore Technologies, Groningen, the Netherlands], Eureka® SOLO [Surmodics, Inc., Eden Prairie, MN, USA])[37]	Clinical*
Stent design	Polymer-free stent (Biofreedom®, Biosensors International Group, Hamilton, Bermuda)[41,42]	Clinical*; preliminary‡
Coating	Endothelial progenitor cell capturing stent (Genous®,[48–50,56] Combo Stent®[38,53] [OrbusNeich Medical, Inc., Fort Lauderdale, FL, USA])	Clinical*
Coating	Titanium-nitride-oxide-coated stents (Titan2™ stent [Hexacath, Rueil-Malmaison, France])[55–61]	Clinical*
Stent platform	Bioabsorbable stent (magnesium stent [Biotronik, Berlin, Germany])[71–76]	Clinical*
Drug delivery	Nanomedicine[79,80]	Preclinical§
Stent platform/ metal alloys	Platinum–chromium alloy stents (Promus Element® and Taxus Element® (Boston Scientific, Maple Grove, MN, USA)[66–69]	Clinical*
Drug delivery	Magnetic targeting stents[81]	Preclinical§
Miscellaneous	Gene-based therapy[82–90]	Preclinical§
Miscellaneous	Systemic treatment[91,93,95–97,99–101,104,105]	Clinical*

*Clinical: development is currently being tested in a clinical setting. ‡Preliminary: first clinical results in small studies await replication in larger trials. §Preclinical: development is currently being tested in animal models

which were approved by the FDA in 2003 and 2004, respectively, were the first two DESs that were approved for use in humans. Although they both effectively reduce rates of restenosis compared with bare-metal stents (BMSs), their local adverse effects on the vasculature are fairly divergent. High concentrations of locally released paclitaxel have been shown to have detrimental effects on the vascular wall in a mouse model,[11] suggesting a narrower therapeutic range of this potent drug. On the other hand, sirolimus has a less-harmful effect than paclitaxel on the vascular wall.[11] Data from comparisons of first-generation DESs show that PESs are associated with a higher risk of ISR and stent thrombosis than SESs.[7,12] Two stents eluting sirolimus analogs—everolimus (Xience V®, Abbott Cardiovascular Systems, Inc., Santa Clara, CA, USA) and zotarolimus (Endeavor®, Medtronic Vascular, Inc., Santa Rosa, CA, USA)—have also been approved by the FDA.

Many studies have been dedicated to comparing the various available DESs. In 2011, the 2year follow-up results of two large-scale, randomized, controlled trials showed a sustained

benefit of everolimus-eluting stents (EESs) over PESs in terms of safety and efficacy.[13,14] On the other hand, zotarolimus-eluting stents (ZESs) were found to have a higher angiographic restenosis rate compared with PESs, although clinically driven repeat revascularization rates were similar for both stent types.[15] In patients receiving routine clinical care, SESs have proven to be superior to ZESs.[16] The 2year outcomes of the RESOLUTE All Comers trial[17] showed sustained similar safety and efficacy between ZESs and EESs. Unfortunately, few data are available on the direct EES versus SES comparison. Therefore, sirolimus and its analogs seem to be marginally superior to paclitaxel, whereas differences between the various limus-eluting stents remain to be elucidated.

In search for greater antirestenotic efficacy and improved long-term safety, new compounds specifically designed for use with DESs are being developed and studied. Biolimus A9 is a novel rapamycin derivative that, like sirolimus, inhibits smooth muscle cell proliferation via binding to the FK506-binding protein 1A and subsequent inhibition of the mammalian target of rapamycin (mTOR) and is specifically developed for local delivery to coronary arteries (Figure 1).[18] Besides its anti-inflammatory and antiproliferative potential and improved pharmacokinetic profile, the increased lipophilicity of biolimus A9 improves uptake by the coronary vessel wall, resulting in a more localized effect and lower systemic drug exposure[19] than sirolimus eluted from the Cypher® stent.[20,21] Compared with first-generation DESs, biolimus A9-eluting stents (BESs) have been shown to be associated with better recovery of endothelial function in coronary arteries, which could be partly explained by the better drug release kinetics.[22]

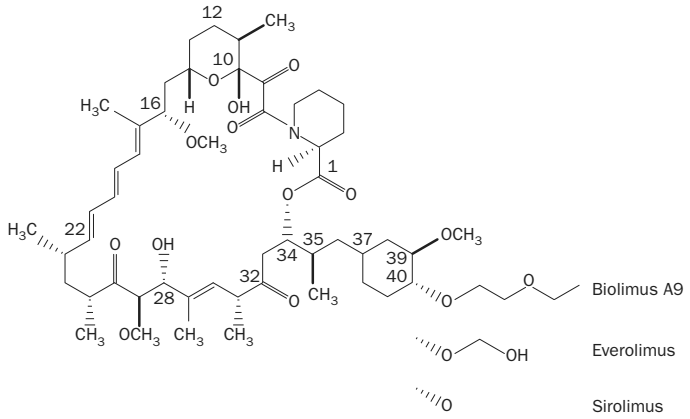

Figure 1: Chemical structure of biolimus A9. This compound consists of a 31-membered triene macrolide lactone that preserves the core sirolimus ring structure with a 2ethoxyethyl group addition to the hydroxyl group at position C (40) of the sirolimus molecule. One rationale for the inclusion of the ethoxyethyl group was to increase lipophilicity and, thus, to improve uptake by the coronary vessel wall. Permission obtained from John Wiley and Sons © Ostojic, M. *et al. Catheter. Cardiovasc. Interv.* **72**, 901–908 (2008).

Novolimus is a metabolite of sirolimus and represents another new antiproliferative mTOR inhibitor specifically developed for the stent. The newly developed DESyne® (Elixir Medical, Sunnyvale, CA, USA) novolimus-eluting stent has been tested in a clinical study, showing superiority over ZESs regarding angiographic in-stent late loss.[23]

Polymer technology

New-generation polymer coatings have been produced with the specific aim of mimicking the endothelial lining in order to prevent late thrombotic complications. Basic research has shown that some polymeric materials could potentially upregulate genes related to inflammation, proliferation, thrombosis, and vasoconstriction[24]—processes that are considered to be pivotal in the development of restenosis.[6]

One example of current progress is the Biolinx® (Medtronic Vascular, Inc.) polymer, currently used in the Endeavor Resolute® ZES. This blend of three different polymers—the hydrophobic C10 polymer to control drug release, the biocompatible and hydrophilic C19 polymer, and polyvinyl pyrrolidone—allows an early burst followed by controlled drug release[25] so that at least 85% of the zotarolimus is released within 60 days and the remainder within 180 days, avoiding long-term release of the drug. Such release patterns are designed to match the delayed healing times seen in complex lesions. The Resolute® ZES was shown to significantly lower target lesion revascularization (TLR) compared with an earlier Endeavor® ZES, which utilized a phosphorylcholine coating.[26]

Another polymer, polyzeneF is highly biocompatible and has anti-inflammatory, bacteria-resistant, and prohealing qualities. The coating ensures that the stent has a very low surface thrombogenicity, potentially reducing the risk of stent thrombosis. Evaluation of cobalt chromium stents nanocoated with polyzeneF in an animal model yielded favorable results.[27] Preliminary studies evaluating the Catania™ (CeloNova Biosciences, Newnan, GA, USA) stent in humans demonstrated a good safety profile and high-level efficacy.[28,29] Efforts to improve polymer stent coatings are ongoing.

Biodegradable polymers

Given the issues of polymer-induced inflammation, thrombosis, and restenosis, the development of biodegradable polymers has become a focus for research. The most-studied biodegradable polymers are polylactic acid and polylactic-co-glycolic acid, which degrade over time and could, therefore, eliminate the problems associated with lack of polymer biocompatibility and polymer-induced inflammation. To date, several biodegradable polymer stents eluting biolimus A9, sirolimus, or paclitaxel have been clinically evaluated, which have so far proven to be effective and safe in the short term (≤30 days) and midterm (≤1 year).[30–32] In 2010, the 3year follow-up data from the LEADERS trial[33] was presented, showing the sustained benefit of BESs with a biodegradable polymer over SESs with a durable polymer. Great expectations exist within the cardiology community that biodegradable-polymer DESs

could become the stents of choice in years to come; the results of the ongoing ISAR-TEST6 trial,[34] testing the safety and efficacy of the Nobori® (Terumo Corporation, Tokyo, Japan) biodegradable polymer BES and the Xience V® permanent polymer ZES will, therefore, be eagerly awaited.

New polymer technology presents some challenges, such as establishing the optimal degradation time, biocompatibility, composition, and formulation of the polymer. Several factors influence the velocity of degradation; therefore, the balance between drug-release kinetics and the rate of polymer degradation, as well as the effects of the degradation products all affect the efficacy of biodegradable polymer stent systems in the coronary vasculature.[35] Furthermore, studies in porcine coronary arteries have shown that even biodegradable polymers can cause inflammatory reactions, which could be attributable to the combination of the parent polymer compound and the biodegradation products.[36] Two new biodegradable polymers (SynBiosys® [InnoCore Technologies, Groningen, the Netherlands] and Eureka® SOLO [SurModics, Inc., Eden Prairie, MN, USA) have been tested in animal studies and yielded fewer acidic byproducts, and had a better degradation rate and biocompatibility profile than polylactic acid and polylactic-co-glycolic acid making them well-tolerated *in vivo*.[37] In a pig model, stainless-steel R Stents® (OrbusNeich Medical, Inc., Fort Lauderdale, FL, USA) with SynBiosys® coating and high-dose sirolimus (5 µg/mm) was associated with the lowest amount of neointima thickness after 28 days when compared with Xience V® and Cypher® stents.[38]

Polymer-free stents

In an attempt to overcome the problems encountered with polymers or their degradation products, 'polymer-free' DESs have been developed and have proven to be safe in clinical studies.[39,40] In an animal study, polymer-free biolimus A9 coated stents (Biofreedom®, Biosensors International Group, Hamilton, Bermuda) demonstrated more sustained intima inhibition, improved healing, and reduced inflammation compared with the polymer-coated sirolimus eluting Cypher® stent at 180-day follow-up.[41] The ongoing first-in-man study of the Biofreedom® stent showed promising results compared with the Taxus® PES.[42]

Polymer-free, dual DESs have been tested over the past few years. No apparent benefit was observed by adding estradiol to a polymer-free SES in the ISAR-PEACE trial.[43] However, results from the ISAR-TEST2 study[44] revealed that a novel, polymer-free sirolimus-eluting and probucol-eluting dual DES was noninferior to the Cypher® SES and the Endeavor® ZES. The antirestenotic efficacy of both the dual DES and the ZES remained durable during the 2year follow-up period.[44] The larger ISAR-TEST5 study,[45] which was powered for clinical events, showed similarly durable results for the dual DES.

Novel prohealing stent coatings

Endothelial progenitor cell-capturing stent

An increased rate of endothelialization is thought to lead to reductions in restenosis and stent thrombosis.[46] This hypothesis underlies the development of the endothelial progenitor cell (EPC)-capturing stent. The bioengineered Genous® (OrbusNeich Medical, Inc.) EPC-capturing stent has a stainless-steel platform that is coated with an abluminal polysaccharide matrix and covalently coupled monoclonal murine antihuman CD34 antibodies. These antibodies bind bone-marrow-derived EPCs from the peripheral blood. These EPCs are hypothesized to differentiate into a functional endothelial layer after immobilization and populate the surface of the stent.[47] The safety and efficacy of the Genous® stent have been shown in preliminary human studies,[48,49] and further evaluation and comparison with other stents is currently ongoing.[50]

Despite its benefit in enhancing re-endothelialization, and thereby possibly preventing stent thrombosis, EPC capturing is not expected to potently inhibit neointimal proliferation. On the contrary, CD34 antibodies have even been shown to capture other progenitor cells, for example, smooth muscle cell progenitor cells, which could exaggerate restenosis.[51] Therefore, a major challenge in the development of an EPC-capturing DES is to maintain sustained inhibition of smooth muscle cell proliferation while promoting formation of a functional endothelial layer. This concept was tested in an animal study showing that immobilization of anti-CD34 antibody on SESs enhances endothelialization.[52] The REMEDEE study[38,53] investigators are currently testing the Combo Stent® (OrbusNeich Medical, Inc.), which incorporates low-dose abluminal sirolimus together with EPC-capturing technology and a biodegradable polymer. The combination of an EPC-capturing stent with a drug-eluting balloon is also an attractive alternative, as has been shown by the results of the PERFECT STENT study.[54]

Titanium-nitride-oxide-coated stent

The Titan2™ stent (Hexacath, Rueil-Malmaison, France) is a stainless-steel stent coated in titanium-nitride oxide that has been shown to inhibit platelet aggregation, minimize fibrin deposition, reduce inflammation, and promote healing.[55] This stent significantly reduced late lumen loss and TLR compared with a BMS at 6months follow-up,[56] with preserved benefits up to 5years.[57] Additionally, the Titan2™ stent demonstrated favorable results compared with the Taxus® PES in a randomized controlled trial of 425 patients with STsegment elevation myocardial infarction,[58] as well as in routine clinical practice.[59] Despite the absence of an antiproliferative drug, use of the Titan2™ stent resulted in less TLR than the Taxus® stent, although this reduction was not statistically significant.[58] The Titan2™ stent was noninferior to the Xience V® EES in the primary results of the large randomized controlled BASE-ACS trial[60] conducted in patients with acute coronary syndrome. However, the Titan2™ stent failed to prove noninferiority to the Endeavor® ZES in terms of angiographic in-stent late lumen

loss at 6 months in the TIDE study,[61] although clinical outcomes at 1 year were comparable for both stent types.

Future prohealing stent designs

A step further to optimize the prohealing stent design is to create a bioactive stent that also elutes a drug (a bioeluting stent). Animal studies of a newly designed titanium-nitride-oxide stent eluting L-arginine, a precursor of nitric oxide with positive effects on endothelium function,[62] or a sulfated polysaccharide extracted from seaweed have shown up to 50% reduction in late lumen loss compared with the standard titanium-nitride-oxide stent.[63] A future clinical trial (the VINCI first-in-man study) is planned to test the efficacy and safety of this new generation of stents.[63]

Another approach to creating a prohealing stent would be to reduce the binding of platelets to an implanted stent, thereby reducing the inflammatory response and allowing surrounding endothelial cells to properly re-endothelialize the stent.[64] A stent created from a bioactive ligand, such as an integrin-binding motif, has been successfully used in noncardiac applications *in vivo* to promote device integration.[65] The ideal ligand should only interact with integrins uniquely present on endothelial cells and not on platelets, inflammatory cells, or smooth muscle cells.[64] Continued *in vitro* and *in vivo* studies with such biomaterials could lead to the creation of next-generation prohealing stent surfaces that promote the endothelialization of the stent while simultaneously inhibiting the adhesion and thrombus formation, and not stimulating smooth muscle cell proliferation.

Stent platforms

Metal alloys

A platinum–chromium alloy developed in the early 2000s has been combined with everolimus on the Promus Element® (Boston Scientific) and with paclitaxel on the Taxus Element® (Boston Scientific) stents, which were granted 'CE' European safety marks in November 2009 and May 2010, respectively. Unlike stainless steel and cobalt–chromium alloys, platinum–chromium has the advantage of increased radial strength enabling the stent to have thinner struts, which have been proven to reduce clinical and angiographic restenosis.[66,67] In PLATINUM,[68] the Promus Element® stent was shown to have comparative efficacy and safety when compared with Xience V®. Similarly, the efficacy and safety of the Taxus Element® stent is comparable with that of the Taxus Express2® (Boston Scientific) stent.[69] In a first-in-man study published in 2010, the Taxus® Petal™ (Boston Scientific) platinum–chromium bifurcation stent was successfully implanted in 25 of 28 patients (89.3%), with satisfactory clinical and angiographic outcomes at 1 year.[70]

Bioabsorbable platforms

The problems encountered with DES have encouraged research into innovative, temporary vascular scaffolds or bioabsorbable stent platforms, which gradually degrade until healing and re-endothelialization have occurred. Eventually, no foreign material is left exposed to the blood, thus mitigating the problem of late stent malapposition and stent thrombosis. These stents have the potential to preserve endothelial function, reactive vasomotion of the artery, and permit late lumen enlargement (expansive remodeling).[71] Initially, a high restenosis rate of 45% was observed in the PROGRESS-AMS trial[72] in which a non-drug-eluting bioabsorbable magnesium stent (Biotronik, Berlin, Germany) was evaluated. Yet more favorable results with stents with a poly-L-lactic acid backbone eluting everolimus (Abbott Vascular, Santa Clara, CA, USA) were reported in the ABSORB trial[71,73] with sustained clinical benefit at 3years follow-up. The first generation (revision 1.0) of bioabsorbable vascular scaffolds showed slight signs of shrinkage at 6 months contributing to late luminal loss.[74] However, the second generation (revision 1.1) showed substantial improvements with efficacy comparable to that of current DESs, and enhanced conformability to the angulations and curvatures of the vessel (Figure 2).[75,76]

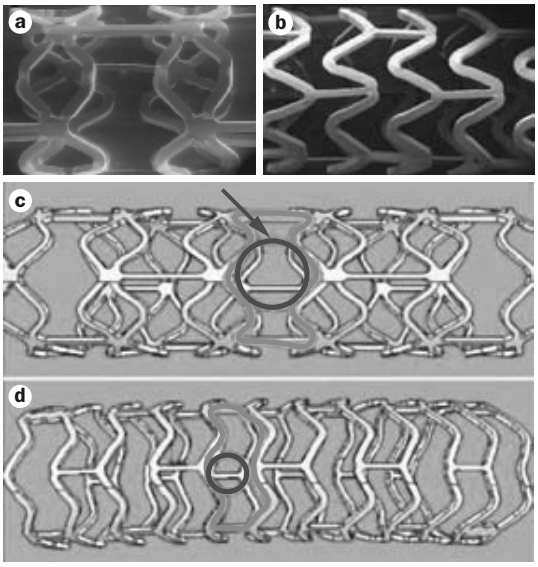

Figure 2: The bioabsorbable stent. a | The first-generation (revision 1.0) and b | the second-generation (revision 1.1) of a bioabsorbable, everolimus-eluting stent. A clear change in the device design between the two generations is evident, with the out-of-phase zigzag pattern connected directly or by straight bridges in revision 1.0 being replaced by the in-phase hoops linked by straight bridges in revision 1.1. c | In addition, the maximum circular (red circles) unsupported cross-sectional areas (green contours) are larger in revision 1.0 than in d | revision 1.1. Parts a | and b | reprinted from *Journal of the American College of Cardiology*, **56** (Suppl. 10), Garg, S. & Serruys, P. W., Coronary stents: looking forward. S43–S78, © 2010, with permission from Elsevier. For parts c | and d |, permission obtained from Wolters Kluwer Health © Serruys, P. W. *et al. Circulation* **122**, 2301–2312 (2010).

Nanomedicine

In addition to its promising application in cancer chemotherapy, great interest has been generated in the application of nanotechnology in optimization of local drug delivery. Nanoparticles are liposomes consisting of lipids and polymers that can be loaded with a drug and used to nanotexture stents, in molding processes to make stents, and for drug delivery from stents.[77] Nanoparticle-mediated drug delivery systems are expected to revolutionize the development of innovative therapeutic devices, allowing local or targeted delivery of the drug with an excellent biocompatibility profile. This strategy controls the concentration and duration of drug release, thereby potentially reducing systemic toxicity.[78] Of the drugs investigated for restenosis prevention and treatment, only paclitaxel and sirolimus have been successfully administered through nanoparticle-based delivery systems and only in preclinical studies.[79,80] Paclitaxel eluted from a cobalt–chromium stent coated with porous carbon–carbon nanoparticles showed promising results with respect to endothelialization and neointimal hyperplasia.[79] Sirolimus incorporated into nanoparticle delivery systems (poly-D,L-lactide) showed improved release kinetics.[80] Furthermore, these sirolimus-loaded nanovehicles selectively inhibited cell viability and proliferation of cultured human coronary artery smooth muscle cells, while human coronary artery endothelial cells were inhibited to a less extent, thus leaving endothelial cells viable to an extent that allows re-endothelialization of a stented vessel and still prevents smooth muscle cell proliferation.[80]

In another approach, Chorny *et al.* have investigated the novel concept of 'magnetic targeting stents' by combining uniform field-induced magnetization and a biocompatible magnetic nanoparticle formulation in a rat model of carotid stenting.[81] Magnetic targeting allows a drug to be delivered on demand to an *in vivo* site with various dosing regimens. These investigators demonstrated that the magnetic nanoparticles loaded with paclitaxel adequately inhibited neointima formation after uniform-field-controlled targeting when compared with nonmagnetically-treated animals.[81] Nanomedicine is, therefore, an innovative and promising perspective in stent design, but has yet to be demonstrated as safe and effective in clinical practice.

Gene-based therapy

Gene-based therapy has emerged over the past few years as a promising tool for the prevention of ISR. Numerous transgenes have shown to be effective in reducing ISR in animal models (Table 2) and various modes of local gene delivery have been developed. An effective method of gene delivery is by means of 'gene-eluting stents', which elute plasmid DNA or adenoviral vectors.[82,83] Pyrrole–imidazole polyamide is a powerful gene-regulating compound ('gene silencer') that inhibits the interaction between proteins, such as transcription factors, and DNA.[84] An *in vivo* animal study conducted by Yao *et al.* showed that synthetic pyrrole–imidazole polyamide can suppress neointimal hyperplasia by downregulation of transforming growth factor β1 and connective tissue growth factor,[85] as well as monocyte chemotactic

Table 2: Preclinical studies of gene therapy for restenosis

Study	Transgene (approved gene name)	Mode of delivery	Findings
Brito *et al.*[82]	eNOS (*NOS3*)	Plasmid-mediated gene delivery from lipopolyplex-embedded stents	Accelerated RE and reduced ISR
Takemoto *et al.*[83]	pE-NTPdase (*ENTPD*)	Plasmid-mediated gene transfer via cationic gelatin-coated stents	Accelerated RE, reduced ISR, and inhibition of subacute IST
Fishbein *et al.*[136]	iNOS (*NOS2*)	Adenoviral-mediated gene delivery from stents	Reduced ISR
Sharifi *et al.*[137]	eNOS (*NOS3*)	Adenoviral-mediated gene delivery from stents	Accelerated RE and inhibition of ISR
Johnson *et al.*[138]	TIMP3	Adenoviral-mediated gene delivery from stents	Reduced ISR
Egashira *et al.*[139]	Anti-MCP1 (anti-*CCL2*)	Plasmid-mediated gene delivery from stents	Reduced ISR
Walter *et al.*[140]	VEGF2 (*VEGFC*)	Gene-eluting stent of naked plasmid DNA	Increased RE and reduced ISR
Brasen *et al.*[141]	EC-SOD (*SOD3*)	Catheter-mediated intramural delivery of adenovirus	Accelerated RE and reduced ISR

Abbreviations: Anti-MCP 1, antimonocyte chemoattractant protein 1; CCL2, chemokine (CC motif) ligand 2; ENTPD, ectonucleoside triphosphate diphosphohydrolase; ECSOD, extracellular superoxide dismutase; eNOS: endothelial nitric oxide synthase; iNOS, inducible nitric oxide synthase; ISR, in-stent restenosis; IST, in-stent thrombosis; NOS2, nitric oxide synthase 2, inducible; NOS3, nitric oxide synthase 3 (endothelial cell); pE-NTPdase, placental ectonucleoside triphosphate diphosphohydrolase; RE, re-endothelialization; SOD3, superoxide dismutase 3, extracellular; TIMP3, tissue inhibitor of matrix metalloproteinase 3; VEGF2, vascular endothelial growth factor 2; VEGFC, vascular endothelial growth factor C.

protein 1, matrix metalloproteinase 9, and intercellular adhesion molecule 1,[86] making it a promising next-generation agent.

Nuclear 'orphan' receptors comprise a group of ligand-activated receptors for which specific ligands have not yet been identified, but which are known to directly bind and interact with the promoter of target genes.[87] Nuclear receptor related proteins 1 and 77 have been identified as having a role in ISR development; overexpression of these proteins inhibits intimal proliferation and ISR in animal models.[88,89] A small-molecule drug that enhances the activity of these receptors, namely 6mercaptopurine, represents an attractive novel target for local intervention in restenosis.[89]

Finally, reducing the proliferative capacity of vascular smooth muscle cells could be of benefit in reducing neointimal hyperplasia following PCI. The biology of microRNAs and their ability to modify smooth muscle biology has been reviewed by O'Sullivan and colleagues.[90] Two microRNAs, mir143 and mir145, were shown to have a key role in the regulation of vascular smooth muscle cells *in vivo* and might, therefore, have therapeutic potential.

Systemic treatment

Since local drug delivery does not eradicate ISR completely, systemic treatment has also been explored, despite the obvious risk of adverse effects. We will briefly discuss the evidence for the antirestenotic effects of several antiproliferative and anti-inflammatory drugs.

The major role of the inflammatory system in restenosis formed the rationale for using prednisone for the prevention of this condition. The IMPRESS trial[91] showed favorable results with oral prednisone in patients undergoing coronary BMS implantation both in angiographic and clinical outcomes. In addition, a subanalysis from the ongoing CEREA-DES trial,[92] reported by Pesarini *et al.* in 2010,[93] showed that high doses of oral prednisone reduced late lumen loss, probably via a reduction in the release of tumor necrosis factor.

Preclinical studies have demonstrated that systemically administered sirolimus (rapamycin) reduces neointimal proliferation after vascular injury.[94] Several clinical trials confirmed the benefit of oral sirolimus in reducing ISR after BMS implantation,[95,96] making it a possible effective and cost-saving alternative to DES implantation. However, the long-term results of the OSIRIS trial,[97] reported by Kufner and co-workers in 2009, showed an attenuated benefit of oral sirolimus after 4 years and, moreover, raised concerns regarding a related increase in newly diagnosed malignancies.

Cilostazol, a phosphodiesterase III inhibitor, has antiproliferative effects[98] and has been shown to reduce intimal hyperplasia and restenosis after both BMS and DES implantation.[99,100] In a meta-analysis published in 2011, Kamal *et al.* concluded that addition of cilostazol to standard dual antiplatelet therapy reduces angiographic restenosis without significantly affecting rates of major adverse cardiac events or bleeding.[101] However, cilostazol was associated with an increase in the incidence of minor adverse effects, such as headaches, gastrointestinal complaints, and palpitations.[102]

Pioglitazone, a thiazolidinedione peroxisome proliferator-activated receptor gamma agonist, is used for the treatment of diabetes. An additional antiatherogenic effect of the drug in vascular cells limiting lesion development in animal models of atherosclerosis has been described.[103] Several clinical studies have demonstrated a reduced incidence of ISR after stent deployment with thiazolidinedione (pioglitazone or rosiglitazone) administration.[104,105]

Although rates of ISR have been shown to be reduced with the systemic use of various drugs, the concentration of drug accumulated at the site of interest is limited by toxicity. Systemic treatment will, therefore, probably never be superior to local drug delivery with DESs. This strategy could, however, be useful as an adjunct to BMS implantation.

RESTENOSIS: PRESENTATION AND OUTCOMES

If measures to prevent the development of restenosis fail, the clinical presentation of this condition is not always benign and can have a spectrum of acuity.[106] Multiple mechanisms

underlie myocardial infarction associated with ISR. An occlusive restenosis can be difficult to differentiate from a thrombotic event and a highly stenotic ISR lesion can promote local non-occlusive thrombosis and lead to a clinical presentation of non-ST-segment elevation myocardial infarction or troponin-positive unstable coronary syndrome.[107] Whether a difference exists between the use of DESs and BMSs in this entity of 'thrombosis on top of restenosis' remains to be elucidated. A pathology study by Nakazawa *et al.* confirmed the occurrence of neoatherosclerosis in the neointimal growth after implantation of both BMSs and DESs, but unstable features of neoatherosclerosis were encountered more frequently and earlier with DESs.[108] Whether this finding translates into a difference in outcomes between stent types is still questionable.[109]

One factor that does influence outcomes associated with ISR is the angiographic pattern of restenosis (Figure 3), which can be broadly classified into focal (<10 mm) and nonfocal (>10 mm) lesions. Mehran *et al.* showed that the pattern of ISR independently predicts the long-term need for revascularization, with an increase in the rate of TLR with increasing ISR class.[110]

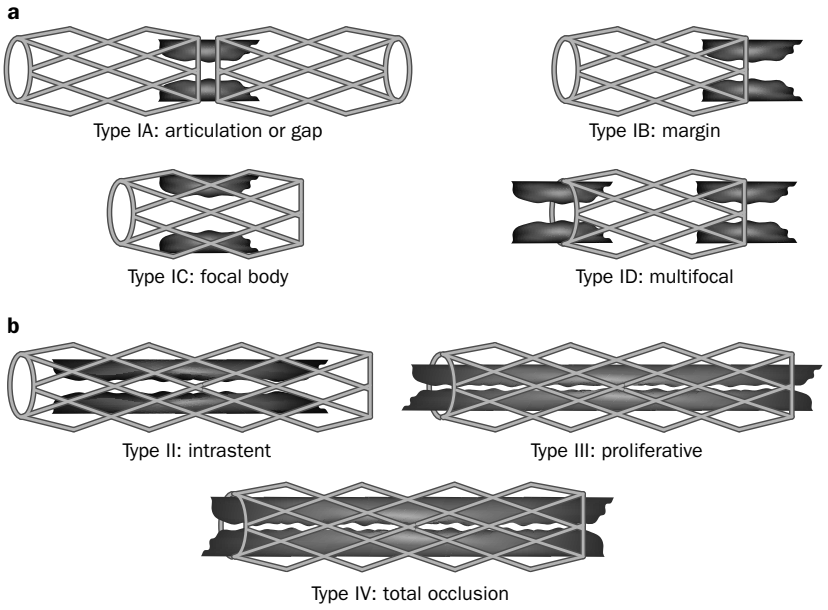

Figure 3: Patterns of in-stent restenosis. Schematic image of four patterns of in-stent restenosis (ISR). a | Pattern I (focal ISR) contains four types (A–D). Restenotic lesions are ≤10 mm and are located at the articulation or gap between stents (Type IA), at either the distal or proximal margin of the stent (Type IB), within the body of a stent (Type IC), or a combination of these distributions (Type ID). b | Patterns II–IV (diffuse ISR) are defined according to the anatomical position of ISR in relation to the previously implanted stent. Type II lesions are >10 mm and do not extend beyond the margins of the stent; Type III lesions are >10 mm and extend beyond the stent margins; Type IV lesions represent total occlusion and have a Thrombolysis in Myocardial Infarction flow grade of 0. Permission obtained from Wolters Kluwer Health © Mehran, R. *et al. Circulation* **100**, 1872–1878 (1999).

The morphologic patterns of DES restenosis are different from those of BMS, favoring a more focal and easily treated pattern with expected improved clinical outcomes.[111] In DES-treated patients, the rates of TLR were significantly higher in diffuse ISR compared with focal ISR.[112]

TREATMENT OF RESTENOSIS

The optimal treatment for ISR remains debatable. The options include vascular brachytherapy; conventional balloon, cutting balloon, or drug-eluting balloon angioplasty; BMS or DES implantation; and CABG surgery. This diversity of available treatments and the variability in the underlying etiology of restenosis make selection of the most appropriate modality difficult. In other words, the treatment of ISR should be tailored and individualized according to the clinical situation and in view of the underlying etiological factors. Several of the treatment options for restenosis are discussed in detail below.

Vascular brachytherapy

Intracoronary brachytherapy was once recommended as an effective treatment for ISR on the basis of data from several randomized, controlled trials published in the early 2000s.[113,114] Antiproliferative δ (iridium192) or β (phosphorus32) irradiation is delivered locally to the target lesions via dedicated catheters. Currently, however, brachytherapy with either β or δ radiation is of very limited use. The difficulty in performing this procedure, particularly handling the radioactive substances, and the increasingly widespread use of DESs has gradually displaced brachytherapy from the armamentarium of the interventionist. Nevertheless, the 5year follow-up data from the SISR study, presented at the 2011 ACC i2 summit, suggest that brachytherapy could be an equivalent treatment option to SES implantation for the treatment of ISR.[115]

Cutting-balloon angioplasty

The cutting balloon consists of a balloon catheter with three to four blades or 'atherotomes' designed to create discrete longitudinal incisions in the atherosclerotic lesion during balloon inflation. Such controlled dilatation theoretically reduces the force needed to dilate an obstructive lesion compared with standard balloon angioplasty and avoid slipping-induced vessel trauma during PCI, potentially decreasing the risk of ISR development.[116] Although this expected benefit was not demonstrated when the device first came into use in the early 1990s,[117] the later REDUCE III study did show that an IVUS-guided cutting balloon procedure followed by BMS implantation yielded restenosis rates similar to those achieved with DESs, thereby, providing an effective alternative.[118] However, use of the cutting balloon remains uncommon for the treatment of ISR, especially when used without stent placement. In 2010, Park *et al.* raised concerns that cutting-balloon angioplasty might be associated with a higher

risk of myocardial infarction than conventional balloon angioplasty;[119] this technique is, therefore, unlikely to become an important ISR treatment modality.

Drug-eluting balloon angioplasty

Non-stent-based local delivery of an antiproliferative drug, particularly using drug-eluting balloons, theoretically represents a very attractive treatment for ISR that avoids the limitations associated with DES platforms. Drug-eluting balloons improve drug delivery by allowing homogenous drug transfer to the entire vessel wall rather than only to the areas covered by stent struts, as with DESs. All currently available drug-eluting balloons use paclitaxel in various coating formulations with a typical dose of 3 μg/mm^2 of balloon surface. Drug-eluting balloon angioplasty has been shown to be more effective than conventional balloon angioplasty,[120] and as effective as PES implantation[121] for the treatment of ISR. However, drug-eluting balloons of course cannot prevent the almost immediate elastic recoil phenomenon. Currently, research in this area is focused on comparisons of the various available drug-eluting balloons. For example, in a preclinical study in an advanced porcine model of coronary restenosis, Joner *et al.* found that the Pantera® Lux (Biotronik, Berlin, Germany; 3.0 μg/mm^2 paclitaxel), the SeQuent® Please (B. Braun Melsungen AG, Berlin, Germany; 3.0 μg/mm^2 paclitaxel), and the Elutax™ (drug-eluting balloons (Aachen Resonance, Aachen, Germany; 2.0 μg/mm^2 paclitaxel) all resulted in delayed healing when compared with conventional balloon angioplasty.[122] However, the investigators also demonstrated significant heterogeneity in neointimal suppression between the balloons, with superiority of Pantera® Lux.[115] This difference was attributed to the 'excipient' used as an effective carrier for paclitaxel in the Pantera® Lux and SeQuent® Please balloons. The 6month results of the PEPPER trial,[123] which were presented at the ACC i2 summit in April 2011, showed excellent results for the Pantera® Lux balloon for the treatment of ISR both in BMSs and DESs. The detailed subgroup analysis, and 12-month follow-up data, are expected to be announced in late 2011.

In the 2010 guidelines for myocardial revascularization published by the European Society of Cardiology, drug-eluting balloons were considered a class IIa indication for the treatment of ISR.[124] Nevertheless, further large studies need to be implemented before these devices can be fully integrated into clinical practice. Patients are currently be recruited for an ongoing trial[125] to investigate the efficacy of a drug-eluting balloons for the treatment of ISR in patients with DESs.

Drug-eluting stents

DESs are known to have fairly low rates of ISR.[4,5] The proportion of restenotic lesions treated with DES in the studies providing this data is, however, low. Since restenotic lesions have a tendency towards recurrent restenosis, as discussed in Part 1 of this Review,[6] the outcomes associated with stent (DES) implantation in these lesions is likely to be different to those for DES placement in *de novo* lesions. In addition, ISR after BMS implantation differs from ISR

associated with DES use and, therefore, a distinction between these two types of restenosis should also be made in terms of treatment.

Favorable outcomes of DES treatment for BMS-related ISR have been reported in several studies, even after long-term follow up.[118–121] Treatment with DES placement was found to be more effective and safer than conventional balloon angioplasty,[126] vascular brachytherapy,[127,128] or BMS implantation within the original stent.[129] DESs should, therefore, be the treatment of choice for the treatment of BMS-related ISR. By contrast, the same cannot be said for DES-related ISR, which continues to be a therapeutic challenge. To date, the treatment of this condition has been investigated in only one randomized controlled trial, which showed comparable efficacy for SES reimplantation or a switch to PES implantation in patients with SES-related ISR.[130] Other small nonrandomized trials have produced inconsistent results, limiting the possibility of drawing any definitive conclusions about the optimal treatment of DES-related ISR.[107]

An individual's resistance to a particular eluted drug can be a factor in restenosis development.[131,132] This hypothesis provides the rationale for switching to a different DES for the treatment of DES-related ISR. However, to date, no clinical study has demonstrated clear clinical benefit of implanting an alternative different DES.[130,133] Whether resistance to sirolimus also implies resistance to other limus derivatives remains questionable, as no reports have been published on the use of zotarolimus, everolimus, or biolimus A9-eluting stents for the treatment of SES-related ISR. Another uncertainty is whether the angiographic pattern of DES-related ISR provides a clue to the involvement of drug resistance. Drug resistance is expected to cause a diffuse pattern of ISR, so perhaps a future study focused on patients with diffuse patterns of ISR would clarify the potential benefits of changing the agent eluted by the stent. In the ongoing prospective, randomized Italian GISE-CROSS trial,[134] treatment with a stent that elutes the same drug as the original restenosed stent (no CROSS group) is being compared with a crossover to an alternative DES in patients with ISR after either PES or SES implantation. The results of this study are eagerly awaited. Patients treated with DES for ISR are at high risk for recurrent ischemic events and should be maintained on dual antiplatelet therapy unless a complication emerges.[107] Therefore, individuals who have a contraindication for, or show noncompliance with, dual antiplatelet therapy should be considered for CABG surgery.

CABG surgery

CABG surgery is usually considered as the 'last resort' treatment for ISR in the clinic. However, this strategy is an appropriate first-line therapy for certain complex cases, such as multivessel ISR, diffuse ISR, multiple subsequent DES restenosis treated by repeat DES implantation, a strong genetic predisposition to ISR that precludes further interventional options, or in cases where dual antiplatelet therapy is not appropriate, as discussed above. To our knowledge, no studies of CABG surgery for the treatment of in-stent restenosis have been conducted.

CONCLUSIONS

Restenosis is a complex disease with a diversity of underlying mechanisms that are still not fully understood. Many innovative technologies, including DESs (with or without specific polymers) and fully biodegradable stents, have been and continue to be developed in the diligent search for an ideal antirestenosis therapy that is both effective and safe in the long term. Developments in the field of gene therapy might also impact future restenosis therapies. Advances in stent design and nanoparticle delivery systems ('nanovehicles') in the past 5 years have already fueled revolutionary changes in the concept of ISR prevention and treatment. In addition, several clinical algorithms for ISR treatment have been proposed on the basis of angiographic pattern of restenosis.[107,134,135] Treatment of ISR should be tailored to the individual, taking into consideration the available evidence and the best strategy for the patient, as well as the best method of treating the lesion. We believe that investing in the prevention of ISR is worth much more than investing in its treatment.

REVIEW CRITERIA

The articles on which this Review is based were identified by searching MEDLINE using the following keywords and Medical Subject Headings (MeSH) terms: "coronary restenosis", "drug-eluting stent", "biodegradable stent", "gene therapy of restenosis", and "nanomedicine". We checked for papers published up to August 2011. Only papers in the English language were included. Although we realize that not all available evidence could be incorporated, the most relevant and influential articles were selected for inclusion in this Review.

ACKNOWLEDGMENTS

J. W. Jukema has received funding from the European Union's Seventh Framework Program (FP7/20072013) under grant agreement n° HEALTHF22009223,004 and he is supported by grants from the Interuniversity Cardiology Institute of the Netherlands (ICIN) and the Durrer Center for Cardiogenetic Research both Institutes of the Netherlands Royal Academy of Arts and Sciences (KNAW), the Netherlands Heart Foundation, the Center for Medical Systems Biology (CMSB), a center of excellence approved by the Netherlands Genomics Initiative/ Netherlands Organization for Scientific Research (NWO), the Netherlands Consortium for Healthy Ageing (NCHA). T. A. N. Ahmed would like to thank the Egyptian Ministry of Higher Education and Asyut University for financially supporting him during his research and clinical fellowship in the Netherlands. P. H. A. Quax is an established investigator of the Netherlands

Heart Foundation (M93001). The funders had no role in the preparation of, or decision to publish, the manuscript.

AUTHOR CONTRIBUTIONS

J. W. Jukema, T. A. N. Ahmed and J. J. W. Verschuren researched data for and wrote the article. All authors contributed to the discussion of content. J. W. Jukema, J. J. W. Verschuren and P. H. A. Quax reviewed/edited the article before submission. J. W. Jukema and T. A. N. Ahmed contributed equally to this paper.

REFERENCES

1. Gruntzig, A. R., Senning, A. & Siegenthaler, W. E. Nonoperative dilatation of coronary-artery stenosis: percutaneous transluminal coronary angioplasty. *N. Engl. J. Med.* **301**, 61–68 (1979).
2. Agema, W. R., Jukema, J. W., Pimstone, S. N. & Kastelein, J. J. Genetic aspects of restenosis after percutaneous coronary interventions: towards more tailored therapy. *Eur. Heart J.* **22**, 2058–2074 (2001).
3. Regar, E. *et al.* Angiographic findings of the multicenter Randomized Study with the Sirolimus-Eluting Bx Velocity Balloon-Expandable Stent (RAVEL): sirolimus-eluting stents inhibit restenosis irrespective of the vessel size. *Circulation* **106**, 1949–1956 (2002).
4. Simsek, C. *et al.* The unrestricted use of sirolimus- and paclitaxel-eluting stents results in better clinical outcomes during 6year follow-up than bare-metal stents: an analysis of the RESEARCH (Rapamycin-Eluting Stent Evaluated At Rotterdam Cardiology Hospital) and TSEARCH (Taxus-Stent Evaluated At Rotterdam Cardiology Hospital) registries. *JACC Cardiovasc. Interv.* **3**, 1051–1058 (2010).
5. Stolker, J. M. *et al.* Predicting restenosis of drug-eluting stents placed in real-world clinical practice: derivation and validation of a risk model from the EVENT registry. *Circ. Cardiovasc. Interv.* **3**, 327–334 (2010).
6. Jukema, J. W., Verschuren, J. J., Ahmed, T. A. & Quax, P. H. Restenosis after PCI. Part 1: pathophysiology and risk factors. *Nat. Rev. Cardiol.* doi:10.1038/nrcardio.2011.132.
7. Stettler, C. *et al.* Outcomes associated with drug-eluting and bare-metal stents: a collaborative network meta-analysis. *Lancet* **370**, 937–948 (2007).
8. Daemen, J. *et al.* Early and late coronary stent thrombosis of sirolimus-eluting and paclitaxel-eluting stents in routine clinical practice: data from a large two-institutional cohort study. *Lancet* **369**, 667–678 (2007).
9. Hassan, A. K. *et al.* Late stent malapposition risk is higher after drug-eluting stent compared with bare-metal stent implantation and associates with late stent thrombosis. *Eur. Heart J.* **31**, 1172–1180 (2010).
10. Cook, S. *et al.* Correlation of intravascular ultrasound findings with histopathological analysis of thrombus aspirates in patients with very late drug-eluting stent thrombosis. *Circulation* **120**, 391–399 (2009).
11. Pires, N. M., Eefting, D., de Vries, M. R., Quax, P. H. & Jukema, J. W. Sirolimus and paclitaxel provoke different vascular pathological responses after local delivery in a murine model for restenosis on underlying atherosclerotic arteries. *Heart* **93**, 922–927 (2007).
12. Schomig, A. *et al.* A meta-analysis of 16 randomized trials of sirolimus-eluting stents versus paclitaxel-eluting stents in patients with coronary artery disease. *J. Am. Coll. Cardiol.* **50**, 1373–1380 (2007).
13. Smits, P. C. *et al.* 2year follow-up of a randomized controlled trial of everolimus- and paclitaxel-eluting stents for coronary revascularization in daily practice. The COMPARE (Comparison of the everolimus eluting XIENCEV stent with the paclitaxel eluting TAXUS LIBERTE stent in all-comers: a randomized open label trial) trial. *J. Am. Coll. Cardiol.* **58**, 11–18 (2011).
14. Stone, G. W. *et al.* Randomized comparison of everolimus- and paclitaxel-eluting stents 2year follow-up from the SPIRIT (Clinical Evaluation of the XIENCE V Everolimus Eluting Coronary Stent System) IV trial. *J. Am. Coll. Cardiol.* **58**, 19–25 (2011).
15. Leon, M. B. *et al.* A randomized comparison of the ENDEAVOR zotarolimus-eluting stent versus the TAXUS paclitaxel-eluting stent in *de novo* native coronary lesions 12-month outcomes from the ENDEAVOR IV trial. *J. Am. Coll. Cardiol.* **55**, 543–554 (2010).
16. Rasmussen, K. *et al.* Efficacy and safety of zotarolimus-eluting and sirolimus-eluting coronary stents in routine clinical care (SORT OUT III): a randomised controlled superiority trial. *Lancet* **375**, 1090–1099 (2010).
17. Silber, S., Windecker, S., Vranckx, P. & Serruys, P. W. Unrestricted randomised use of two new generation drug-eluting coronary stents: 2year patient-related versus stent-related outcomes from the RESOLUTE All Comers trial. *Lancet* **377**, 1241–1247 (2011).
18. Sehgal, S. N. Sirolimus: its discovery, biological properties, and mechanism of action. *Transplant Proc.* **35**, 7S–14S (2003).

19. Ostojic, M. *et al.* The pharmacokinetics of biolimus A9 after elution from the Nobori stent in patients with coronary artery disease: the NOBORI PK study. *Catheter. Cardiovasc. Interv.* **72**, 901–908 (2008).
20. Ostojic, M. C. *et al.* The pharmacokinetics of biolimus A9 after elution from the BioMatrix II stent in patients with coronary artery disease: the Stealth PK study. *Eur. J. Clin. Pharmacol.* **67**, 389–398 (2011).
21. Vetrovec, G. W. *et al.* Sirolimus PK trial: a pharmacokinetic study of the sirolimus-eluting Bx Velocity stent in patients with *de novo* coronary lesions. *Catheter. Cardiovasc. Interv.* **67**, 32–37 (2006).
22. Hamilos, M. I. *et al.* Differential effects of drug-eluting stents on local endothelium-dependent coronary vasomotion. *J. Am. Coll. Cardiol.* **51**, 2123–2129 (2008).
23. Serruys, P. W. *et al.* A randomised comparison of novolimus-eluting and zotarolimus-eluting coronary stents: 9month follow-up results of the EXCELLA II study. *EuroIntervention* **6**, 195–205 (2010).
24. Hezi-Yamit, A. *et al.* Novel high-throughput polymer biocompatibility screening designed for SAR (structure-activity relationship): application for evaluating polymer coatings for cardiovascular drug-eluting stents. *Comb. Chem. High Throughput Screen* **12**, 664–676 (2009).
25. Udipi, K. *et al.* The next generation Endeavor Resolute stent: role of the BioLinx polymer system. *EuroIntervention* **3**, 137–139 (2007).
26. Talarico, G. P. *et al.* Exploring the possible clinical impact of polymer coating in DES technology: clinical outcome of consecutive patients treated by zotarolimus-eluting Endeavor stent and zotarolimus-eluting Resolute stent [abstract 42]. *Eurointervention* **7** (Suppl. M), M27 (2011).
27. Radeleff, B. *et al.* Restenosis of the CYPHER-Select, TAXUS-Express, and PolyzeneF nanocoated cobalt-chromium stents in the minipig coronary artery model. *Cardiovasc. Intervent. Radiol.* **31**, 971–980 (2008).
28. Tamburino, C. *et al.* Firstinman 1year clinical outcomes of the Catania coronary stent system with nanothin polyzeneF in *de novo* native coronary artery lesions: the ATLANTA (Assessment of The LAtest Non-Thrombogenic Angioplasty stent) trial. *JACC Cardiovasc. Interv.* **2**, 197–204 (2009).
29. La Manna, A. *et al.* One-year outcomes of CATANIA coronary stent system with nanothin polyzeneF in a real-world unselected population: assessment of the latest nonthrombogenic angioplasty stent 2 (ATLANTA2) study. *Eurointervention* **6** (Suppl. H), H13 (2010).
30. Windecker, S. *et al.* Biolimus-eluting stent with biodegradable polymer versus sirolimus-eluting stent with durable polymer for coronary revascularisation (LEADERS): a randomised non-inferiority trial. *Lancet* **372**, 1163–1173 (2008).
31. Byrne, R. A. *et al.* Randomized, non-inferiority trial of three limus agent-eluting stents with different polymer coatings: the Intracoronary Stenting and Angiographic Results: Test Efficacy of 3 Limus-Eluting Stents (ISARTEST4) Trial. *Eur. Heart J.* **30**, 2441–2449 (2009).
32. Krucoff, M. W. *et al.* A novel bioresorbable polymer paclitaxel-eluting stent for the treatment of single and multivessel coronary disease: primary results of the COSTAR (Cobalt Chromium Stent With Antiproliferative for Restenosis) II study. *J. Am. Coll. Cardiol.* **51**, 1543–1552 (2008).
33. Serruys, P. W. *et al.* LEADERS: 3year follow-up from a prospective, randomized, trial of biolimus A9-eluting stents with a bioabsorbable polymer vs sirolimus-eluting stents with a durable polymer [abstract TCT26]. *J. Am. Coll. Cardiol.* **56** (13 Suppl. 1), B9 (2010).
34. US National Institutes of Health. Test efficacy of biodegradable and permanent limus-eluting stents (ISAR-TEST6). *ClinicalTrials.gov* [online], http://clinicaltrials.gov/ct2/show/NCT01068106 (2010).
35. Vorpahl, M., Finn, A. V., Nakano, M. & Virmani R. The bioabsorption process: tissue and cellular mechanisms and outcomes. *Eurointervention* **5** (Suppl. F), F28–F35 (2009).
36. van der Giessen, W. J. *et al.* Marked inflammatory sequelae to implantation of biodegradable and non-biodegradable polymers in porcine coronary arteries. *Circulation* **94**, 1690–1697 (1996).
37. Lockwood, N. A. *et al. In vitro* and *in vivo* characterization of novel biodegradable polymers for application as drug-eluting stent coatings. *J. Biomater. Sci. Polym. Ed.* **21**, 529–552 (2010).
38. Granada, J. F. *et al.* Development of a novel prohealing stent designed to deliver sirolimus from a biodegradable abluminal matrix. *Circ. Cardiovasc. Interv.* **3**, 257–266 (2010).
39. Byrne, R. A. *et al.* Randomised trial of three rapamycin-eluting stents with different coating strategies for the reduction of coronary restenosis: 2year follow-up results. *Heart* **95**, 1489–1494 (2009).

40. Byrne, R. A. *et al.* Durability of antirestenotic efficacy in drug-eluting stents with and without permanent polymer. *JACC Cardiovasc. Interv.* **2**, 291–299 (2009).
41. Tada, N. *et al.* Polymer-free biolimus A9-coated stent demonstrates more sustained intimal inhibition, improved healing, and reduced inflammation compared with a polymer-coated sirolimus-eluting cypher stent in a porcine model. *Circ. Cardiovasc. Interv.* **3**, 174–183 (2010).
42. Costa, R. *et al. De novo* coronary lesions treated with the novel polymer-free BiolimusA9 coated stents: Four- and twelve-month angiographic results from the prospective, randomized, multicenter BIOFREEDOM clinical trial [abstract 188]. *EuroIntervention* **7** (Suppl. M) (2011).
43. Adriaenssens, T. *et al.* Does addition of estradiol improve the efficacy of a rapamycin-eluting stent? Results of the ISAR-PEACE randomized trial. *J. Am. Coll. Cardiol.* **49**, 1265–1271 (2007).
44. Byrne, R. A. *et al.* 2year clinical and angiographic outcomes from a randomized trial of polymer-free dual drug-eluting stents versus polymer-based Cypher and Endeavor drug-eluting stents. *J. Am. Coll. Cardiol.* **55**, 2536–2543 (2010).
45. Massberg, S. *et al.* Polymer-free sirolimus- and probucol-eluting versus new generation zotarolimus-eluting stents in coronary artery disease: the Intracoronary Stenting and Angiographic Results: Test Efficacy of Sirolimus- and Probucol-Eluting Versus Zotarolimus-Eluting Stents (ISAR-TEST 5) Trial. *Circulation* **124**, 624–632 (2011).
46. Kipshidze, N. *et al.* Role of the endothelium in modulating neointimal formation: vasculoprotective approaches to attenuate restenosis after percutaneous coronary interventions. *J. Am. Coll. Cardiol.* **44**, 733–739 (2004).
47. Shirota, T., Yasui, H., Shimokawa, H. & Matsuda, T. Fabrication of endothelial progenitor cell (EPC)-seeded intravascular stent devices and *in vitro* endothelialization on hybrid vascular tissue. *Biomaterials* **24**, 2295–2302 (2003).
48. Co, M. *et al.* Use of endothelial progenitor cell capture stent (Genous Bio-Engineered R Stent) during primary percutaneous coronary intervention in acute myocardial infarction: intermediate- to long-term clinical follow-up. *Am. Heart J.* **155**, 128–132 (2008).
49. Lee, Y. P. *et al.* Endothelial progenitor cell capture stent implantation in patients with STsegment elevation acute myocardial infarction: one year follow-up. *EuroIntervention* **5**, 698–702 (2010).
50. Klomp, M., Beijk, M. A., Verouden, N. J., Tijssen, J. G. & de Winter, R. J. Design and rationale of the TRI-stent adjudication study (TRIAS) program. *Am. Heart J.* **158**, 527–532 (2009).
51. Inoue, T. *et al.* Mobilization of CD34-positive bone marrow-derived cells after coronary stent implantation: impact on restenosis. *Circulation* **115**, 553–561 (2007).
52. Nakazawa, G. *et al.* Anti-CD34 antibodies immobilized on the surface of sirolimus-eluting stents enhance stent endothelialization. *JACC Cardiovasc. Interv.* **3**, 68–75 (2010).
53. US National Institutes of Health. Safety and effectiveness study of combo bio-engineered everolimus eluting stent (REMEDEE). *ClinicalTrials.gov* [online], http://clinicaltrials.gov/ct2/show/NCT00967902 (2011).
54. Wöhrle, J. *et al.* Prospective randomised trial evaluating a paclitaxel-coated balloon in patients treated with endothelial progenitor cell capturing stents for *de novo* coronary artery disease. *Heart* **97**, 1338–1342 (2011).
55. Garg, S. & Serruys, P. W. Coronary stents: looking forward. *J. Am. Coll. Cardiol.* **56**, S43–S78 (2010).
56. Windecker, S. *et al.* Randomized comparison of a titaniumnitrideoxide-coated stent with a stainless steel stent for coronary revascularization: the TiNOX trial. *Circulation* **111**, 2617–2622 (2005).
57. Moschovitis, A. *et al.* Randomised comparison of titaniumnitrideoxide coated stents with bare metal stents: five year follow-up of the TiNOX trial. *EuroIntervention* **6**, 63–68 (2010).
58. Karjalainen, P. P. *et al.* Two-year follow-up after percutaneous coronary intervention with titaniumnitrideoxide-coated stents versus paclitaxel-eluting stents in acute myocardial infarction. *Ann. Med.* **41**, 599–607 (2009).

59. Karjalainen, P. P., Annala, A. P., Ylitalo, A., Vahlberg, T. & Airaksinen, K. E. Long-term clinical outcome with titaniumnitrideoxide-coated stents and paclitaxel-eluting stents for coronary revascularization in an unselected population. *Int. J. Cardiol.* **144**, 42–46 (2010).
60. Karjalainen, P. P. A prospective, randomised and multicenter trial comparing a Titan2 BAS and XienceV stent: the BASE-ACS trial. Presented at EuroPCR 2011.
61. Pilgrim, T. *et al.* Comparison of titaniumnitrideoxide-coated stents with zotarolimus-eluting stents for coronary revascularization a randomized controlled trial. *JACC Cardiovasc. Interv.* **4**, 672–682 (2011).
62. Lin, P. H. *et al.* Rheolytic pharmacomechanical thrombectomy in experimental chronic deep vein thrombosis: effect of Larginine on thrombogenicity and endothelial vasomotor function. *World J. Surg.* **31**, 664–675 (2007).
63. Fajadet, J. The future of bioactive stents: TiTAN OPTIMAX and VINCI Bio Active Eluting stent. Presented at EuroPCR 2011.
64. Meyers, S. R., Kenan, D. J., Khoo, X. & Grinstaff M. W. Bioactive stent surface coating that promotes endothelialization while preventing platelet adhesion. *Biomacromolecules* **12**, 533–539 (2011).
65. Barber, T. A. *et al.* Peri-implant bone formation and implant integration strength of peptide-modified p(AAMcoE G/AAC) interpenetrating polymer network-coated titanium implants. *J. Biomed. Mater. Res. A* **80**, 306–320 (2007).
66. Kastrati, A. *et al.* Intracoronary stenting and angiographic results: strut thickness effect on restenosis outcome (ISAR-STEREO) trial. *Circulation* **103**, 2816–2821 (2001).
67. Pache, J. *et al.* Intracoronary stenting and angiographic results: strut thickness effect on restenosis outcome (ISARSTEREO2) trial. *J. Am. Coll. Cardiol.* **41**, 1283–1288 (2003).
68. Stone, G. W. *et al.* A prospective, randomized evaluation of a novel everolimus-eluting coronary stent: the PLATINUM (A Prospective, Randomized, Multicenter Trial to Assess an Everolimus-Eluting Coronary Stent System [PROMUS Element] for the Treatment of up to Two *De Novo* Coronary Artery Lesions) trial. *J. Am. Coll. Cardiol.* **57**, 1700–1708 (2011).
69. Kereiakes, D. J. *et al.* Clinical and angiographic outcomes after treatment of *de novo* coronary stenoses with a novel platinum chromium thin-strut stent: primary results of the PERSEUS (Prospective Evaluation in a Randomized Trial of the Safety and Efficacy of the Use of the TAXUS Element Paclitaxel-Eluting Coronary Stent System) trial. *J. Am. Coll. Cardiol.* **56**, 264–271 (2010).
70. Ormiston, J. A., Lefèvre, T., Grube, E., Allocco, D. & Dawkins, K. D. First human use of the Taxus Petal Paclitaxel-eluting bifurcation stent. *EuroIntervention* **6**, 46–53 (2010).
71. Serruys, P. W. *et al.* A bioabsorbable everolimus-eluting coronary stent system (ABSORB): 2year outcomes and results from multiple imaging methods. *Lancet* **373**, 897–910 (2009).
72. Erbel, R. *et al.* Temporary scaffolding of coronary arteries with bioabsorbable magnesium stents: a prospective, non-randomised multicenter trial. *Lancet* **369**, 1869–1875 (2007).
73. Onuma, Y. *et al.* Three-year results of clinical follow-up after a bioresorbable everolimus-eluting scaffold in patients with *de novo* coronary artery disease: the ABSORB trial. *EuroIntervention* **6**, 447–453 (2010).
74. Tanimoto, S. *et al.* Comparison of *in vivo* acute stent recoil between the bioabsorbable everolimus-eluting coronary stent and the everolimus-eluting cobalt chromium coronary stent: insights from the ABSORB and SPIRIT trials. *Catheter. Cardiovasc. Interv.* **70**, 515–523 (2007).
75. Serruys, P. W. *et al.* Evaluation of the second generation of a bioresorbable everolimus drug-eluting vascular scaffold for treatment of *de novo* coronary artery stenosis: six-month clinical and imaging outcomes. *Circulation* **122**, 2301–2312 (2010).
76. Gomez-Lara, J. *et al.* A comparison of the conformability of everolimus-eluting bioresorbable vascular scaffolds to metal platform coronary stents. *JACC Cardiovasc. Interv.* **3**, 1190–1198 (2010).
77. Martinez, A. W. & Chaikof, E. L. Microfabrication and nanotechnology in stent design. *Wiley Interdiscip. Rev. Nanomed. Nanobiotechnol.* **3**, 256–268 (2011).
78. Brito, L. & Amiji, M. Nanoparticulate carriers for the treatment of coronary restenosis. *Int. J. Nanomedicine* **2**, 143–161 (2007).

79. Bhargava, B. *et al.* A novel paclitaxel-eluting porous carbon–carbon nanoparticle coated, nonpolymeric cobalt–chromium stent: evaluation in a porcine model. *Catheter. Cardiovasc. Interv.* **67**, 698–702 (2006).
80. Luderer, F. *et al.* Biodegradable sirolimus-loaded poly(lactide) nanoparticles as drug delivery system for the prevention of in-stent restenosis in coronary stent application. *J. Biomater. Appl.* **25**, 851–875 (2011).
81. Chorny, M. *et al.* Targeting stents with local delivery of paclitaxel-loaded magnetic nanoparticles using uniform fields. *Proc. Natl. Acad. Sci. U. S. A.* **107**, 8, 346–**8**, 351 (2010).
82. Brito, L. A., Chandrasekhar, S., Little, S. R. & Amiji, M. M. Non-viral eNOS gene delivery and transfection with stents for the treatment of restenosis. *Biomed. Eng. Online* **9**, 56 (2010).
83. Takemoto, Y. *et al.* Human placental ectonucleoside triphosphate diphosphohydrolase gene transfer via gelatin-coated stents prevents in-stent thrombosis. *Arterioscler. Thromb. Vasc. Biol.* **29**, 857–862 (2009).
84. Lai, Y. M. *et al.* Synthetic pyrrole-imidazole polyamide inhibits expression of the human transforming growth factor-beta1 gene. *J. Pharmacol. Exp. Ther.* **315**, 571–575 (2005).
85. Yao, E. H. *et al.* A pyrrole-imidazole polyamide targeting transforming growth factor-beta1 inhibits restenosis and preserves endothelialization in the injured artery. *Cardiovasc. Res.* **81**, 797–804 (2009).
86. Yao, E. H. *et al.* Novel gene silencer pyrrole-imidazole polyamide targeting lectin-like oxidized low-density lipoprotein receptor1 attenuates restenosis of the artery after injury. *Hypertension* **52**, 86–92 (2008).
87. Wang, Z. *et al.* Structure and function of Nurr1 identifies a class of ligand-independent nuclear receptors. *Nature* **423**, 555–560 (2003).
88. Bonta, P. I. *et al.* Nuclear receptor Nurr1 is expressed in and is associated with human restenosis and inhibits vascular lesion formation in mice involving inhibition of smooth muscle cell proliferation and inflammation. *Circulation* **121**, 2023–2032 (2010).
89. Pires, N. M. *et al.* Activation of nuclear receptor Nur77 by 6mercaptopurine protects against neointima formation. *Circulation* **115**, 493–500 (2007).
90. O'Sullivan, J. F., Martin K. & Caplice, N. M. Microribonucleic acids for prevention of plaque rupture and in-stent restenosis: "a finger in the dam". *J. Am. Coll. Cardiol.* **57**, 383–389 (2011).
91. Versaci, F. *et al.* Immunosuppressive Therapy for the Prevention of Restenosis after Coronary Artery Stent Implantation (IMPRESS Study). *J. Am. Coll. Cardiol.* **40**, 1935–1942 (2002).
92. US National Institutes of Health. Cortisone or drug-eluting stents (DES) as compared to bare-metal stents (BMS) to eliminate restenosis. *ClinicalTrails.gov* [online], http://clinicaltrials.gov/ct2/show/NCT00369356 (2011).
93. Pesarini, G. *et al.* Cytokines release inhibition from activated monocytes, and reduction of in-stent neointimal growth in humans. *Atherosclerosis* **211**, 242–248 (2010).
94. Gallo, R. *et al.* Inhibition of intimal thickening after balloon angioplasty in porcine coronary arteries by targeting regulators of the cell cycle. *Circulation* **99**, 2164–2170 (1999).
95. Hausleiter, J. *et al.* Randomized, double-blind, placebo-controlled trial of oral sirolimus for restenosis prevention in patients with in-stent restenosis: the Oral Sirolimus to Inhibit Recurrent In-stent Stenosis (OSIRIS) trial. *Circulation* **110**, 790–795 (2004).
96. Rodriguez, A. E. *et al.* Percutaneous coronary intervention with oral sirolimus and bare metal stents has comparable safety and efficacy to treatment with drug eluting stents, but with significant cost saving: long-term follow-up results from the randomised, controlled ORAR III (Oral Rapamycin in ARgentina) study. *EuroIntervention* **5**, 255–264 (2009).
97. Kufner, S. *et al.* Long-term risk of adverse outcomes and new malignancies in patients treated with oral sirolimus for prevention of restenosis. *JACC Cardiovasc. Interv.* **2**, 1142–1148 (2009).
98. Kubota, Y. *et al.* Pharmacologic treatment of intimal hyperplasia after metallic stent placement in the peripheral arteries. An experimental study. *Invest. Radiol.* **30**, 532–537 (1995).
99. Douglas, J. S. Jr. *et al.* Coronary stent restenosis in patients treated with cilostazol. *Circulation* **112**, 2826–2832 (2005).
100. Lee, S. W. *et al.* Drug-eluting stenting followed by cilostazol treatment reduces late restenosis in patients with diabetes mellitus the DECLARE-DIABETES Trial (A Randomized Comparison of Triple Antiplatelet

Therapy with Dual Antiplatelet Therapy After Drug-Eluting Stent Implantation in Diabetic Patients). *J. Am. Coll. Cardiol.* **51**, 1181–1187 (2008).

101. Jennings, D. L. & Kalus, J. S. Addition of cilostazol to aspirin and a thienopyridine for prevention of restenosis after coronary artery stenting: a meta-analysis. *J. Clin. Pharmacol.* **50**, 415–421 (2010).
102. Kamal, A. K., Naqvi, I., Husain, M. R. & Khealani, B. A. Cilostazol versus aspirin for secondary prevention of vascular events after stroke of arterial origin. *Cochrane Database of Systematic Reviews*, Issue 7. Art. No.: CD008076. doi:10.1002/14651858.CD008076.pub2 (2011).
103. Hsueh, W. A. & Law, R. E. PPARgamma and atherosclerosis: effects on cell growth and movement. *Arterioscler. Thromb. Vasc. Biol.* **21**, 1891–1895 (2001).
104. Rosmarakis, E. S. & Falagas, M. E. Effect of thiazolidinedione therapy on restenosis after coronary stent implantation: a meta-analysis of randomized controlled trials. *Am. Heart J.* **154**, 144–150 (2007).
105. Takagi, T. *et al.* A prospective, multicenter, randomized trial to assess efficacy of pioglitazone on in-stent neointimal suppression in type 2 diabetes: POPPS (Prevention of In-Stent Neointimal Proliferation by Pioglitazone Study). *JACC Cardiovasc. Interv.* **2**, 524–531 (2009).
106. Rathore, S. *et al.* A comparison of clinical presentations, angiographic patterns and outcomes of in-stent restenosis between bare metal stents and drug eluting stents. *EuroIntervention* **5**, 841–846 (2010).
107. Dangas, G. D. *et al.* In-stent restenosis in the drug-eluting stent era. *J. Am. Coll. Cardiol.* **56**, 1897–1907 (2010).
108. Nakazawa, G. *et al.* The pathology of neoatherosclerosis in human coronary implants bare-metal and drug-eluting stents. *J. Am. Coll. Cardiol.* **57**, 1314–1322 (2011).
109. Singh, I. M. *et al.* Clinical outcomes of drug-eluting versus bare-metal in-stent restenosis. *Catheter. Cardiovasc. Interv.* **75**, 338–342 (2010).
110. Mehran, R. *et al.* Angiographic patterns of in-stent restenosis: classification and implications for long-term outcome. *Circulation* **100**, 1872–1878 (1999).
111. Cosgrave, J. *et al.* Drug-eluting stent restenosis the pattern predicts the outcome. *J. Am. Coll. Cardiol.* **47**, 2399–2404 (2006).
112. Solinas, E. *et al.* Angiographic patterns of drug-eluting stent restenosis and one-year outcomes after treatment with repeated percutaneous coronary intervention. *Am. J. Cardiol.* **102**, 311–315 (2008).
113. Leon, M. B. *et al.* Localized intracoronary gamma-radiation therapy to inhibit the recurrence of restenosis after stenting. *N. Engl. J. Med.* **344**, 250–256 (2001).
114. Waksman, R., Raizner, A. E., Yeung, A. C., Lansky, A. J. & Vandertie, L. Use of localised intracoronary beta radiation in treatment of in-stent restenosis: the INHIBIT randomised controlled trial. *Lancet* **359**, 551–557 (2002).
115. Holmes, D. R. Jr. *et al.* 5year final results of the SISR (Sirolimus-Eluting Stents versus Vascular Brachytherapy for In-Stent Restenosis) trial [abstract 2904–9]. *J. Am. Coll. Cardiol.* **57** (Suppl. S), E1641 (2011).
116. Mauri, L. *et al.* Cutting balloon angioplasty for the prevention of restenosis: results of the Cutting Balloon Global Randomized Trial. *Am. J. Cardiol.* **90**, 1079–1083 (2002).
117. Unterberg C. *et al.* Cutting balloon coronary angioplasty--initial clinical experience. *Clin. Cardiol.* **16**, 660–664 (1993).
118. Ozaki, Y. *et al.* A quantitative coronary angiography-matched comparison between a prospective randomised multicenter cutting balloon angioplasty and bare metal stent trial (REDUCE III) and the Rapamycin-Eluting Stent Evaluation At Rotterdam Cardiology Hospital (RESEARCH) study. *EuroIntervention* **6**, 400–406 (2010).
119. Park, S. J. *et al.* Comparison of plain balloon and cutting balloon angioplasty for the treatment of restenosis with drug-eluting stents vs bare metal stents. *Circ. J.* **74**, 1837–1845 (2010).
120. Scheller, B. *et al.* Treatment of coronary in-stent restenosis with a paclitaxel-coated balloon catheter. *N. Engl. J. Med.* **355**, 2113–2124 (2006).
121. Unverdorben, M. *et al.* Paclitaxel-coated balloon catheter versus paclitaxel-coated stent for the treatment of coronary in-stent restenosis. *Circulation* **119**, 2986–2994 (2009).

122. Joner, M. *et al.* Comparative assessment of drug-eluting balloons in an advanced porcine model of coronary restenosis. *Thromb. Hemost.* **105**, 864–872 (2011).
123. Hehrlein, C. *et al.* International first in man trial with a novel drug-eluting balloon in patients presenting with in-stent restenosis (PEPPER) [abstract 2904–8]. *J. Am. Coll. Cardiol.* **57** (Suppl. S) E1640 (2011).
124. Wijns, W. *et al.* Guidelines on myocardial revascularization: the Task Force on Myocardial Revascularization of the European Society of Cardiology (ESC) and the European Association for Cardio-Thoracic Surgery (EACTS). *Eur. Heart J.* **31**, 2501–2555 (2010).
125. US National Institutes of Health. Treatment of drug-eluting stent (DES) in-stent restenosis with SeQuent® Please paclitaxel eluting percutaneous transluminal coronary angioplasty (PTCA) catheter. *ClinicalTrials.gov* [online], http://clinicaltrials.gov/ct2/show/NCT00998439 (2011).
126. Alfonso, F. *et al.* Long-term clinical benefit of sirolimus-eluting stents in patients with in-stent restenosis results of the RIBS-II (Restenosis Intra-stent: Balloon angioplasty vs. elective sirolimus-eluting Stenting) study. *J. Am. Coll. Cardiol.* **52**, 1621–1627 (2008).
127. Holmes, D. R. Jr. *et al.* Sirolimus-eluting stents vs vascular brachytherapy for in-stent restenosis within bare-metal stents: the SISR randomized trial. *JAMA* **295**, 1264–1273 (2006).
128. Stone, G. W. *et al.* Paclitaxel-eluting stents vs vascular brachytherapy for in-stent restenosis within bare-metal stents: the TAXUS V ISR randomized trial. *JAMA* **295**, 1253–1263 (2006).
129. Singh, I. M. *et al.* Drug-eluting stents versus bare-metal stents for treatment of bare-metal in-stent restenosis. *Catheter. Cardiovasc. Interv.* **76**, 257–262 (2010).
130. Mehilli, J. *et al.* Randomized trial of paclitaxel- versus sirolimus-eluting stents for treatment of coronary restenosis in sirolimus-eluting stents: the ISAR-DESIRE 2 (Intracoronary Stenting and Angiographic Results: Drug Eluting Stents for In-Stent Restenosis 2) study. *J. Am. Coll. Cardiol.* **55**, 2710–2716 (2010).
131. Huang, S., Bjornsti, M. A. & Houghton, P. J. Rapamycins: mechanism of action and cellular resistance. *Cancer Biol. Ther.* **2**, 222–232 (2003).
132. Orr, G. A., Verdier-Pinard, P., McDaid, H. & Horwitz, S. B. Mechanisms of Taxol resistance related to microtubules. *Oncogene* **22**, 7280–7295 (2003).
133. Cosgrave, J. *et al.* Repeated drug-eluting stent implantation for drug-eluting stent restenosis: the same or a different stent. *Am. Heart J.* **153**, 354–359 (2007).
134. Costa, M. A. Treatment of drug-eluting stent restenosis. *Am. Heart J.* **153**, 447–449 (2007).
135. Aminian, A., Kabir, T. & Eeckhout, E. Treatment of drug-eluting stent restenosis: an emerging challenge. *Catheter. Cardiovasc. Interv.* **74**, 108–116 (2009).
136. Fishbein, I. *et al.* Bisphosphonate-mediated gene vector delivery from the metal surfaces of stents. *Proc. Natl Acad. Sci. U. S. A.* **103**, 159–164 (2006).
137. Sharif, F. *et al.* Gene-eluting stents: adenovirus-mediated delivery of eNOS to the blood vessel wall accelerates re-endothelialization and inhibits restenosis. *Mol. Ther.* **16**, 1674–1680 (2008).
138. Johnson, T. W. *et al.* Stent-based delivery of tissue inhibitor of metalloproteinase3 adenovirus inhibits neointimal formation in porcine coronary arteries. *Arterioscler. Thromb. Vasc. Biol.* **25**, 754–759 (2005).
139. Egashira, K. *et al.* Local delivery of anti-monocyte chemoattractant protein1 by gene-eluting stents attenuates in-stent stenosis in rabbits and monkeys. *Arterioscler. Thromb. Vasc. Biol.* **27**, 2563–2568 (2007).
140. Walter, D. H. *et al.* Local gene transfer of phVEGF2 plasmid by gene-eluting stents: an alternative strategy for inhibition of restenosis. *Circulation* **110**, 36–45 (2004).
141. Brasen, J. H. *et al.* Extracellular superoxide dismutase accelerates endothelial recovery and inhibits in-stent restenosis in stented atherosclerotic Watanabe heritable hyperlipidemic rabbit aorta. *J. Am. Coll. Cardiol.* **50**, 2249–2253 (2007).