CARDIOLOGY Rounds®

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Drug-eluting stents for the treatment of coronary artery disease

Part 2: Trials with rapamycin and other coating agents

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Despite their success, coronary stenting procedures may be limited by subsequent in-stent restenosis. To help control this occurrence, local delivery of antirestenotic compounds using drug-eluting stents may be the most important addition to the armamentarium of the interventional cardiologist since the introduction of the stainless steel coronary stent. Part 1 of this topic, in the June/July issue of *Cardiology Rounds*, presented information about initial studies with drug-eluting stents, including trials with paclitaxel. Part 2, in this issue, focuses on studies examining other drugs that are being used to coat stents (eg, rapamycin, QP2, actinomycin D), new stent systems (BiodivYsio Matrix LO stents and BiodivYsio Matrix HI stents), and biodegradable stents that are currently under investigation.

Sirolimus-coated stents

The first hard clinical data on the potential of drug-eluting stents to prevent restenosis came from trials examining sirolimus (rapamycin) coated devices. Sirolimus is a natural macrocyclic lactone produced by *Streptomyces hygroscpicus* (found in the soil of Easter Island), with potent antiproliferative, anti-inflammatory, and immunosuppressive effects. It was developed by Wyeth-Ayerst Laboratories and approved by the FDA for the prophylaxis of renal transplant rejection in 1999. Sirolimus is a hydrophobic drug, with a low solubility in aqueous solutions. It passes easily through cell membranes because of its lipophilicity, enabling intramural distribution and prolonged tissue retention.

Sirolimus binds to an intracellular binding protein (immunophilin) known as FK Binding Protein-12 (FKBP-12). The sirolimus/FKBP-12 complex binds to, and inhibits, the activation of the mammalian Target of Rapamycin (mTOR), a key regulatory serine-threonine kinase. The inhibition of mTOR inhibits the translation of a family of mRNAs that code for proteins essential for cell-cycle progression and induces the cyclin-dependent kinase inhibitor p27, ultimately causing cell-cycle arrest (Figure 1).[1,2] A cDNA array analysis of atherectomy samples from patients with symptomatic in-stent restenosis has shown elevated levels of the sirolimus receptor, FKBP-12.[3] In vitro and preclinical animal studies have shown that sirolimus can prevent injury–triggered smooth muscle proliferation.[4-10] In addition, preclinical studies have shown a significant reduction in strut-associated inflammation, suggesting a potential for an additional mechanism in the inhibition of neointimal hyperplasia.[11]

Drug-eluting Bx VELOCITY stents can be produced by coating the stainless steel with a thin layer of a non-erodable methacrylate and an ethylene-based co-polymer containing 185 µg of sirolimus.

Clinical trials with sirolimus-eluting stents

Results of the first human implantations of sirolimus-eluting stents were reported by Sousa et al.[12] Thirty patients with symptomatic coronary artery disease were included in their pilot study, designed to test the feasibility of the implantation of sirolimus-eluting Bx VELOCITY stents. Half the patients received a slow-release device, the other half were treated with fast-release stents. Sirolimus is gradually secreted from slow-release Bx VELOCITY stents, with >80% released *in vivo* within the first 30 days (Figure 2). At 4-month follow-up, there was minimal intimal hyperplasia in both groups as measured by intravascular ultrasound (IVUS) or quantitative coronary angiography (QCA), 11.0 ± 3.0%. These favourable results persisted to 12-month follow-up with minimal intimal hyperplasia (2 ± 5% in the slow release group and 2 ± 3% for the fast release group).[13]

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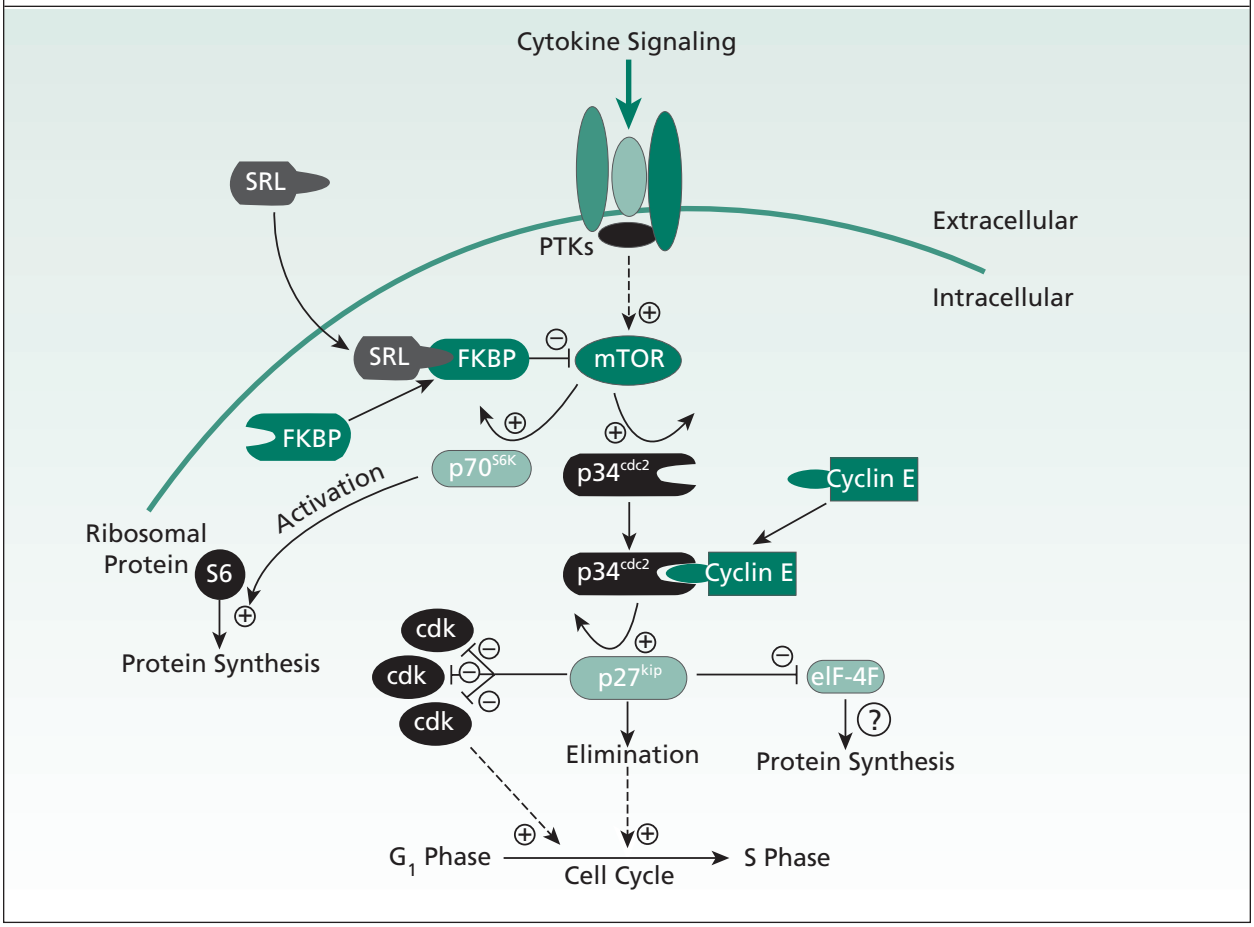
Figure 1: Mechanism of action of sirolimus (rapamycin). Although the pre-drug sirolimus (SRL) binds to FKBP-12, the complex that is formed between SRL and FKBP binds to the mammalian target of rapamycin (mTOR). The SRL–FKBP–mTOR complex inhibits biochemical pathways that are required for cell progression through the late G1 phase or entry into the S phase of the cell cycle. Thus, unlike cyclosporine (CsA), SRL blocks cytokine signal transduction. SRL is thought to target: (1) the 70-kD S6 protein kinase p70S6K; (2) the eukaryotic initiation factor eIF-4F; (3) the G1-controlling cyclin-dependent kinase (cdk) proteins, such as the D2 cycline cdk2, the D2 cycline cdk6 or the E cycline cdk2 and (4) the kinase inhibitory protein Kip1 (p27kip), which blocks cell progression to the S phase. p34cdc2 = a kinase; PTKs = protein tyrosine kinases.



The results of the clinical implantation of 15 slow-release rapamycin-coated Bx VELOCITY stents have been reported by Rensing et al.[14] Thirteen patients were available for 6-month follow-up and there were no adverse cardiac events reported, none had angiographic restenosis, and no in-stent or edge restenosis (> 50% diameter stenosis) was observed.

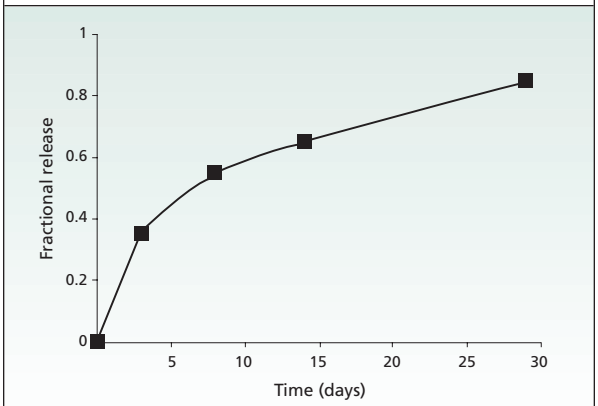
The encouraging results of the Phase I clinical trials led to the initiation of the Phase II, RAVEL (Randomized Study with the Sirolimus-eluting VELOCITY Balloon Expandable Stent) trial.[15] The trial enrolled 238 patients at 19 centres across Europe and Latin America. Patients were randomized to receive either a bare Bx VELOCITY stent, or a sirolimus-eluting Bx VELOCITY (Cypher™) stent coated with a 5 µm thick coating of sirolimus-polymer. At 6-month follow-up, late loss in luminal diameter (primary endpoint) in the cohort treated with the sirolimus-eluting stent was significantly lower (-0.01 ± 0.33 mm) than that in the control group (0.80 ± 0.53 mm, $P<0.001$). Binary restenosis rates (> 50% diameter stenosis) among the 120 patients who received the drug-eluting device were reported as 0% compared with 26.6% in the group that received the uncoated stent. At 1-year follow-up, major cardiac event rates were 5.8% in the treated group and 28.8% in the control group ($P<0.001$). Subacute stent thrombosis did not occur in either group.

Enrollment in the United States randomized study (SIRIUS trial) comparing the Cypher device to an uncoated Bx VELOCITY stent is complete.[16] SIRIUS is a randomized, controlled trial of 1101 subjects with single *de novo* coronary artery lesions, designed to examine the safety and efficacy of sirolimus-coated devices (slow-release, 109 µg sirolimus/cm^3) versus placebo. The primary endpoint of the SIRIUS trial is target vessel failure at 9 months (cardiac death, myocardial infarction, target vessel revascularization). There are 55 investigational centres participating in the U.S. and subjects will be followed for 5 years. Data from the SIRIUS trial will be used to obtain FDA market clearance for the Cypher device. Enrollment in the E-SIRIUS trial (Europe and Latin America) is currently underway.

QP2 (7-hexanoyltaxol)

A more hydrophobic derivative of paclitaxel, 7-hexanoyltaxol (QP2), a taxane, has been tested on a unique stent-delivery

Figure 2: *In vivo* release kinetics of sirolimus from a slow-release kinetics coated Bx VELOCITY stent. Sirolimus is released in a controlled manner from a polymer matrix bound to the stent.



platform for the prevention of restenosis. The mechanism of activity is similar to that of paclitaxel, in that it inhibits microtubule formation by inhibiting microtubule depolymerization, thus interfering with the cell cycle. QP2 is only about half as soluble as paclitaxel. The efficacy of QP2 for the inhibition of restenosis when delivered locally on a stent platform has been tested using the QuaDDS-QP2 stent (Boston Scientific Corporation Inc./Quanam Medical, Santa Clara, CA, U.S.A.). The QuaDDS-QP2 stent is based on the uncoated QueST stent platform (Quanam Medical Corporation). While the QueST stent is a laser cut, stainless steel, tubular stent, the QuaDDS stent is a QueST stent covered with a series of 2 mm wide polymer sleeves made with an acrylate polymer and formed into rigid sleeves. The sleeves are approximately 0.0025 inches (0.06 mm) thick. The stent length determines the number of sleeves that are placed equidistant from each other over the length of the stent. The nonbiodegradeable proprietary polymer sleeve is loaded with QP2 by dissolving the drug into a solvent that absorbs into and swells the polymer. The solvent is subsequently removed by vacuum drying. The total dose per sleeve is approximately 800 µg of QP2; the 13-mm stent (4 sleeves) carries 3.2 mg and the 17-mm stent (5 sleeves) carries 4.0 mg of QP2.

Clinical trials with QP2 eluting stents

In the first clinical study of the QuaDDS-QP2 stent, 14 QuaDDS-QP2 stents were implanted in 13 patients and 18 bare QueST (control) stents in 14 patients.[17,18] Both 13-mm and 17-mm stents were implanted. After 18 months, the binary restenosis rate (>50% diameter stenosis) in the coated-stent group was 0% as compared to 54% in the control group. The incidence of major adverse cardiac events (MACE) after 18 months was 0% in the drug-eluting stents and 15% in the control group. Two-year follow-up data showed no binary restenosis and a target lesion revascularization rate of 0. IVUS analysis revealed only minimal neointimal proliferation.[18]

Based on the promising results of this pilot study, the phase II SCORE (Study to COmpare REstenosis Rate Between QueST and QuaDDS-QP2) trial was initiated. The primary endpoint of this randomized, multicentre trial was target vessel revascularization with an anticipated reduction in restenosis rate to < 20% as compared to a rate of 24% to 42% seen with traditional, stainless steel stents. Four hundred patients from 17 centres in Europe and Australia were to be enrolled in this trial. Only those with *de novo* lesions were included. Implanted QuaDDS-QP2 stents were either 13 or 17 mm in length, and the target lesion had to be suitable for stenting with a single stent. Interim analysis of safety outcomes led to the termination of the SCORE trial. At the time of termination, 266 patients were enrolled. There was no stent thrombosis seen in the control group and a 5.5% stent thrombosis rate was present in the QuaDDS-QP2 group. An observed increase in periprocedural myocardial infarctions was usually related to side-branch occlusions caused by the polymer bands. MACE at 30 days in the treated group was 10.2%, predominantly due to subacute stent thrombosis and myocardial infarction.

Actinomycin D

Guidant has developed an actinomycin D-eluting stent for the prevention of restenosis; the MULTI-LINK TETRA D stent. Actinomycin D is an antibiotic that has been approved as an anticancer chemotherapeutic agent. It binds DNA, preventing cell division and protein production. Actinomycin D is cell cycle non-specific, with the result that cells in all phases of the proliferation cycle are affected by the drug. Actinomycin D is currently approved in most European countries and in the U.S. with the indication for treatment of carcinoma of the testes and uterus, Wilms tumor, and other neoplasms. The MULTI-LINK TETRA D stent is coated with a T.R.U.E. Coat™ (Targeted Release Uniform Elution) polymer, a bioinert coating on the stent that contains actinomycin D. Preclincal studies have shown significant inhibition of neointimal proliferation and complete re-endothelialization of the treated site at the 30-day time point with 2.5 µg/cm^3 and 10 µg/cm^3 doses

Clinical studies with actinomycin D-eluting stents

The ACTION (ACTinomycin-eluting stent Improves Outcomes by reducing Neointimal hyperplasia) trial will be the basis for CE Mark approval application for the MULTI-LINK TETRA D device. The ACTION trial enrolled 360 patients at 25 centres in Europe, Australia, and New Zealand. Two doses of actinomycin D were tested and compared with bare stents. The trial was halted due to safety concerns, after follow-up completion of the first 90 patients enrolled in Europe.

Phosphorylcholine

The proprietary phosphorylcholine technology of Biocompatibles is well suited to stent-mediated drug delivery. Biocompatibles has modified the phosphorylcholine coating by increasing the thickness on the outer (tissue) side of the stent in order to maximize delivery of the compound to the vessel wall, while minimizing the systemic loss. The modified phosphorylcholine coating has the ability to absorb and release a wide range of drugs.

There are 2 phosphorylcholine-coated drug delivery formats currently available; BiodivYsio Matrix LO stents and BiodivYsio Matrix HI stents.

The BiodivYsio Matrix LO stents have a coating that is specially designed to absorb and deliver drugs that are water-soluble in either an aqueous or organic solvent, with a molecular weight less than 1200 daltons.

BiodivYsio Matrix HI stents are covered with a coating that interacts with negatively-charged components found in many large biological molecules such as DNA, heparin, and oligonucleotides. It will easily adsorb and deliver compounds with molecular weights greater than 1200 daltons.

The BiodivYsio Matrix stents may be loaded with a variety of compounds by simply immersing them in a solution of the drug at the appropriate concentration for several minutes. The release profile of specific drugs from the matrix is a reflection of their solubility in an aqueous medium; however, the profile is also affected by interactions with domains within the polymer for the more hydrophobic compounds. The more hydrophobic the drug, the longer the elution time.

Trials using BiodivYsio Matrix stents

A number of preclinical studies have been performed with a range of drugs using the BiodivYsio Matrix systems. The *in vivo* release of compounds like angiopeptin,[19] dexamethasone, methylprednisolone, the matrix metalloprotease inhibitor, batimastat, radioactive antisense oligonucleotides,[20] 17ß-estradiol,[21] and Resten-NG[22] (AVI-4126, AVI BioPharma, Inc.; an advanced 6-ring morpholino backbone neutrally charged c-myc antisense compound) from the BiodivYsio Matrix LO system have been tested and shown to be effective for the prevention of restenosis in animal models.

Several clinical trials using the Biocompatibles BiodivYsio Matrix LO drug-eluting system are currently underway. The STRIDE (Study of Anti-restenosis with BiodivYsio Matrix LO Dexamethasone Eluting Stent) study is a multicentre, prospective registry study. The study objectives were to evaluate the safety and efficacy of the BiodivYsio Matrix LO stent with dexamethasone. Dexamethasone is a anti-inflammatory corticosteroid used to inhibit the inflammatory response and reduce tissue injury due to trauma. The mode of action of dexamethasone targets many of the inflammation processes, including:

- the inhibition of cyclo-oxygenase-2 (COX-2), which reduces prostaglandin synthesis
- the inhibition of the transcription gene for phospholipase A2 (PLA2); PLA2 gives rise to the prostanoids, platelet-activating factor (PAF), and leukotrienes
- the induction of the anti-inflammatory protein mediator lipocortin-1.

It is thought that delivery of dexamethasone to the site of injury from a stent could prove beneficial in the inhibition of cytokines and lead to a reduction in the proliferation of inflammatory cells around the stent struts, with a resultant reduction in restenosis. In Belgium, 71 patients at 8 sites have been recruited into the STRIDE study. The rate of MACE in the STRIDE trial was 3.3%, with no thrombotic events reported, either acute or subacute, during the 6-month follow-up. The binary angiographic restenosis rate (>50% diameter stenosis) was 13.3%.

The antimigratory compound, batimastat, has been tested on the BiodivYsio Matrix drug-eluting stent system in a number of clinical trials. Batimastat is a broad-spectrum matrix metalloproteinase inhibitor (MMPI) developed by British Biotech, the UK bio-pharmaceutical company. It is a low-molecular weight peptide mimetic containing a hydroxamate group that chelates the zinc atom in the active site of the metalloproteinase (MMP) and thereby inhibits the enzyme. Batimastat is a potent, but reversible, inhibitor of the matrix metalloproteinases, and displays IC50s in the low nanomolar range against all three classes of MMPs; collagenases, stromelysins, and gelatinases (alternatively referred to as type IV collagenases). Collectively, these enzymes can degrade all of the components of the extracellular matrix and induce cell migration and proliferation. The injury caused by the stent to the vessel wall and the resulting smooth muscle cell proliferation causes expression of several members of the MMP family, and batimastat can inhibit the cell migration and proliferation process.

The BATMAN (BiodivYsio Batimastat SV Stent Versus Balloon Angioplasty for the Reduction of Restenosis in Small Coronary Arteries) (Americas) and BRILLIANT (Batimastat (BB-94) Antirestenosis Trial Utilizing the BiodivYsio Local Drug Therapy PC Stent) (European Union) programs were clinical studies designed to evaluate the safety and efficacy of the Batimastat-eluting BiodivYsio Matrix stent. BATMAN I was a pilot, safety trial performed in Latin America. BRILLIANT I was designed to demonstrate safety of the Batimastat BiodivYsio stent. This multicentre registry enrolled 150 patients and follow-up included 6-month angiographic assessment and clinical follow-up at 1, 6, and 12 months. BRILLIANT II was to be a 400 patient, multicentre, double-blind, randomized trial conducted at centres in the UK, France, Belgium, and Holland, comparing the clinical performance of the batimastat-loaded BiodivYsio stent relative to a BiodivYsio stent without the drug. Six-month angiographic and clinical follow-up on an initial group of patients from BRILLIANT I has indicated that the batimastat BiodivYsio stent did not show the benefit that was evident in the preclinical studies. This led to suspension of recruitment into the BRILLIANT II trial and cancellation of further BATMAN clinical trials. Completed and ongoing clinical trials of drug-eluting stents are summarized in Table 1.

Biodegradable stents

Although once a very active area of research, interest into the development of a suitable biodegradable stent with pharmacologically active agents incorporated into the polymeric matrix has waned considerably. To be effective, a drug-releasing biodegradable stent must be biocompatible, not cause an inflammatory reaction, and the breakdown products must be non-toxic. Stent delivery must be reliable, the devices must have high radial strength, and stent degradation should occur in a reasonable time (12- to 24-months). The ideal stent would deliver drugs locally that inhibit restenosis, in concentrations that are effective without inducing tissue injury. The excellent long-term biocompatability of stainless steel stents, combined with the considerable difficulties in developing a polymeric stent with a high performance delivery system, radiopacity, and structural characteristics competitive with stainless steel devices (like radial hoop strength) have focused efforts away from the development of such devices.

Table 1: Summary of completed and on-going trials of stent based local drug delivery

Trial Name (Company)	Stent	Number of Patients	Design
RAVEL (Cordis/J&J)	Bx Velocity	238	Efficacy of rapamycin eluting stents (Europe and Latin America) PRDBC study PE: Late loss at 6 months
SIRIUS (Cordis/J&J)	Bx Velocity	1100	Efficacy of rapamycin eluting stents (U.S.A.) PRDBC study PE: 9 month target lesion failure
TAXUS I (BS)	NIR	61	Safety and feasibility of implantation of paclitaxel eluting stents PRDBC study PE: 30 day MACE
TAXUS II (BS)	NIR	536	Efficacy of rapamycin eluting stents PRDBC study Slow release vs. bare & moderate release vs. bare PE: Plaque volume by IVUS at 6 months
TAXUS III (BS)	NIR	30	Safety and feasibility of implantation of paclitaxel eluting stents for instent restenosis Registry series PE: 30 day MACE & 6-month angiographic and IVUS follow up
TAXUS IV (BSX)	Express	2000	Efficacy of paclitaxel eluting stents in *de novo* lesions and in-stent restenosis using both slow & intermediate release formulations PRDBC PE: 9-month follow up
ACTION (GDT)	MULTI-LINK	360	Efficacy of Actinomycin D eluting stents (2 arms of 120 patients testing different doses + bare stent) PE: 6-month follow up – **HALTED**
ELUTES (Cook)	V-Flex Plus	180	Safety and efficacy of paclitaxel coated stents using 4 doses compared to bare PRDBC PE: % diameter stenosis and late loss at 6 months
PATENCY (Cook)	Logic PTX	50 safety trial 1200 de novo 450 instent rest	Testing of Taxol coated stent
DELIVER (Cook/GDT)	Penta	800-1000	Testing of Taxol coated stent
ASPECT (Cook)	Supra-G	171	2 arms of 57 patients testing different doses of paclitaxel + control bare stent PRDBC study PE: 6 month binary restenosis rate
SCORE (BS/Quanum)	QueST	400	Efficacy of 7-hexanoyltaxol coated stents PRDBC **TERMINATED** after enrollment of 266 patients due to high adverse event rate
STRIDE (Biocompatibles)	BiodivYsio	71	Safety and feasibility of implantation of dexamethasone eluting Registry series
BRILLIANT I (Biocompatibles)	BiodivYsio	150	Safety and feasibility of implantation of Batimastat eluting stents Registry series – **HALTED**
BRILLIANT I (Biocompatibles)	BiodivYsio	400	Safety and feasibility of Batimastat eluting stents PRDBC – **HALTED**

PE = Primary endpoint; PRDBC = Patient randomized, double-blind, controlled; MACE = Major adverse cardiac events; IVUS = Intravascular ultrasound

Two such biodegradable devices however, warrant mention. The Duke Biodegradable Stent[23] and the Igaki-Tamai biodegradeable stent are made from a special form of poly-L-lactide (PLLA), and are capable of incorporating pharmacologically active agents. Both self-expanding and balloon expandable versions of the Duke stent have been designed and tested in animals,[24] with promising results, while some clinical data exists with the use of the Igaki-Tamai stent.[25]

Conclusion

Drug-coated stents have shown promise in early trials to prevent coronary in-stent restenosis. It remains to be seen whether rapamycin, paclitaxel, resten-NG, or dexamethasone will prove most effective as a stent coating. As with all new technology, initial enthusiasm must be tempered until final results of randomized, clinical trials have been reported, and long-term follow-up is complete. In this regard, the 1-year results from a paclitaxel derivative-eluting stent have not met the promise of initial findings. Long-term clinical and angiographic results of 15 patients treated for in-stent restenosis with the 7-hexanoyltaxol (QP2)-eluting polymer stent system (QuaDS) have been reported.[26] At 6-months, 2 patients had restenosis (13.3%), while at 12 months, 8 of 13 patients (61.5%) had restenosis. Although the problem may have been due to a late foreign body reaction to the polymer sleeve, or due to a lack of efficacy of the taxol-

derivative drug, the results highlight the need for caution when examining the efficacy of drug-eluting stents in general. In addition, late thrombotic occlusion has been documented in drug-eluting stent trials, emphasizing another drawback of this promising technology. Cost-effectiveness of this new technology has also not been adequately assessed. The higher up-front costs of drug-eluting stents and protracted antiplatelet therapy may not be offset by the avoidance of subsequent procedures to correct restenosis, particularly if this comes at the expense of a higher thrombotic complication rate. Despite these drawbacks, positive results reported thus far may prove the drug-eluting implantable device to be the most important addition to the armamentarium of the interventional cardiologist since the introduction of the stainless steel coronary stent.

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