Pro-healing drug-eluting stents: a role for antioxidants?

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ABSTRACT

Current strategies to lower the incidence of ISR (in-stent restenosis) following PCI (percutaneous coronary intervention) are aimed at modifying arterial healing after stent injury. This can impair endothelial recovery and render the vessel prone to acute thrombosis. As early restoration of endothelial integrity inhibits neointimal growth and thrombosis, alternative approaches which encourage this process may provide a more effective long-term result after PCI. Oxidative stress is enhanced after PCI and participates in the regulation of endothelial regeneration and neointimal growth. Moreover, evidence suggests antioxidants improve re-endothelialization and inhibit ISR. By promoting, rather than blocking, the healing process, antioxidant and other therapies may offer an alternative or additional approach over the antiproliferative approaches common to many current devices.

INTRODUCTION

The enthusiasm surrounding BMS (bare metal stents) as a durable treatment for atherosclerotic coronary disease was restricted by ISR (in-stent restenosis) which occurred in between 10 and 60% of cases, depending on lesion and patient characteristics [1]. Accordingly, since the introduction of coronary stents, much work has been done to understand the biological mechanism of ISR so that preventative measures can be developed. It is important to ensure that a device which inhibits ISR does not impair other important biological processes, as this may result in clinical failure. This review will discuss the mechanism of ISR as a proliferative healing response to arterial injury and the effectiveness of first-generation DES (drug-eluting stents) in tackling this problem. It will also consider the role of oxidative stress in vascular repair, with a focus on the potential role of antioxidant therapy to both promote endothelial regeneration and prevent ISR, so that an optimal clinical result can be achieved.

ISR AS A RESPONSE TO INJURY

It is clear that implantation of a coronary stent causes significant injury to the surrounding artery wall. The process of ISR closely resembles the natural wound healing process, typically occurring over several weeks. An integrated view of the molecular and cellular events leading to ISR has been proposed by Welt and Rogers [2]. Stent deployment causes severe endothelial denudation, which leads to platelet and fibrin deposition on the...
injured artery wall. Activated platelets expressing adhesion molecules, such as P-selectin, attach to circulating leucocytes via platelet receptors, such as P-selectin glycoprotein ligand. Leucocytes roll along the injured wall and then bind tightly to the surface through the leucocyte integrin Mac-1 (CD11b/CD18) class of adhesion molecules via direct attachment to platelet receptors GPIIbα and through cross-linking with fibrinogen to the GPIIbIIIa receptor. Under the influence of chemokines, such as MCP-1 (monocyte chemoattractant protein-1), IL (interleukin)-6 and IL-8, released from VSMCs (vascular smooth muscle cells) and resident macrophages, leucocytes infiltrate the artery wall. Growth factors, such as FGF (fibroblast growth factor), PDGF (platelet-derived growth factor), IGF (insulin-like growth factor), TGF-β (transforming growth factor-β) and VEGF (vascular endothelial growth factor), are released from platelets, leucocytes and VSMCs, which stimulate VSMCs to proliferate and migrate from the media into the neointima. Ongoing VSMC proliferation, macrophage infiltration and extracellular matrix production causes NIH (neointimal hyperplasia), the pathognomonic feature of ISR. Luminal narrowing due to elastic recoil and negative remodelling common after balloon angioplasty is prevented by the stent struts, but the neointimal response is exaggerated and proportional to the degree of stent injury [3]. Endothelial repair involves EC (endothelial cell) migration, which is the critical and rate-limiting initiating step, followed by EC proliferation [4]. As the denuded endothelium regenerates, it completely recovers the neointimal surface, allowing the vessel to return to normal function.

So far, most attempts to inhibit NIH have been based upon disruption of the normal healing process. Although many devices have had initial success, it is now becoming clear that a strategy designed to prevent arterial healing may significantly impair endothelial regeneration and remain suboptimal in terms of other important clinical outcomes, such as stent thrombosis.

**IMPORTANCE OF ENDOTHELIAL REGENERATION**

The vascular endothelium is an essential component of the artery wall, therefore delayed or incomplete healing is undesirable for a number of reasons. First, the early regrowth of a functional endothelial layer is capable of attenuating NIH, the principle cause of ISR. After injury, ECs regulate VSMC proliferation by the release of well-characterized growth promoters and inhibitors [5]. Damage to the endothelium results in the activation of VSMC proliferation, whereas repair of the endothelium leads to the reversal of this process and restoration of VSMC quiescence [6]. EPCs (endothelial progenitor cells) are implicated in endothelial regrowth, and intravenous transfusion of EPCs has been shown to reduce NIH in a mouse model of arterial injury [7]. A pilot study in patients using stents coated with anti-CD34 antibodies to target EPC surface antigens has shown encouraging clinical efficacy with a low incidence of ISR [8]. Gene transfer of VEGF in a rabbit model of balloon injury has resulted in inhibition of NIH in some cases [9], but not in others [10], and the role of catheter-based local VEGF gene delivery after human angioplasty is under development [11]. A strategy utilizing VEGF-gene-eluting stents may offer an effective technique if the results of a promising rabbit study can be reproduced [12].

In addition to providing a mechanism of ISR prevention, the regeneration of the endothelium is integral to the maintenance of normal coronary vascular tone through the action of a number of vasoactive substances including NO. Endothelial vasomotor dysfunction is a characteristic precursor to many cardiovascular disease states and predicts the risk of subsequent vascular events.

Finally, and crucially following stent deployment, regrowth of a functional endothelium is fundamental to luminal patency. Normally, the intact endothelial monolayer provides a non-thrombogenic surface for blood flow and acts as the primary regulator of haemostasis and thrombosis. The endothelium serves as a non-permeable barrier between circulating platelets and agonists, such as collagen, widely present in plaque and artery wall, which can stimulate platelet aggregation. It also restricts exposure of blood coagulation factors to the subendothelial layer, which is rich in tissue factor, the primary trigger of the coagulation system. ECs directly inhibit thrombosis via the antiplatelet effects of released NO [13], prostacyclin [14] and endothelial cell CD39, an ecto-ADPase [15]. Endothelial-derived heparan sulfate, thrombomodulin and tissue factor pathway inhibitor are inhibitors of coagulation [16]. The endothelium regulates the endogenous fibrinolytic system by the release of endothelial tPA (tissue plasminogen activator), which plays a significant role in thrombus dissolution during acute coronary syndromes [17]. Consequently, an absent or functionally deficient endothelium provides unfavourable conditions which impair the natural defence of the coronary circulation against acute thrombosis, particularly in the milieu of an intrinsically thrombogenic metal stent (Figure 1).

**FIRST-GENERATION DES**

DES have dramatically reduced the incidence of ISR [18]. The two most commonly used devices are the polymer-based sirolimus-eluting stent (Cypher; Cordis) and the polymer-based paclitaxel-eluting stent (Taxus; Boston Scientific). These DES limit NIH by inhibiting the cell cycle of proliferating cells. Sirolimus-eluting
Figure 1  Effect of PCI on the artery wall
A healthy endothelium normally prevents thrombosis through the actions of prostacyclin (PGI$_2$), ADPase, tPA and NO. Early re-endothelialization is required to protect the artery from thrombosis and can limit NIH. PCI injury causes major O$_2^-$ release, which promotes NIH and impairs re-endothelialization. Antioxidants may limit NIH and encourage re-endothelialization by scavenging O$_2^-$. First-generation DES reduce NIH, but also impair re-endothelialization.

Clinical Consequences of First-Generation DES
Owing to suboptimal endothelial regeneration following DES treatment, combined antiplatelet therapy with aspirin and clopidogrel needs to be extended by at least several months during the perceived re-endothelialization period. If prolonged dual antiplatelet regimes are used, DES do not appear to increase the risk of stent thrombosis at 12 months compared with BMS [31]. However, as follow-up continues beyond a year, there is a concern that DES may present an increased risk of late myocardial infarction and death, a clinical surrogate of stent thrombosis [32,33]. Although complete patient level meta-analyses of the randomized trials with DES demonstrate no increase in cardiovascular events compared with BMS, there is a significantly increased risk of late stent thrombosis [34]. Consequently, there is now a considerable responsibility upon the interventional community to ensure that the next generation of DES are safe, and inevitably that means ensuring the endothelium is able to regenerate in a timely fashion.

Newer ‘Sirolimus Analogue’ DES
Following the introduction of the sirolimus- and paclitaxel-eluting stents and particularly since the reporting of late stent thrombosis with current devices, there has been interest in testing novel DES with alternative biological profiles. By modifying the chemical structure of...
sirolimus slightly, it is possible to create derivatives with improved tissue absorption and differential effects on cell proliferation. Zotarolimus is a highly lipophilic sirolimus analogue with antiproliferative and anti-inflammatory properties. A zotarolimus-eluting stent has been tested as part of the Endeavor stent (Medtronic Vascular), utilizing a cobalt alloy stent platform and highly bioabsorbable phosphorylcholine polymer. This zotarolimus-eluting stent effectively reduced ISR compared with BMS [35], but not compared with sirolimus-eluting stents, where angiographic late luminal loss was increased [36]. Nevertheless, although the efficacy of DES remains heavily reliant on an ability to limit occlusive ISR, complete abolition of NIH is no longer deemed necessary and may in fact reflect inadequate tissue coverage over the stent. In fact, a mild degree of subclinical luminal loss may represent a good compromise between antiproliferative efficacy and safety profile. The polymer-based everolimus-eluting cobalt chromium stent (Xience V; Advanced Cardiovascular Systems) has demonstrated efficacy in terms of reducing the incidence of ISR compared with BMS [37] and paclitaxel-eluting stents [38]; however, the long-term safety of this (and the zotarolimus-eluting stent) is unknown.

Localized hypersensitivity reactions in the artery wall associated with long-term exposure to the stent polymer [23] have prompted new attempts to provide effective drug elution from the stent without the necessity of a permanent polymer. One such development is the introduction of the bioabsorbable polymer which is completely biodegraded after a few months, removing the chronic stimulus for polymer-induced inflammatory reactions after drug elution is complete. An everolimus-eluting stent with bioabsorbable polymer is currently undergoing investigation, and early trials demonstrate a reduction in the incidence of ISR compared with BMS [39,40]. Other workers have reported preliminary safety and efficacy data for a biolimus A9-eluting stent with a bioabsorbable polymer [41]. A recent development in the field is the incorporation of dual drug technology, an example of which is the testing of a pimecrolimus/paclitaxel-eluting coronary stent system with a bioabsorbable polymer [42]. Pimecrolimus is believed to have additional anti-inflammatory properties, by inhibiting the production and release of pro-inflammatory cytokines. Some newer DES have omitted the polymer altogether, controlling antiproliferative drug release using a microporous or reservoir-based stent design. So far, there is satisfactory angiographic efficacy data for a non-polymer rapamycin-eluting stent [43], paclitaxel-eluting stent [44] and tacrolimus-eluting stent [45], although the latter had disappointing neointimal suppression compared with its uncoated version.

Preliminary findings have been collected with fully bioabsorbable DES, possibly the ideal platform for drug delivery if optimal biocompatibility and mechanical properties can be successfully incorporated [46]. Interestingly, in terms of drug selection, there is limited preclinical data suggesting everolimus [47] or tacrolimus [48,49] may have superior effects on EC biology compared with sirolimus; however, it is perhaps unduly optimistic to expect that the effect on arterial healing after PCI (percutaneous coronary intervention) will differ greatly in human studies. Worryingly, recent patient registries suggest that the incidence of thrombosis induced by first-generation DES in clinical practice was underestimated by earlier randomized trials [50], and long-term safety data on these sirolimus analogue DES are awaited with interest.

**EVIDENCE FOR OXIDATIVE STRESS FOLLOWING ANGIOPLASTY**

Oxidative stress plays a central role throughout the atherosclerotic process. From the formation of the fatty streak in early atherogenesis to the triggering of plaque rupture in acute coronary syndromes, the effect of increased oxidative stress on the coronary vasculature is profound. Oxygen is an abundant molecule found in the body and can undergo univalent reduction to form $O_2^-$ (superoxide anion), a powerful ROS (reactive oxygen species) and major component of oxidative stress. The formation of $O_2^-$ in cardiovascular disease occurs through the action of a number of enzymes, the foremost of which is NOX (NADPH oxidase). This enzyme is active in ECs, leucocytes and platelets, but VSMCs and fibroblasts are the principle source of activity following angioplasty. The extensive mechanical trauma of PCI causes a large number of ROS to be released, proportional to the degree of injury. Animal models of coronary angioplasty have shown that production of $O_2^-$ occurs immediately after balloon injury as a result of NOX activity and this is sustained for several days [51,52]. Supporting evidence for enhanced oxidative stress following PCI in humans has been confirmed by coronary venous sampling [53]. Similar to its important role in other biological processes, oxidative stress is a critical mediator of arterial healing in response to injury.

**OXIDATIVE CONTROL OF CELLULAR PROCESSES AFTER ARTERIAL INJURY**

It is clear that oxidative stress is enhanced after arterial injury and, by influencing multiple signalling pathways involved in the pathophysiology of vascular repair, it appears to play a major role in the regulation of NIH [54]. Early transient exposure to oxidized glutathione, a known usual consequence of oxidative stress, is capable of amplifying cell proliferation and NIH, which is sustained for weeks after arterial balloon injury and is mediated
through a redox-active metal-dependent pathway [55]. The activation of the transcription factor NF-κB (nuclear factor κB) is enhanced by redox processes after injury [51], and this may have a lasting effect on the gene programme involved in NIH, including expression of VCAM-1 (vascular cell adhesion molecule-1), MCP-1 and other pro-inflammatory factors [56,57]. ROS serve as second messengers to activate many intracellular proteins and enzymes, including the EGFR (epidermal growth factor receptor), c-Src, p38 MAPK (mitogen-activated protein kinase), Ras and Akt/PKB (protein kinase B), which suggests a major role in the regulation of VSMC growth and migration, modification of extracellular matrix and modulation of endothelial function [58]. The response of VSMCs to PDGF (which includes tyrosine phosphorylation, MAPK stimulation, DNA synthesis and chemotaxis) is at least partly dependent on elevated intracellular levels of the ROS H2O2 [59].

The prominent influence of oxidative stress on NIH after vascular injury is matched by a major involvement in the regulation of endothelial recovery. oxLDL (oxidized LDL (low-density lipoprotein)) is formed by the oxidative modification of native LDL in the bloodstream and is widely present in coronary artery lesions. Atherosclerotic plaques enriched with high levels of oxLDL are more likely to become unstable [60], and plasma oxLDL is acutely elevated after PCI [61]. oxLDL is toxic to EPCs [62], which are likely to suffer from impaired antioxidant defences in the presence of atherosclerosis [63]. oxLDL is also a potent inhibitor of EC migration and this occurs via an O2− -dependent mechanism [64]. As a result, oxLDL may influence healing of a stent deeply embedded into coronary lesions such that the rate of endothelialization is suboptimal, even with BMS. The inhibitory effect of oxLDL on EC migration in culture is blocked by the antioxidant vitamin E [65]. Uptake of the lipophilic antioxidants probucol and vitamin E both stimulate EC proliferation in culture [66] and are protective against the harmful effects of other ROS [67]. NO released by the endothelium encourages migration and growth of ECs [68], and eNOS (endothelial NO synthase) expression is increased in regenerating endothelium following injury [69]. However, in situations where there is major oxidative stress, such as following PCI, there is widespread scavenging of NO by local ROS. An example of this is the reaction of NO with O2− to form peroxynitrite, one of the most potent endocellular oxidants [70]. The protective effect of NO on endothelial regeneration is therefore lost and, instead, peroxynitrite is produced, which is itself harmful to ECs [71]. These experimental findings support a role for antioxidant therapy delivered to the site of arterial injury to defend the regenerating endothelium against the deleterious effects of oxLDL, O2−, peroxynitrite and other toxic ROS, while allowing NO to have a protective effect on the healing process.

**EFFECTS OF ANTIOXIDANTS ON RESTENOSIS AND HEALING AFTER ANGIOPLASTY**

The experimental work supporting the role of antioxidants to inhibit NIH and improve endothelial repair is reinforced by many *in vivo* studies suggesting that strategies to decrease oxidative stress reduce restenosis and can encourage re-endothelialization after PCI (Table 1).

As the major source of ROS after balloon injury is via NOX, inhibitors of this enzyme have been tested and found to reduce NIH in animal models of restenosis [72,73]. SOD (superoxide dismutase) is an enzyme which readily metabolizes O2−, converting it into the less reactive molecule H2O2. Delivery of extracellular SOD gene therapy to the artery wall after balloon denudation of the rabbit aorta led to reduced NIH and improved endothelial recovery [74]. Another study in atherosclerotic rabbit iliac arteries showed that gene transfer of both SOD and catalase (an enzyme which decomposes H2O2) was able to dramatically reduce the level of ROS release from the artery wall after balloon angioplasty [75]. This was accompanied by reduced neointimal inflammation and less restenosis, with improved re-endothelialization and endothelial function. Despite some evidence that NO encourages EC growth *in vitro*, l-arginine (NO precursor) had no effect on re-endothelialization in denuded rabbit iliac arteries, although it effectively inhibited neointimal growth [76].

Early trials of probucol administration in animal models of balloon angioplasty demonstrated a reduction in NIH and subsequent restenosis [77,78]. Probucol restricts the severity of NIH by inhibiting VSMC proliferation via enhanced G1/S-phase growth arrest and improving endothelial healing [79]. A major mechanism by which probucol mediates these beneficial effects is believed to be via the up-regulation of HO-1 (haem oxygenase-1), which induces VSMC apoptosis (through the production of haem breakdown products such as CO, biliverdin and bilirubin) and promotes EC function [80]. In keeping with these findings, supplementation of probucol inhibited NIH and improved functional re-endothelialization in a rabbit model of aortic balloon injury [79]. Owing to the positive animal studies, probucol has now been extensively tested in clinical trials, perhaps more than any other antioxidant compound. The MVP (Multivitamins and Probucol) trial and PART (Probucol Angioplasty Restenosis trial) both demonstrated a clear reduction in restenosis after coronary angioplasty [81,82]. A subsequent IVUS (intravascular ultrasound) substudy of the MVP trial showed that the beneficial effect of oral probucol was related primarily to improvements in post-angioplasty remodelling [83]. Investigation in the stent era has continued with a variety of clinical trials examining the effects of probucol on ISR. The use of probucol approximately halved ISR rates in a human angiographic study, although the effect became significant...
Table 1 Summary of the main antioxidant studies for restenosis and re-endothelialization

<table>
<thead>
<tr>
<th>Study</th>
<th>Antioxidant</th>
<th>Dose</th>
<th>Setting</th>
<th>Main findings</th>
</tr>
</thead>
<tbody>
<tr>
<td>Jacobson et al. [72]</td>
<td>NOX inhibitor</td>
<td>IP minipump</td>
<td>Rat carotid balloon injury</td>
<td>Reduced NIH (P &lt; 0.05)</td>
</tr>
<tr>
<td>Douron et al. [73]</td>
<td>NOX inhibitor</td>
<td>Gene transfer</td>
<td>Rat carotid balloon injury</td>
<td>Reduced NIH (P &lt; 0.05)</td>
</tr>
<tr>
<td>Laukkanen et al. [74]</td>
<td>SOD</td>
<td>Gene transfer</td>
<td>Rabbit aortic balloon injury</td>
<td>Reduced NIH and improved re-endothelialization (both P &lt; 0.001)</td>
</tr>
<tr>
<td>Durand et al. [75]</td>
<td>SOD/CAT</td>
<td>Gene transfer</td>
<td>Rabbit iliac balloon injury</td>
<td>Reduced restenosis and improved re-endothelialization (both P &lt; 0.05)</td>
</tr>
<tr>
<td>Schneider et al. [77]</td>
<td>Probucol</td>
<td>Oral; 0.75% (w/w)</td>
<td>Rabbit aortic balloon injury</td>
<td>Reduced NIH (P &lt; 0.001)</td>
</tr>
<tr>
<td>Miyachi et al. [78]</td>
<td>Probucol</td>
<td>Oral; 1 g/day</td>
<td>Human coronary stent</td>
<td>Reduced restenosis (P &lt; 0.001)</td>
</tr>
<tr>
<td>Lau et al. [79]</td>
<td>Probucol</td>
<td>Oral; 1 g/day</td>
<td>Human coronary stent</td>
<td>Reduced restenosis (17 compared with 32%, P = NS)</td>
</tr>
<tr>
<td>Tanous et al. [89]</td>
<td>Probucol</td>
<td>Oral; 1% (w/w)</td>
<td>Human coronary stent</td>
<td>Reduced restenosis and NIH (both P &lt; 0.05), and improved re-endothelialization (P = 0.008)</td>
</tr>
<tr>
<td>Tardif et al. [81]</td>
<td>Probucol</td>
<td>Oral; 1 g/day</td>
<td>Human PTCA</td>
<td>Reduced restenosis (mainly due to improved remodelling) (P = 0.003) and reduced repeat PTCA (P = 0.009)</td>
</tr>
<tr>
<td>Yokoi et al. [82]</td>
<td>Probucol</td>
<td>Oral; 1 g/day</td>
<td>Human PTCA</td>
<td>Reduced restenosis (P &lt; 0.01)</td>
</tr>
<tr>
<td>Sekiya et al. [84]</td>
<td>Probucol</td>
<td>Oral; 500 mg/day</td>
<td>Human coronary stent</td>
<td>Reduced restenosis rate (21 compared with 24%; P = NS) but became significant only when combined with cilostazol (P &lt; 0.05)</td>
</tr>
<tr>
<td>Kim et al. [85]</td>
<td>Probucol</td>
<td>Oral; 500 mg/day</td>
<td>Human coronary stent</td>
<td>Reduced restenosis rate (17 compared with 32%, P = NS)</td>
</tr>
<tr>
<td>Wakeyama et al. [86]</td>
<td>Probucol</td>
<td>Oral; 500 mg/day</td>
<td>Human coronary stent</td>
<td>Reduced NIH (P &lt; 0.001) and reduced restenosis (P = 0.1) in combination with candesartan compared with candesartan alone</td>
</tr>
<tr>
<td>Tardif et al. [87]</td>
<td>AGI-1067</td>
<td>Oral; 280 mg/day</td>
<td>Human coronary stent</td>
<td>Increased follow-up LA (P &lt; 0.05) due to greater acute gain</td>
</tr>
<tr>
<td>Nunes et al. [88]</td>
<td>Probucol</td>
<td>Oral; 1 g/day</td>
<td>Human coronary stent</td>
<td>No effect on NIH or restenosis</td>
</tr>
<tr>
<td>Kim et al. [90]</td>
<td>Carvedilol</td>
<td>Stent delivery</td>
<td>Pig coronary DES</td>
<td>No effect on NIH or restenosis</td>
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<td>Tardif et al. [87]</td>
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<td>Pig coronary DES</td>
<td>Reduced NIH (P = 0.004) and reduced restenosis (P = 0.002)</td>
</tr>
</tbody>
</table>

only when the drug was combined with the phosphodiesterase inhibitor cilostazol [84]. Another trend to reduced ISR was found in another clinical trial [85]; however, the study design was limited by inadequate drug loading of oral probucol, which accumulates slowly in tissues. A clinical trial designed to determine the effect of candesartan and probucol on ISR found no benefits from angiotensin receptor blockade; however, if probucol was used, there were significant reductions in angiographic late loss and NIH as determined by IVUS analysis [86]. The large CART-1 (Canadian Antioxidant Restenosis Trial) demonstrated efficacy of both oral probucol and AGI-1067 (a probucol analogue) in the prevention of ISR, although the effects were driven by a larger acute gain of luminal dimensions in the antioxidant groups [87]. In a more recent clinical study, oral probucol failed to reduce ISR following PCI, as determined by IVUS [88]. However, this result must be treated with caution as notable confounding factors known to increase the risk of ISR were present in the probucol group, such as the treatment of significantly smaller vessels and a higher incidence of diabetes and acute lesions. A recent animal study which looked specifically at the effects of probucol on healing after stent injury reported a considerable improvement in stent endothelialization accompanied by a reduction in NIH and less evidence of stent thrombosis [89]. In this trial, probucol therapy also reduced leukocyte accumulation around the stent struts, suggesting its anti-inflammatory effects may play a significant role in neointimal suppression.

The studies mentioned above testing probucol in particular as a treatment to reduce restenosis after balloon angioplasty or stenting have relied on oral administration. Studies which demonstrated the most impressive reductions in ISR were generally performed in animals, where oral dosing is possible at a level which is not possible in clinical practice. The application of stent-based delivery of antioxidants may offer an ideal opportunity to achieve optimal local tissue concentrations while minimizing toxic systemic side effects. Preliminary work has been done with carvedilol, a β-blocker with potent antioxidant activity. It has been shown recently that implantation of a carvedilol-coated stent in a porcine model is capable of inhibiting ISR.
and providing complete re-endothelialization [90]. The same study failed to demonstrate a beneficial effect with a probucol-coated stent, although there were serious concerns about adequate drug delivery.

CONCLUSIONS

In summary, it is clear that endothelial recovery is essential to maintain safety and performance of coronary stents. ROS are released in large amounts following PCI and are closely linked to restenosis and endothelial regeneration. The use of antioxidant compounds may suppress detrimental complications, such as restenosis, while encouraging vital processes, such as early and complete re-endothelialization and recovery of EC function. Although virtually abolishing late luminal loss, the current DES have failed to reassure the cardiology community with regard to the antiproliferative effects on the artery wall. As a consequence, the inadequately healed coronary segment provides a focal point for potentially catastrophic events which frequently result in a large myocardial infarction and high risk of death. The stage is set for a new generation of DES, of which there are many already under development, and it is likely that stents which tackle the overwhelming influence of ROS on the arterial healing process will offer an alternative or additional approach to overcome the new Achilles’ heel of DES.

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