New Drug−Eluting Stents

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ABSTRACT

The introduction of drug-eluting stents (DES) has rapidly and profoundly affected the field of interventional cardiology, and DESs are now used in a majority of intracoronary stenting procedures. As a result of the innumerable "trial-and-error" endeavors, DESs have emerged as a potential solution for solving the problem of restenosis. DESs are coated stents capable of releasing single or multiple bioactive agents into the bloodstream and the surrounding tissues. The efficacy and safety of DESs might differ depending on the pharmacologic agents and stent delivery systems that are used. Recent research has focused on the various constituents of DESs, including the stent backbone, the materials used as drug-delivery vehicles, and the physicochemical properties of the pharmacotherapeutic agents themselves. Stent-induced mechanical arterial injury and a foreign body response to the prosthesis incite acute and chronic inflammation in the vessel wall, along with the elaboration of cytokines and growth factors that induce multiple signaling pathways to activate smooth muscle cell migration and proliferation. Utilization of antiproliferative agents delivered locally via the drug-eluting stents has dramatically reduced the stent restenosis rate. The polymer-regulated delivery of both paclitaxel and sirolimus at the site of arterial injury has been shown to reduce the clinical and angiographic restenosis rates after stent implantation in de novo coronary lesion. Other DESs have yielded somewhat less brilliant results or even true failures, while a number of new drugs and new stent platforms are now under clinical or preclinical evaluation. In this review, we describe the main clinical trials on DESs and the most recent information that has been derived from observational studies and registries. Moreover, the preliminary results on the new DESs are also summarized. (**Korean Circulation J 2005;35:197−205**)

KEY WORDS : Coronary disease ; Stents ; Restenosis.

Introduction

Although several studies have indicated overwhelmingly positive results with using stent-based drug delivery for the prevention of restenosis,[1)2)] and early clinical trials of several agents have also seemed promising, larger studies with longer-term follow-up have subsequently led to the conclusion that the efficacy and safety might differ among the pharmacologic agents and among the stent delivery systems. Consequently, the research focus has been directed toward the various constituents of drug-delivery stents, which include the stent backbone, the materials used as drug-delivery vehicles, and the physicochemical properties of the pharmacotherapeutic agents themselves. The concept of using stents as vehicles for the prolonged and sufficient intramural delivery of drugs is appealing. Stents represent an ideal platform for local drug delivery because of their permanent scaffolding properties that prevent vessel recoil and negative remodeling. In addition, the stents represent drug reservoirs, inasmuch as medications are released from various coatings at different time intervals. In principle, most of the DES technologies face many potential limitations (Table 1).[3)]

Future generations of drug-delivery stents will require each of these above parameters to be optimized to provide the greatest possible efficacy and safety. Although a specific targeted mechanism of action is an important consideration, many agents have been demonstrated to have multiple mechanisms by which they might suppress the restenotic process. Based on the mechanism of action of the biological compound and its target in the restenotic process, drug-eluting stents (DES) may be generally classified into the immunosuppressive, antiproliferative, antiinflammatory, antithrombotic and prohealing stents. These types of DESs are summarized on Table 2.[4)]

Stents eluting antiinflammatory agents

There is increasing evidence that inflammation plays an important role in the initiation and development of neoint-

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imal hyperplasia and the subsequent restenosis. Because of their role in restenosis, inflammatory cells seemed to be an optimal target in the fight against restenosis.

Corticosteroid-eluting stents

Indeed, corticosteroids have long been known to reduce the influx of mononuclear cells, to inhibit monocyte and macrophage function, and to influence smooth muscle cell proliferation.[5] However, the data that is available on the utility of antiinflammatory DESs is limited.

The Study of anti-RestenosIs with the BiodivYsio Dexamethasone-Eluting stent (STRIDE)[6] was a multicenter pilot study that was conducted to evaluate the acute safety and efficacy of the dexamethasone-eluting stent (0.5 μ g/mm^2 of stent) when it was implanted in patients with de novo single-

vessel disease. This study included 71 patients and 42% of them had unstable angina. An appropriately sized Biodiv-Ysio Matrix Lo stent that was loaded with a total dexamethasone dose of 0.5 μ g/mm^2 was used. The binary restenosis rate was 13.3% and the late loss was 0.45 mm. This study demonstrated the feasibility and safety for the implantation of a dexamethasone-eluting stent, and the study also demonstrated its effect on in-stent neointimal hyperplasia.

Hoffmann et al.[7] evaluated the safety and efficacy of a dexamethasone-eluting stent having a special high dexamethasone-loading dose for the treatment of de novo coronary lesions in 30 patients. Eight patients experienced in-stent restenosis (restenosis rate 31%) at the 6-month follow-up, and the in-stent late lumen loss was 0.96 ± 0.63 mm due to an average intimal hyperplasia obstruction area of $32 \pm 21\%$, indicating that high-dose dexamethasone-loaded stents do not significantly reduce neointimal proliferation.

Tranilast-eluting stents

Tranilast, N-(3,4-dimethoxycinnamoyl) anthranilic acid, inhibits the release or the production of chemical mediators and cytokines by the inflammatory cells and macrophages, and it interferes with the proliferation and migration of vascular medial smooth muscle cells that is induced by platelet-derived growth factor and transforming growth factor-β_1.[8] The anti-inflammatory effects of tranilast have been demonstrated for the inhibition of prostaglandin E$_2$, thromboxane B$_2$, transforming growth factor-β_1 and interleukin-8 in in vitro models, and tranilast has also shown it ability to attenuate the proinflammatory activity of human monocytes.[8] Further,

Table 1. Pitfalls and corresponding variables influencing drug-eluting stent performance

Pitfalls	Variables
Bio and blood compatibility	Physicochemical properties of the polymer and drug
Limited surface area (usually <20%) of current stents	Drug potency; total amount of drug
Maintain drug properties after coating	Degree of cross-linking
Heterogeneous underlying tissue characteristics	Drug solubility
Sterilization and stent expansion	Polymer and drug elasticity
Inflammation	Porosity of the polymer, molecular weight of the polymer, thickness of the coating, degree and mode of degradation; drug toxicity; local drug concentration (per mm^2); drug solubility

Table 2. Drug-eluting stents: pharmacologic reduction of restenosis

Anti-inflammatory Immunomodulators	Anti-proliferative	Migration inhibitors, ECM-modulators	Promote healing and re-endothelization
Dexamethasone	QP-2, Taxol	Batimastat	BCP671
M-prednisolone	Actinomycin	Prolyl hydroxylase inhibitors	VEGF
Interferon γ-1b	Methotrexate	Halofuginone	Estradiols
Leflunomide	Angiopeptin	C-proteinase inhibitors	NO donors
Sirolimus (and analogues)	Vincristine	Probucol	EPC antibodies
Tacrolimus	Mitomycin	Abciximab	Biorest
Mycophenolic acid	Statins		Advanced coatings
Mizoribine	C-MYC antisense		Carvedilol
Statins	Sirolimus (and analogues)		Abciximab
Cyclosporine	RestenASE		
Tranilast	2-chloro-deoxyadenosine		
Biorest	PCNA ribozyme		
Abciximab	Abciximab		

ECM: extracellular matrix, PCNA: proliferating cell nuclear antigen, VEGF: vascular endothelial growth factor, NO: nitric oxide, EPC: endothelial progenitor cell

in various animal models, tranilast has been shown to reduce neointimal and adventitial thickening after vascular wall injury.[9)10)] Systemic use of this agent for the prevention of restenosis was tested in a large multicenter trial, but the results were disappointing.[11)] Initial experiments with the biodegradable Igaki-Tamai stent loaded with 184 μg of tranilast per stent have been initiated, but the results are still pending.

Stents eluting immunosuppressive agents

Encouraged by the early experience with ionizing radiation therapy, researchers have proposed sophisticated pharmacological strategies for interfering with cell cycle division.[12)] Xenobiotic molecules (rapamycin, FK506, cyclosporine, and analogues) and antimetabolites (mycophenolate mofetil) have been utilized.

Rapamycin analogue-eluting stents

Everolimus, [40-O-(2-hydroxyethyl)-rapamycin], is an inhibitor of the mammalian target of rapamycin (mTOR). It has been shown to inhibit proliferation of hematopoietic and nonhematopoietic cells. Although the immunosuppressive activity of everolimus is 2- to 3-fold lower than sirolimus in vitro, animal studies have shown the potent antirestenotic effect of everolimus when it is given orally or via a DES.[13)] The S-Stent (Biosensor) has been impregnated with a blend of everolimus and a slowly biodegradable hydroxyacid polylactic acid polymer.

The First Use To Underscore Reduction in restenosis with everolimus (FUTURE) study[14)] was the first human evaluation of the everolimus-eluting stent (EES) for the treatment of noncomplex coronary lesions. Forty-two patients with de novo coronary lesions (2.75 to 4.00 mm vessels; lesion length: <18 mm) were prospectively randomized in a 2:1 ratio to receive either the EES (n=27) or a metallic stent (n=15). At the 6-month follow-up, the EES had a lower in-stent late lumen loss (0.10±0.22 vs 0.85±0.32 mm, respectively, p< 0.0001) and a lower in-segment diameter stenosis (20.7± 12.3% vs 37.0±15.8 respectively), than the metallic stent.

In the second feasibility trial that included diabetics, the multicenter trial FUTURE II confirmed the initial beneficial findings of FUTURE I in a total study population of 64 patients with a 1:2 randomization for comparing with a bare metal control stent. Based on these results, the FUTURE program has now been expanded by Guidant with two large-scale multicenter studies, FUTURE III and IV, which will evaluate this stent design in a larger patient population. Fur-

thermore, the FUTURE IV study is planned to demonstrate the non-inferiority of this stent concept in a head-to-head comparison with an approved DES concept.

ABT-578 (methyl rapamycin) is a new synthetic analog of rapamycin that is designed to inhibit smooth muscle cell proliferation, which is a key contributor to restenosis, by blocking the function of the mTOR cell cycle regulatory protein. Given these pharmacodynamics, ABT-578 was considered beneficial for intracoronary delivery to arrest the processes responsible for neointimal hyperplasia after angioplasty and stenting. Consequently, the ABT-578-eluting ENDEAVOR stent system has been created, and it represents a potential new alternative for treating patients with coronary heart disease.

In order to evaluate the safety, feasibility and efficacy of this stent design, the ENDEAVOR clinical program has been started and it includes three randomized clinical trials. ENDEAVOR I is the first-in-human trial that included 100 patients with native de novo coronary lesions. The recently presented 4-month follow-up data has demonstrated the safety and feasibility of this new drug-eluting stent (DES) concept with a 4-month major adverse cardiac events rate of 2.0%. In order to evaluate this stent system in a larger patient population, as well as with more complex lesion subsets, the multicenter study ENDEAVOR II has been started that includes a total of 1,200 patients. The enrollment for this study was completed in January 2004. The aim of the US multicenter ENDEAVOR III study is to create a head-to-head comparison of the ENDEAVOR ABT-578-eluting stent system with the already approved sirolimus-eluting Cypher stent in 369 patients. If the results of both the pivotal studies ENDEAVOR II and III confirm the efficacy that has been observed so far for the ENDEAVOR stent design, the ENDEAVOR stent will be established as a new and promising contender in the field of DES.[15)]

FK506 (Tacrolimus)-eluting stents

Tacrolimus is a hydrophobic immunosuppressive agent that has been used clinically to prevent renal transplant rejection. It binds to the FKBP12 protein, but its mechanism of action differs from sirolimus. Tacrolimus has been shown to inhibit the release of proinflammatory cytokines and it inhibits the activation of T cells. Initial in vitro and in vivo studies have failed to demonstrate the inhibition of smooth muscle cell proliferation with tacrolimus.[16)] Preclinical studies on tacrolimus-eluting stents for the treatment of native coronary artery lesions have demonstrated the safety and efficacy of this

stent concept with a significant reduction of neointimal proliferation within the study's implanted stents. However, the clinical trial programs for the first tacrolimus-eluting stent system for the treatment of native coronary lesions (the Preliminary Safety Evaluation of NanoporousTacrolimus-eluting stent, PRESENT I and II) and saphenous vein graft lesions (The EndoVascular Investigation Determining the safety of New Tacrolimus-eluting stent grafts, EVIDENT) have failed to prove the clinical benefit of the stent systems that were tested, and they did not demonstrate the impact of specific stent designs, especially the drug carrier characteristics, on the patients' outcome. The progressive PRESET study, which will evaluate a directly coated tacrolimus-eluting stent, will provide important insights on the potential of tacrolimus for the prevention of neointimal proliferation in clinical practice without the results being affected by any additional artificial surface compounds.

Mycopehnolic acid-eluting stents

Mycophenolic acid (MPA) is the active metabolite of mycophenolate mofetil, an antibiotic derived from cultures of the Penicillium species, and MPA has both antineoplastic and immunosuppressive properties. The Duraflex stent (Avantec Vascular Devices), is coated with a 5-μm layer of polyhydrocarbon polymer loaded with MPA, and it showed a 40% reduction in neointimal proliferation compared with the control in a porcine coronary model (Guy Leclerc, MD, Montreal Heart Institute, Montreal, Canada, personal communication, 2002).

The Inhibition with MPA of Coronary restenosis Trial (IMPACT) is a multicenter study that included 150 patients having de novo coronary lesions. Slow-release (45 days) and fast-release (15 days) eluting stents coated with 4.5 μg of MPA/mm^2 were compared with the bare Duraflex stents. The preliminary results suggest no differences in angiographic outcomes between the groups, but the final data are still pending.

Stents eluting antiproliferative agents

A number of antineoplastic medications have been considered for the prevention of restenosis. Paclitaxel and its derivatives are the most investigated compounds of this medication group.

Angiopeptin-eluting stents

Somatostatin, an angiopeptin analogue, has been shown to reduce tissue response to several growth factors, including platelet-derived growth factor, basic fibroblast and insulin-like growth factors. In humans, the systemic administration of angiopeptin improved the clinical outcome after angioplasty, but it showed no effect on restenosis.[17]

Armstrong et al.[18] have reported the release kinetics and distribution of angiopeptin-loaded phosphorylcholine (PC)-coated drug delivery (DD) BiodivYsio stents, and they assessed their safety and efficacy for reducing neointima formation. I125-angiopeptin-loaded DD-PC-coated stents were implanted into human saphenous vein segments ex vivo, and the I125 angiopeptin was detected in the medial layer at 1 hour after implantation. When implanted into pig coronary arteries, I125 angiopeptin was found adjacent to the stent at time intervals up to 28 days, and no significant amounts were found elsewhere. To assess the efficacy, twelve angiopeptin-loaded DD-PC-coated stents, twelve non-loaded DD-PC stents, ten standard PC-coated stents and 8 uncoated stents were implanted into normal porcine coronary arteries. The stents were harvested at 28 days and the neointima formation was assessed by computerized morphometry. No adverse tissue reactions were seen with any of the PC-coated stents. No significant differences were seen for the neointimal or luminal cross-sectional areas between the study groups. Delivery of angiopeptin from the drug delivery PC-coated stents was deemed safe, but this did not lead to a significant reduction in neointimal growth at 28 days, within the parameters of this study.

The SWAN study (First Human Experience With Angiopeptin-Eluting Stent), an open-label registry, tested the feasibility of implanting angiopeptin-eluting BiodivYsio stents in 13 patients having coronary de novo lesions. Thirteen stents were loaded with 22 μg of angiopeptin, and 1 stent was loaded with 126 μg of the drug. There were no in-hospital or 30-day MACEs (Vincent On-Hing Kwok, MD, Grantham Hospital, Hong Kong, China, unpublished data, 2002). The long-term follow-up data are still pending.

Tyrosine kinase inhibitor-eluting stents

Tyrosine kinases are both transmembrane and intracellular protein kinases, and they are fundamental to a number of extracellular signals that regulate the proliferation, differentiation and specific functions of differentiated cells.[19] The activities of vascular smooth muscle cells (SMCs) such as proliferation, migration and matrix production contribute to restenosis following clinical interventions with angioplasty

and stent placement. Because the activation of platelet-derived growth factor (PDGF)-receptor tyrosine kinase (PDGFr-TK) influences these processes and promotes restenosis, an inhibitor of the PDGFr-TK, TKI963, has been investigated.

Bilder et al.[20] have reported the efficacy of TKI963 for blocking stent-induced restenosis, as was analyzed by intravascular ultrasound (IVUS). The in vivo stent-induced restenosis in swine coronary artery was reduced by the oral administration of TKI963 (1.25, 2.5 and 5 mg/kg BID for 28 days). Dose related decreases of late lumen cross-sectional area (CSA) loss, plaque CSA growth, and plaque volume in the stent were observed, as was determined by IVUS (33−62% at 1.25 mg/kg BID to 66−92% at 5 mg/kg BID, depending on the parameters), compared with the controls. Poly-L-lactic acid (185 kDa) biodegradable stents loaded with ST638 (0.8 mg), a specific tyrosine kinase inhibitor, were implanted into pig coronary arteries. After 3 weeks, the amount of neointimal proliferation was significantly decreased in the ST638 stents compared with its inactive metabolite (ST494).[21] Further clinical studies are still pending.

Actinomycin D-eluting stents

Actinomycin D is an anticancer drug that selectively inhibits RNA synthesis. Little information is available about the use of actinomycin D for the prevention of smooth muscle cell proliferation and restenosis.

The ACTION (Actinomycin Eluting Stents Improve Outcomes by Reducing Neointimal Hyperplasia) study[22] was a large randomized trial designed to test the safety and the performance of the actinomycin D-coated Multilink-Tetra stent (Guidant Corp., Santa Clara, California) for the treatment of patients with single de novo native coronary lesions. This trial randomized 360 patients to receive either a DES (with 2.5 or 10 microg/cm^2 of actinomycin D) or a metallic stent (MS). When the early monitoring revealed an increased rate of repeat revascularization, the protocol was amended to allow for additional follow-up for the DES patients. Angiographic control of the MS patients was no longer deemed mandatory. The in-stent late lumen loss and that at the proximal and distal edges were higher in both DES groups than in the MS group, and this resulted in higher six-month and one-year MACE (34.8% and 43.1% vs. 13.5%, respectively), and these findings were exclusively driven by the target vessel revascularization without excess death or myocardial infarction. So, the researchers concluded that all anti-proliferative drugs will not uniformly show a drug class effect for the prevention of restenosis.

C-myc antisense-eluting stent

Upregulation of genes such as c-myc, which regulates cell division, leads to cellular proliferation. Antisense oligonucleotides have the ability to block critical phases of the smooth muscle cell growth cycle. Inhibition of several cellular proto-oncogenes has been shown to inhibit smooth muscle cell proliferation in vitro and to reduce neointimal thickening in vivo. C-myc antisense oligonucleotides have also been shown to inhibit both inflammation and extracellular matrix production.[23]

Kipshidze et al.[24] reported that an advanced c-myc-eluting PC stent blocked c-myc expression, and it significantly inhibited myointimal hyperplasia; further, this style of stent allowed for complete reendothelialization and a proper healing response in the porcine coronary model. However, the first clinical experience using the catheter-based local delivery of c-myc antisenseoligonucleotides was disappointing.[25]

Stents eluting antithrombosis agents

Vessel injury with the resulting platelet aggregation and thrombus formation plays a prominent role in the development of restenosis.[26] Antithrombotic pharmacological approaches to inhibit restenosis, however, have proven ineffective. Nitric oxide and glycoprotein IIb/IIIa inhibitors have been used as stent coatings, but their efficacy has yet to be demonstrated.[27]

Platelet glycoprotein IIb/IIIa inhibitor-eluting stent

Platelet activation and aggregation induces arterial thrombosis and this plays a pivotal role in the pathophysiology of acute coronary syndrome.[28] The development of drugs that inhibit fibrinogen binding to the platelet glycoprotein IIb/IIIa receptor has expanded the therapeutic options for treating thrombotic disorders.[29] Abciximab is a potent inhibitor that blocks the final pathway of platelet aggregation and this drug decreases the short-term and long-term event rates after percutaneous coronary intervention.[30-33] Besides its blocking effect for platelet aggregation, abciximab reacts to CD11b/CD18 of vascular endothelial cells and macrophages, and it inhibits the inflammatory reaction and proliferation of vascular smooth muscle cells.[34-37] The possible mechanisms responsible for inhibition of neointimal hyperplasia by abciximab may be this drug's anti-platelet, anti-inflammatory, anti-proliferative, and pro-healing actions.

Hong et al.[38] performed a prospective, randomized trial to compare abciximab-coated stents, which were implanted in 43 patients, with control stents, which were implanted in 42 patients. The coronary angiograms at follow-up showed that the restenosis rate and late loss were 14% and 0.33 ± 0.28 mm, respectively, in the abciximab stent group and 28.6% and 0.64 ± 0.32 mm, respectively, in the control stent group. On follow-up IVUS, the intrastent lumen area and intrastent neointimal hyperplasia area were 5.7 ± 1.6 mm^2, 2.0 ± 1.6 mm^2, respectively, in the abciximab stent group and 4.2 ± 0.8 mm^2 and 3.4 ± 1.7 mm^2, respectively, in the control stent group (p=0.001, 0.001, respectively), and the increase of the neointimal hyperplasia area was 2.0 ± 1.6 mm^2 and 3.4 ± 1.7 mm^2, respectively (p=0.001). They concluded that the abciximab stent was a feasible treatment and it produced a significant inhibition of neointimal hyperplasia, and it also showed a potential therapeutic benefit in the prevention of stent restenosis.

The major advantages of the abciximab-coated stent may be its safety in the thrombus-burden lesions of patients with acute coronary syndrome, the possibility of using it to deliver a short course of anti-platelet therapy and its effectiveness in diabetic patients. We are currently conducting a clinical study using abciximab-coated in patients with acute myocardial infarction.

Hirudin/iloprost-eluting stent

A combination of hirudin and iloprost were blended with a polylactic acid polymer in a homogeneous thin layer and this was loaded onto a stent. While the iloprost was slowly released by the breakdown of the polymer, about 60% of the hirudin was eluted in the first 24 hours.[39] Decreased neointimal formation was observed in sheep and pig injury models that were treated with this antithrombotic-eluting stent, but the clinical data are still pending.

Stents eluting extracellular matrix modulators

The extracellular matrix constitutes a major component of the restenotic lesion and therefore, it represents a potential target for antirestenosis therapy. Matrix metalloproteinases (MMP), and particularly MMP-2 (72-kDa type IV collagenase) and MMP-9 (92-kDa type IV collagenase), have the ability to digest collagen and facilitate smooth muscle cell migration. Batimastat, a nonspecific MMP inhibitor, and other MMP inhibitors have been shown to inhibit neointimal hyperplasia in animal models.[40][41]

The BRILLIANT-I (Batimastat Anti-Restenosis Trial Utilizing the Biodivysio Local Delivery PC-Stent) was a multicenter study designed to test the feasibility of using a batimastat-eluting stent to treat de novo coronary lesions in 173 patients. Although the safety of this system was demonstrated, the late loss was 0.88 mm, and 21% of the patients developed binary restenosis (De Scheerder, MD, unpublished data, 2002). Further clinical studies have not yet been planned.

Stents eluting prohealing agents

The promotion of healing in the vascular endothelium may be a more natural, and consequently, a safer approach for the prevention of restenosis. Endothelial denudation and dysfunction are common at the site of endovascular interventions and this has been associated with vessel thrombosis and restenosis.[42] In addition, delayed reendothelialization has been associated with the late side effects of potent antiproliferative therapies like radiation therapy.[43] The immediate restoration of endothelial function might abort the initiation of restenosis. Endothelial cell seeding has been proposed as the ultimate method to assure immediate stent endothelialization,[44] but cell viability has been a limitation. Stents may be used to attract the circulating endothelial cells.

R stents (Orbus Medical Technologies) are coated with antibodies to the CD34 receptors on the progenitor circulating endothelial cells, and these stents have been implanted into pig coronary arteries. Preliminary results have suggested the feasibility of capturing endothelial cells in-situ (Michael Kutryk, MD, St Michael's Hospital, Toronto, Canada, unpublished data, 2002). These nondrug-based stents would ultimately promote elution of biological active substances through a functioning endothelium monolayer. The effects of these ingenious stents on restenosis remain to be demonstrated.

Nitric oxide, vascular endothelial growth factor and 17-β-estradiol have also been tested as prohealing and antirestenotic agents.

Estradiol-eluting stents

Estradiol may improve vascular healing, reduce the smooth muscle cell migration and proliferation, and promote local angiogenesis.[45] Recently, estradiol-eluting phosphorylcholine-coated stents (Abbott/Biocompatibles) implanted into porcine coronary arteries reduced the neointimal hyperplasia by 40% compared with the control stents.[46]

EASTER (Estrogen and Stent to Eliminate Restenosis)[47] was a single-center feasibility study that tested 17-β-est-

radiol-eluting BiodivYsio stents in 30 patients with de novo coronary lesions. A total of two patients experienced intra-stent narrowing that exceeded 50%, as observed on angio-graphy, whereas no patients experienced edge restenosis. One patient had focal intra-stent restenosis (60% diameter stenosis) with no symptoms and a negative stress test, whereas the other patient had diffuse restenosis that required target vessel revascularization. No other patient experienced any major adverse cardiac event. Follow-up IVUS revealed a neointi-mal hyperplasia volume of 32.3 ± 16.4 mm^3, whereas the stent volume was 143.7 ± 43.7 mm^3, resulting in a neointimal volume obstruction of $23.5 \pm 12.5\%$. None of the patients had > or = 50% volume obstruction, as tested by IVUS. A second phase of the EASTER study is ongoing in Italy.

Anti-oxidant stents

Carvedilol has an activity to inhibit smooth muscle cell proliferation and migration, and it also has an anti-oxidation effect. Probucol has a vascular protecting activity and it reduced stent restenosis by improving the lumen dimension at the stent placement site. Carvedilol is a neurohumoral ant-agonist with multiple actions. It was originally discovered as a beta-adrenoreceptor antagonist. However, subsequent res-earch has revealed that this agent possessed potent antioxidant and free radical scavenger properties. In addition, carvedilol inhibits the vascular SMC proliferation induced by a broad group of mitogens such as platelet derived growth factor (PDGF), fibroblast growth factor (FGF), endothelin-1, serum and thrombin, and it produced 84% suppression of neointimal hyperplasia in a rat carotid injury model. The antimitogenic action of carvedilol on vascular smooth muscle has recently been proven to be due to the inhibition of mitogen-activated protein kinase activity and it was also due to its regulation of cell cycle progression.[48]

Carvedilol is highly lipophilic, which promotes a rapid cellular uptake, and a stent containing carvedilol may achieve a high local concentration in vessel walls when it is placed in contact with the walls. Since probucol had been discovered as an antioxidizing agent, it has been developed and sold as a lipid-lowering agent. It is an anti-oxidant and reduces resteno-sis after coronary argioplasty, and has recently been identified as a vascular protectant.[49]

BiodivYsio phosphorylcholine-coated stents were dip-coa-ted with carvedilol (5 mg/mL) and probucol (50 mg/mL) by immersing the stents in methanolic carvedilol and probucol solution, respectively. The stents were deployed in pigs and histopathologic analysis was done 4 weeks later. On histo-morphometry, the neointimal area decreased by 42% and the lumen area increased by 20%, resulting in a 43% reduction of the area of stenosis in the carvedilol-coated stent groups compared with the control stent groups. For the probucol-coated stent, the lumen area, the neointimal area, and the stenosis area were not significantly different compared with control stents. There were less proliferating nuclear cell anti-gen-positive cells in the carvedilol-coated stent compared with the control stent and the probucol stent. The carvedilol-coated stent, but not a probucol-coated stent, inhibits neointimal hyperplasia in a porcine stent restenosis model.[50] We are conducting clinical trials using carvedilol loaded stents in our cardiac catheterization laboratory.

Conclusion

In our animal catheterization laboratory, we are developing a new generation of DESs by using double coating techno-logy or by using natural polymers to overcome the problem of polymer-mediated thrombosis or inflammation, and also to enhance healing after stenting.

Future generations of stents will likely be engineered for optimally delivering drugs to specific lesions. Moreover, refin-ing the bare metal stent platform will continue for enhancing the acute procedural success. Furthermore, it is likely that novel polymer materials and pharmacologic agents will be tested for their biological activity on specific disease states and/or on various vascular systems.

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