CARDIOLOGY Rounds®

As presented in the rounds of the Division of Cardiology, St. Michael's Hospital, University of Toronto

Drug-eluting stents for the treatment of coronary artery disease Part 4: New results from clinical trials and future directions.

By MICHAEL J. B. KUTRYK, MD, PhD, FRCPC

The implantation of drug-eluting stents has become the percutaneous treatment of choice for many patients with coronary lesions. In 2002, two issues of *Cardiology Rounds* reviewed the development and early trials of drug-eluting stents for the treatment of coronary artery disease. Because several important new multicentre clinical trials with updated information have been published over the past year, the aim of both the November and December 2003 issues of *Cardiology Rounds* is to provide an update for our readers. The November issue summarized data from trials with sirolimus-eluting stents (FIM, RAVEL, SIRIUS, and the RESEARCH registry) and paclitaxel-eluting stents (ELUTES, ASPECT, DELIVER I and II, and TAXUS I-V). Part 4, in this issue, continues with an examination of QP-2, actinomycin D, phosphorylcholine, everolimus, and 17ß-estradiol loaded BiodivYsio Matrix LO–eluting stents. Future directions for this rapidly evolving treatment are also discussed.

Clinical trials with QP2 (7-hexanoyltaxol)-eluting stents

7-hexanoyltaxol, (QP2), a taxane, has been tested on a unique stent delivery platform for the prevention of restenosis. QP2 is a more hydrophobic derivative of paclitaxel that causes similar disruptions of the cell cycle by inhibition of microtubule formation. 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, California, U.S.A.). The QuaDDS-QP2 stent was based on the uncoated QueST stent platform (Quanam Medical Corporation). 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, rigid polymer sleeves that are approximately 0.0025 inches (0.06 mm) thick and placed equidistant from each other over the length of the stent. The non-biodegradable proprietary polymer sleeve is loaded with QP2 by dissolving the drug in a solvent that absorbs into and swells the polymer; the solvent is then 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.

In the first clinical study of the QuaDDS-QP2 stent, 14 QuaDDS-QP2 stents were implanted in 13 patients and 18 control bare QueST stents were implanted in 14 patients.[1,2] Both 13 mm and 17 mm stents were used. 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 stent group and 15% in the control group. Two-year follow-up data showed no binary restenosis and a target lesion revascularization (TLR) rate of 0. Intravascular ultrasound (IVUS) analysis revealed only minimal neointimal proliferation.[2]

Based on the promising results of this pilot study, the phase II, the **SCORE** (**S**tudy to **C**ompare **R**estenosis Rate Between QueST and QuaDDS-QP2) trial was initiated. The primary endpoint of this randomized, multicentre trial was target vessel revascularization (TVR) with an anticipated reduction in restenosis rate to <20% as compared to a rate of 24% to 42% seen with traditional stainless steel

St. Michael's Hospital
30 Bond St.,
Suite 7049, Queen Wing
Toronto, Ont. M5B 1W8
Fax: (416) 864-5941

stents. Four hundred patients from 17 centres in Europe and Australia were to be enrolled in this trial; only patients 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, however, 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. There was also an increase in peri-procedural myocardial infarctions (MIs) that were usually related to side-branch occlusion caused by the polymer bands. MACE at 30 days in the treated group was 10.2%, predominantly due to subacute stent thrombosis and MI. Further development of the QuaDDS-QP2 stent has been suspended.

Clinical studies with actinomycin D

In preclinical studies, the Multilink tetra-D stent (Guidant), coated with a T.R.U.E. Coat™ (Targeted Release Uniform Elution) polymer containing actinomycin D, demonstrated significant inhibition of neointimal proliferation and complete re-endothelialization of the treated site at the 30-day time point with the 2.5 μg/cm^2 and 10 μg/cm^2 doses. Actinomycin D functions by binding DNA in all phases of cell cycle proliferation, thereby preventing cell division and protein production.

The **ACTION** (**Act**inomycin Eluting Stent **I**mproves **O**utcomes by Reducing **N**eointimal Hyperplasia) trial was a randomized, single-blind, clinical trial designed to evaluate the safety and performance of the Multilink tetra-D actinomycin-D-eluting stent system. A total of 360 patients at 28 clinical sites in Europe, Brazil, Australia, and New Zealand were randomized to 3 arms and received either a high-dose (10 μg/cm^2) or low-dose (2.5 μg/cm^2) actinomycin-D-coated or non-coated stent. Clinical follow-up was planned for 30 days, and 6 and 12 months, with angiographic follow-up at 6 months. The ACTION study was completed, but the Safety Committee directed that the randomization code be prematurely broken and follow-up accelerated due to a higher incidence of restenosis in patients treated with the actinomycin-D-eluting stent. Quantitative angiography (QCA) at 6 months demonstrated greater late loss in the drug-eluting stent arms (0.76 mm, control vs 1.01 mm, low-dose vs 0.93 mm, high-dose; $p<0.05$). In addition, binary restenosis rates were significantly higher in the low-dose drug treatment arms compared to bare stent (25% vs 11%; $p<0.05$). Proximal and distal edge restenosis was also more common in the drug-eluting stent arms. While no significant increases in death or MI were found, TLR was dramatically higher in the drug-eluting stent arms (17.5% low-dose and 23.1% high-dose vs 9.1% control) leading to a significant difference in the combined primary endpoint (18.3 % low-dose, 28.1% high-dose, 10.2% control; $p<0.002$ for high-dose compared to control). Based on these discouraging results, Guidant suspended all further development of actinomycin-D-eluting stents. The evidence from the ACTION trial further illustrates that results from animal data cannot be readily generalized to human populations.

Trials using phosphorylcholine-coated stents

The phosphorylcholine technology of Abbott Vascular Devices is well-suited for stent-mediated drug delivery. The 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 were designed specifically for water-soluble drugs with a molecular weight of <1200 daltons.
- The BiodivYsio Matrix HI stent was designed for interaction with negatively-charged components (eg, DNA, heparin, and oligonucleotides) and will easily adsorb and deliver compounds with molecular weights >1200 daltons.

The use of BiodivYsio Matrix systems has been shown to be effective in preventing restenosis in a number of pre-clinical studies. Animal studies have been performed using a range of drugs that include angiopeptin,[3] dexamethasone, methylprednisolone, the matrix metalloprotease inhibitor Batimastat, radioactive antisense oligonucleotides,[4] 17ß-estradiol,[5] and Resten-NG[6] (AVI-4126, AVI BioPharma, Inc.) an advanced 6-ring morpholino backbone neutrally charged c-myc antisense compound.[6]

The **STRIDE** (**St**udy of Anti-**R**estenosis with BiodivYsio Matrix LO **D**examethasone-**E**luting Stent) study was a multicentre prospective registry series. The study objectives were to evaluate the safety and efficacy of the BiodivYsio Matrix LO stent with dexamethasone (Dexamet stent). Dexamethasone is an anti-inflammatory corticosteroid that is used to inhibit the inflammatory response and reduce tissue injury due to trauma. The rationale behind the development of the Dexamet stent was that delivery of dexamethasone to the site of injury could prove beneficial through the inhibition of cytokines and lead to a reduction in inflammatory cell proliferation around the stent struts, with a resultant reduction in restenosis. Seventy-one patients at 8 sites in Belgium were recruited into the STRIDE study. It demonstrated that implantation of a phosphorylcholine-coated coronary stent coated with dexamethasone (0.5 μg/mm^2) resulted in a 52.1% improvement in late lumen loss (0.45mm) and an 80.6% reduction in the occurrence of MACE (3.3%) at 6-month follow-up when compared to the results of the earlier DISTINCT trial that evaluated phosphorylcholine-coated stents without a drug coating. The results of the STRIDE trial were used to obtain CE-mark approval in Europe for the Dexamet stent.

The antimigratory compound Batimastat was 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 MMP, thereby inhibiting the enzyme. Batimastat is a potent, but reversible, inhibitor of the MMPs and displays IC50s in the low nanomolar range against all 3 classes of MMPs: collagenases, stromelysins, and gelatinases (alternatively referred to as type IV collagenases). Collectively, these enzymes can degrade all

the components of the extracellular matrix and induce cell migration and proliferation. The injury to the vessel wall caused by a stent and the resulting smooth muscle cell proliferation causes expression of several members of the MMP family. Batimastat can inhibit the cell migration and proliferation process.

The **BRILLIANT-I** [**B**atimastat (BB-94] Anti**r**estenosis **T**ri**a**l uti**l**izing the BiodivYsio Loc**a**l Drug Delivery PC Ste**nt**) study was a 173-patient safety trial that included patients from 24 clinical sites in France, Belgium, and the Netherlands, and was designed to evaluate the safety and efficacy of the Batimastat-eluting BiodivYsio Matrix stent. Six-month angiographic and clinical follow-up on an initial group of patients from BRILLIANT I indicated that there was no evidence of benefit with the Batimastat BiodivYsio stent in pre-clinical studies, demonstrating a 6-month binary restenosis rate of 21% and a total MACE rate of 18%. Based on the discouraging results of the BRILLIANT-I trial, enrollment of patients into the double-blind, randomized BRILLIANT-II clinical trial was halted and further development of the Batimastat-eluting stent was suspended.

The **EASTER** (**E**strogen **a**nd **S**tents **t**o **E**liminate **R**estenosis) pilot trial was designed to evaluate the safety of 17ß-estradiol loaded BiodivYsio Matrix LO stent system in treating *de novo* coronary artery lesions. The study was a 30-patient, single-site, registry series with 6-month angiographic and IVUS follow-up. The primary endpoint was safety and late loss at 6 months. The average 17ß-estradiol dose released from the stent was 2.54 µg/mm^2. At 6-month follow-up, there were no reported deaths or MIs. There was a 3.3% rate of TLR and the event-free survival was 93.4%. Late loss at 6-month follow-up was 0.54 ± 0.44 mm. The 200-patient, 5-site, prospective, randomized EASTER trial has been completed and results will soon be released.

A summary of the on-going and completed drug-eluting stent trials is shown in Table 1.

Everolimus-eluting stent

The **FUTURE I** clinical trial was a prospective, randomized, single-blind trial evaluating the safety of an everolimus-eluting stent utilizing an ultra-thin, resorbable polymer drug-delivery coating vs a bare metal stent platform in *de novo* lesions. Everolimus, a rapamycin analogue previously studied for organ transplant applications, also exerts its immunosuppressant effect by inhibiting the mammalian target of rapamycin (mTOR). Eleven patients were treated with a control metallic stent (S-Stent; Biosensors International, Singapore) and 25 patients received an everolimus-eluting S-Stent (Challenge stent). Six-month angiographic follow-up analyses demonstrated a significant reduction in angiographic late loss (0.1 mm in the everolimus-eluting stent group compared to 0.83 mm in the control arm). IVUS follow-up demonstrated that patients who received the everolimus-eluting stent had a statistically significant reduction in the percent of neointimal volume compared to the control group. No angiographic in-stent binary restenosis was observed in the everolimus-treated arm. Both the safety and efficacy results from FUTURE I at 6 months were sustained at the 12-month follow-up. Twenty-four patients who had received the everolimus-eluting stent were evaluated at 12 months. No new MACE occurred between 6 and 12 months, with no incidence of repeat intervention required. Preliminary angiographic analysis of 8 patients showed no new binary restenosis events. In 6 patients who underwent follow-up IVUS, the results were consistent with 6-month results, demonstrating minimal re-narrowing of the artery (luminal volume obstruction).

Results reported from the 6-month follow-up of **FUTURE II**, a prospective, randomized, multicentre, double-blind trial that included 64 patients (21 receiving the Challenge stent and 43 receiving a bare metal device) confirmed the 6-month results of the FUTURE I trial. FUTURE II, which included a more complex patient group than FUTURE I, reported a 4.8% rate for MACE in the everolimus-eluting stent arm at 6 months. Angiographic endpoint results were positive, with 0% in-stent restenosis in the everolimus arm vs 19.4 % in the control arm.

Guidant has acquired Biosensors' drug-eluting stent technology and is applying everolimus to its own proprietary eluting stent system. **VISION-E** is a two-phase trial that will be conducted outside the U.S. Phase 1 is a dose-ranging study that will include 3 arms using different concentrations of everolimus in Guidant's proprietary polymer coating on Guidant's Vision cobalt chromium stent, and a fourth control arm. The study will be conducted at 15 sites and will enroll a total of 140 patients. Phase 2 of this study will continue with the everolimus concentration that demonstrated the best result in phase 1 and will enroll 150 patients.

Tacrolimus-eluting stents

The results of the **PRESENT** (**Pre**liminary **S**afety **E**valuation of **N**anoporous **T**acrolimus **E**luting Stents) and **EVIDENT** (**E**ndo-**V**ascular **I**nvestigation **D**etermining the Safety of a New Tacrolimus **E**luting Ste**nt** Graft) clinical studies examining the effectiveness of tacrolimus in native coronary arteries and saphenous vein grafts have recently been released. Structurally, tacrolimus resembles sirolimus and binds to the same intracellular binding protein or immunophilin (FKBP-12). Unlike sirolimus, tacrolimus does not block the activation of mTOR.

The **PRESENT I** safety study tested a Jomed FlexMaster low-dose (60 µg tacrolimus) tacrolimus-eluting stent employing Jomed's proprietary nanoporous ceramic layer of aluminum oxide as the delivery platform. The PRESENT I study was halted after the enrollment of 22 patients into the treatment group. There were no MACE reported at 30 days (primary endpoint); however, the 6-month MACE rate was 13.6% in the treatment group. Late loss in the treated group was 0.81 mm and the binary restenosis rate was 19%. The **PRESENT II** registry study tested a high-dose (230 µg) tacrolimus-eluting stent and enrolled 30 patients. The primary endpoint, MACE at 30 days, was 0, but at 6 months, MACE was 32.0% in the tacrolimus-treated group.

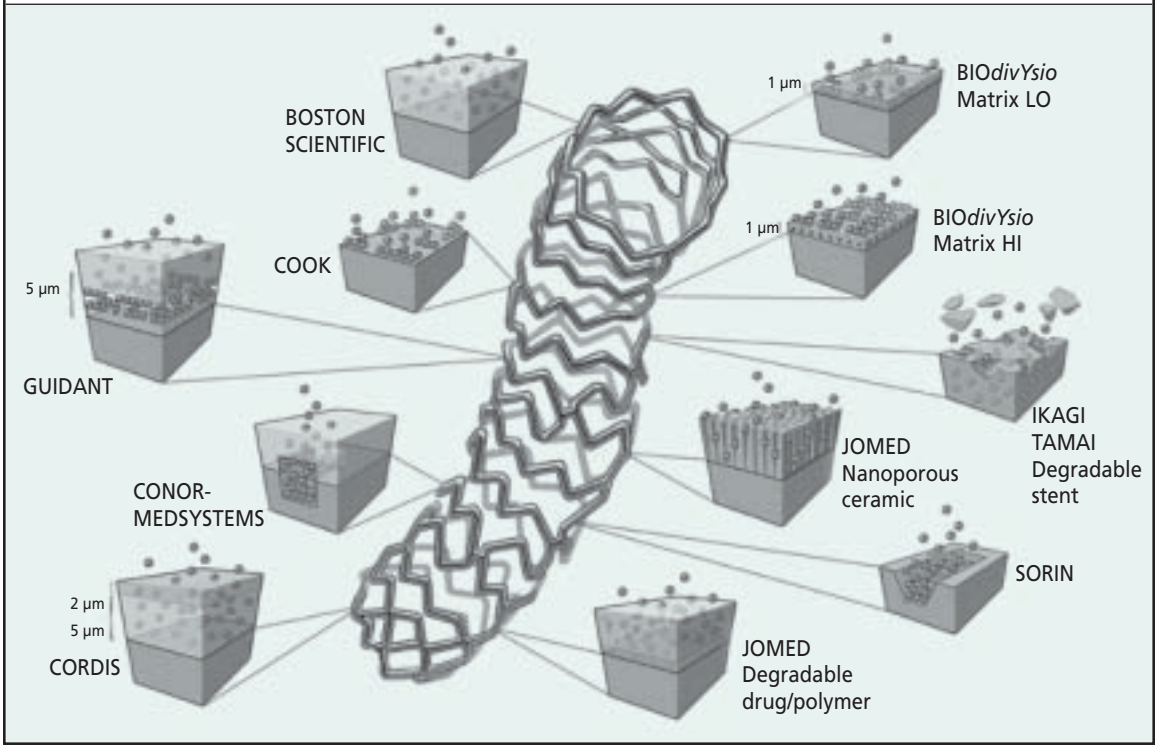
The **EVIDENT** registry study enrolled 20 patients and was designed to examine the safety of the implantation of tacrolimus (325 mg) eluting, ePTFE-covered, Jomed stents in *de novo* saphenous vein graft lesions. The 30-day MACE rate

Table 1: Ongoing and completed drug-eluting stent trials

Trial Name (Company)	Stent	# of Patients	Lesion Type	Design
Rapamycin, Sirolimus				
RAVEL (Cordis/J&J)	CYPHER vs Bx Velocity	238	*De novo* lesions	Efficacy of rapamycin eluting stents (Europe and Latin America) PRDBC study; PE: Late loss at 6 months
SIRIUS (Cordis/J&J)	CYPHER vs Bx Velocity	1101	*De novo* lesions	Efficacy of rapamycin eluting stents (U.S.A.); PRDBC study PE: 9 month target lesion failure
E-SIRIUS (Cordis/J&J)	Bx Velocity	350	*De novo* lesions	Efficacy of rapamycin eluting stents (Europe and Latin America) PRDBC study; PE: 9 month target lesion failure
FIM (Cordis/J&J)	Slow release vs fast release Bx Velocity	45	*De novo* lesions	Safety of fast- and slow-release rapamycin eluting stents Registry; PE: Safety and efficacy
ISR (Cordis/J&J)	Bx Velocity	41	In-stent restenosis	Safety of rapamycin eluting stents for in-stent restenosis Registry; PE: Safety and efficacy
BIFURCATION (Cordis/J&J)	Bx Velocity	21	*De novo* bifurcation lesions	Safety of rapamycin eluting stents for in-stent restenosis Registry; PE: Safety and efficacy
FREEDOM (Cordis/J&J)	Bx Velocity	1500	*De novo* lesions in diabetics	CABG vs multi-vessel stenting with rapamycin eluting stents in diabetics; PRC study; PE: MACE at 1 year
RESEARCH (Cordis/J&J)	Bx Velocity	563	"Real world"	Efficacy of rapamycin eluting stents in "real world" lesions, consecutive patients; Registry; PE: Safety and Efficacy
Paclitaxel, Taxol				
TAXUS I (BS)	Slow release NIR vs bare NIR	61	*De novo* lesions	Safety and feasibility of implantation of paclitaxel eluting stents PRDBC study; PE: 30 day MACE
TAXUS II (BS)	Slow release and moderate release vs bare NIR	536	*De novo* lesions	Efficacy of paclitaxel eluting stents, slow release vs. bare and moderate release vs. bare PRDBC study; PE: Plaque volume by IVUS at 6 months
TAXUS III (BS)	Drug-eluting NIR	30	In-stent restenosis	Safety and feasibility of implantation of paclitaxel eluting stents for instent restenosis; Registry series PE: 30 day MACE and 6-month angiographic and IVUS follow-up
TAXUS IV (BS)	Slow release Express vs bare Express	1326	*De novo* lesions	Efficacy of paclitaxel eluting stents in *de novo* lesions up to 28 mm long and 3.75 mm in diameter using a slow release formulation; PRDBC; PE: 9 month follow up
TAXUS V (BS)	Slow release Express vs bare Express	1512	*De novo* long lesions and small diameter lesions, In-stent restenosis	Efficacy of paclitaxel eluting vs bare stents in *de novo* lesions up to 44 mm in length and as small as 2.25 mm in diameter, paclitaxel eluting stents vs brachytherapy in pts with ISR PRDBC/PRC; PE: 9 month target vessel revascularization
TAXUS VI (BS)	Moderate release Express vs bare Express	448	*De novo* long lesions	Efficacy of moderate-release paclitaxel eluting stents in long lesions (≥18 mm,≤40 mm) PRDBC; PE: 9 month target vessel revascularization
ELUTES (Cook)	V-Flex Plus	192	*De novo* lesions	Safety and efficacy of paclitaxel coated stents using four doses compared to bare PRDBC; PE: % diameter stenosis and late loss at 6 months
DELIVER (Cook/GDT)	Achieve stent vs bare Penta stent	1043	*De novo* lesions	Efficacy of paclitaxel eluting stents for *de novo* lesions PRDBC; PE: target vessel failure at 9 months
DELIVER II (Cook/GDT)	Achieve stent vs bare Penta	1533	*De novo* lesions	Efficacy of paclitaxel eluting stents for lesions at high risk for restenosis; PRDBC; PE: target vessel revascularization at 6 months
ASPECT (Cook)	Supra-G	177	*De novo* lesions	2 arms of 57 patients testing different doses of paclitaxel and control bare stent; PRDBC; PE: 6 month binary restenosis rate
Actinomycin D				
ACTION (GDT)	Drug eluting MULTI-LINK vs bare	360	*De novo* lesions	Efficacy of Actinomycin D eluting stents using 2 doses compared to bare; PRDBC; TRIAL TERMINATED MARCH 2002
7-Hexanoyltaxol				
SCORE (BS/Quanum)	QueST stent vs bare stent	400	*De novo* lesions	Efficacy of 7-hexanoyltaxol coated stents; PRDBC TRIAL TERMINATED AFTER ENROLLMENT OF 266 PATIENTS
Dexamethasone				
STRIDE (Biocompatibles)	BiodivYsio	71	*De novo* lesions	Safety and feasibility of implantation of dexamethasone eluting stents; Registry; PE: Safety
Batimastat				
BRILLIANT I (Biocompatibles)	BiodivYsio	150	*De novo* lesions	Safety and feasibility of implantation of Batimastat eluting stents Registry; PE: Safety
BRILLIANT II (Biocompatibles)	BiodivYsio	400	*De novo* lesions	Safety and feasibility of Batimastat eluting stents PRDBC; TRIAL TERMINATED
Tacrolimus				
EVIDENT (Jomed)	JoStent Stent Graft	30	*De novo* lesions in saphenous vein grafts	Safety and feasibility of tacrolimus eluting stent graft in SVGs Registry series; PE: 30 day MACE
PRESENT I (Jomed)	Ceramic Flexmaster (low dose)	22	*De novo* lesions	Safety and efficacy of tacrolimus eluting ceramic coated stents compared with control; Registry series; TRIAL HALTED
PRESENT II (Jomed)	Ceramic Flexmaster (high dose)	30	*De novo* lesions	Safety and efficacy of tacrolimus eluting ceramic coated stents compared with control; Registry series; PE: 30 day MACE
Everolimus				
FUTURE (Biosensors)	Challenge stent	36	*De novo* lesions	Safety and efficacy of everolimus eluting stents compared with control; PRSBC; PE: Safety and 6 month restenosis
17-beta estradiol				
EASTER (BiodivYsio)	BiodivYsio Matrix LO	30	*De novo* lesions	Safety and efficacy of 17b-Estradiol loaded stents Registry series; PE: Safety and late loss at 6 months

J&J = Johnson and Johnson, BS = Boston Scientific, GDT = Guidant,
PRDBC = Prospective randomized double-blind controlled, PRC = prospective randomized controlled,
PRSBC = Prospective randomized single-blind controlled, PE = Primary endpoint

Figure 1: Stent-mediated delivery methods



1. Boston Scientific; polystyrene-polyisobutylene polystyrene copolymer intermediate layer
2. Cook; non-polymerized albumin coating
3. Guidant; ethylene-vinyl acetate intermediate layer
4. Conor-Medsystems: polylactide/glycolide copolymer intermediate layer
5. Cordis: ethylene-vinyl acetate and poly(n-butyl methacrylate) polymer intermediate layers
6. Abbot/Jomed: ethylene-vinyl acetate intermediate layer
7. Sorin: no coating
8. Jomed: nanoporous ceramic
9. Igaki Tamai: poly-L-lactic acid stent
10. BiodivYsio Matrix LO; phosphorylcholine coating
11. BiodivYsio Matrix HI; phosphorylcholine coating.

was 0%, while the 6-month MACE rate was 36.4%. The binary restenosis rate at 6 months was 27%.

Conclusion

Two major milestones in the evolution of the subdiscipline of interventional cardiology were the development of the angioplasty balloon by Andreas Gruentzig and the introduction of the coronary artery stent. The development of the drug-eluting stent has been called the third revolution in this rapidly evolving field.[11] Although it has only been 3 years since the release of the incredible first clinical results of the First in Man (FIM) trials,[12,13] drug-eluting stents have monopolized all discussions of new stent technologies. With a few notable exceptions, outcomes from subsequent studies using different pharmacologic preparations and eluting matrices have been highly positive, although less than perfect. There is a growing faction of dissenting cardiologists who believe that drug-eluting stents are not the answer to all of the interventionalist's problems. Criticism of the indiscriminate use of drug-eluting stents as a panacea for all lesion subsets, in all clinical situations, stems from the recent results of longer-term studies in broader patient populations that show the emergence of troubling clinical issues. Cases of restenosis at the stent edges and within the body of the stent have been observed. Animal studies of drug-eluting stents have shown the presence of fibrin, inflammatory cells, incomplete endothelialization, and at 3 months, with sirolimus, when the drug has been completely eluted from the stent, neointimal growth is at levels comparable to that seen with bare stainless-steel stents. Delayed endothelialization has also been seen in human arteries treated with drug-eluting stents[14] and there is concern that as human trials provide longer-term data, late restenosis may become apparent. There is speculation that the complete inhibition of healing provided by drug-eluting stents may prevent encapsulation of the stent with resultant stent mal-apposition and possible dislodgment. Results from the RAVEL study have shown that late, incomplete, stent apposition has been detected more frequently in drug-eluting stent-treated groups, however, its occurrence has not translated into clinical adverse events at 1 year.[15]

The acceptance of drug-eluting stents has followed the same course as all newly introduced technologies.

The initial period of overblown enthusiasm has been quickly followed by a period of intellectual reproach. It is clear that for a relatively new technology, the use of drug-eluting stents has had an unprecedented impact on the practice of interventional cardiology. It is unlikely that one drug released by a single matrix on a particular stent design will show the same efficacy in all clinical situations. More biologically friendly coatings that promote, rather than inhibit, natural healing processes, are being rapidly developed. An example of such an approach is the use of immobilized antibodies to circulating endothelial progenitor cells as a means of "autoseeding" intravascular devices. Such technologies show promise for use in combination with drug-eluting stent platforms and may, in fact, provide a more physiological alternative to their use. With the development of better devices, uniquely engineered to be specific for each lesion subset, the dream of a "coup" over surgical revascularization techniques might be realized.

References

1. Grube E, Gerckens U, Rowold S, Yeung AC, Stertzer SH. Inhibition of in-stent restenosis by a drug-eluting polymer stent: pilot trial with 18 month follow-up. *Circulation* 2000;102:II-554.
2. Honda Y, Grube E, de la Fuente LM, Yock PG, Sterzer SH, Fitzgerald PJ. Novel drug delivery stent: intravascular ultrasound observations from the first human experience with the QP2-eluting polymer stent system. *Circulation* 2001;104:380-83.
3. Armstrong J, Gunn J, Holt CM, et al. Local angiopeptin delivery from coronary stents in porcine coronary arteries [abstract]. *Eur Heart J* 1999; 20:1929.
4. Gobeil F, Leclerc G, Martel R, et al. BiodivYsio stent based local drug delivery of short DNA oligonucleotide coupled with radiation (Oligloe) reduces neointimal hyperplasia in a swine coronary restenosis model [abstract]. *Circulation* 2001;104(suppl.):II-507.
5. New G, Moses JW, Roubin GS, et al. Estrogen eluting stents selectively reduce intimal hyperplasia without impeding re-endothelialization in a porcine coronary model [abstract]. *Circulation* 2001;104(suppl.):II-509.
6. Kim HS, Yazdi HA, Seaborn R, et al. Antisense morpholino compound (AVI-4126) eluting phosphorylcholine-coated (PC) stent inhibits c-myc expression and myointimal hyperplasia in the porcine model [abstract]. *Circulation* 2001;104(suppl.):II-545.
7. Gammon RS, Chapman GD, Agrawal GM, et al. Mechanical features of the Duke biodegradable intravascular stent [abstract]. *J Am Coll Cardiol* 1991;17 Suppl:235A.
8. Tsuji T, Tamai H, Igaki K, et al. Biodegradable stents as a platform to drug loading. *Int J Cardiovasc Intervent* 2003;5:13-6.
9. Labinaz M, Zidar JP, Stack RS, Phillips HR. Biodegradable stents: the future of interventional cardiology? *J Intervent Cardiol* 1995;8:395-405.
10. Tamai H, Igaki K, Kyo E, et al. Initial and 6-month results of biodegradable poly-l-lactic acid coronary stents in humans. *Circulation* 2000;102: 399-404.
11. Chieffo A, Colombo A. Drug-eluting stents. *Minerva Cardioangiol* 2002;50: 419-29.
12. Rensing BJ, Vos J, Smits PC, et al. Coronary restenosis elimination with a sirolimus eluting stent: first European human experience with 6-month angiographic and intravascular ultrasound follow-up. *Eur Heart J* 2001;22: 2135-30.
13. Sousa JE, Costa MA, Abizaid A, et al. Sustained supression of neointimal proliferation by sirolimus-eluting stents: one year angiographic and intravascular ultrasound follow-up. *Circulation* 2001;104:2007-11.
14. Guagliumi G, Farb A, Musumeci G, et al. Images in cardiovascular medicine. Sirolimus-eluting stent implanted in human coronary artery for 16 months: pathological findings. *Circulation* 2003;107:1340-1.
15. Serruys PW, Degertekin M, Tanabe K, et al. Intravascular ultrasound findings in the multicenter, randomized, double-blind RAVEL (Randomized study with the sirolimus-eluting Velocity balloon-expandable stent in the treatment of patients with de novo native coronary artery Lesions) trial. *Circulation* 2002;106(7):798-803.

Upcoming meetings

26-28 February 2004
Cardiovascular Topics at Johns Hopkins
Baltimore, MD
CONTACT: CME Office
Tel: 410-955-2959
Fax: 410-955-0807
E-Mail: cmenet@jhmi.edu

7-10 March 2004
53rd Annual Scientific Session of the American College of Cardiology
New Orleans, LA
CONTACT: The American College of Cardiology
Tel: 800-253-4636, ext. 694 / 301-897-5400
Fax: 301-897-9745
E-Mail: resource@acc.org

22-26 March 2004
The 19th Annual Interventional Cardiology 2004: The International Symposium
Snowmass Village, CO
CONTACT: Laurel Steigerwald
Tel: 714-799-1617 ext 26
Fax: 714-799-1686
E-Mail: education@promedica-intl.com

Change of address notices and requests for subscriptions to *Cardiology Rounds* are to be sent by mail to P.O. Box 310, Station H, Montreal, Quebec H3G 2K8 or by fax to (514) 932-5114 or by e-mail to info@snellmedical.com. Please reference *Cardiology Rounds* in your correspondence. Undeliverable copies are to be sent to the address above.

This publication is made possible by an educational grant from

Novartis Pharmaceuticals Canada Inc.