Insights From The Portland DES Symposium

Part III: How will multivessel DES-PCI progress in 2004?

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This article is the final installment of a three-part series of coronary topics from The Portland DES Symposium.

The Portland DES symposium was conducted on October 2, 2003, to review the current status of clinical trials on drug-eluting stents (DESs), discuss the impact of the DES on the practice of percutaneous coronary intervention (PCI), and identify methods to optimize clinical outcomes. In Parts I and II of this series, the applications of DESs for the management of bifurcation lesions and in patients with unstable angina was discussed.[1,2] Technical and clinical trial summaries for the Cypher (Cordis Corporation, a Johnson & Johnson company, Miami, FL) and the Taxus Express[2] (Boston Scientific Corporation, Natick, MA) stents and guidelines for adjunctive pharmacotherapy during DES-PCI in patients with unstable angina were provided. In this installment, the clinical aspects related to managing patients with multivessel coronary artery disease undergoing DES-PCI will be reviewed. A detailed discussion of such management is beyond the scope of this article but is available to the reader for review.[3-5]

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CURRENT RESEARCH

As stated in Part II of this series, the majority of published data with the DES pertains to clinical application of this technology in relatively low-risk, noncomplex patient and coronary lesion subsets. In fact, multivessel or multilesion PCI was prohibited in the largest randomized clinical trials conducted with sirolimus- and paclitaxel-eluting stents.[6,7] Recently, data from large single- and multicenter registry trials of DESs (e-Cypher, RESEARCH, WISDOM) have also provided initial clinical outcome data for patients undergoing multivessel DES-PCI.[8-11]

THE RESEARCH TRIAL

The RESEARCH trial (Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital) is the largest published single-center experience for a DES in the "real world" practice of interventional cardiology.[9-11] The RESEARCH registry was implemented in April 2002 after CE approval of the sirolimus-eluting stent in Europe. In this registry, all patients eligible for PCI with sirolimus-eluting stents were compared with a matched consecutive patient control cohort of bare metal stent patients immediately before the RESEARCH study.

The patients in the sirolimus stent group more frequently had multivessel disease, more type C lesions, received more stents, and had more bifurcation stenting. Fifty-four percent of the sirolimus group and 48% of the control group had multivessel PCI. In the sirolimus group, 97% of the patients had angiographic success (<30% residual stenosis in the presence of TIMI-3 flow) for all lesions treated. At 1 year, the cumulative rate of cardiac death, myocardial infarction, or target vessel revascularization was 9.7% in the sirolimus group and 14.7% in the control or pre-sirolimus group.[9] The risk of 1-year clinically driven target lesion revascularization was 3.7% in the sirolimus group and 10.9% in the control group. Multivariate analysis identified utilization of sirolimus-eluting stents to be independently associated with a reduced risk of adverse clinical events (death, myocardial infarction, target lesion revascularization). Diabetes mellitus (Hazard ratio, 1.81; 95% CI, 1.10–2.99; P=.02) and number of stented segments (Hazard ratio, 1.25; 95% CI, 1.01–1.55; P=.04) were multivariate predictors of clinically driven target lesion revascularization. In the multivessel disease cohort, sirolimus-eluting stent implantation significantly reduced the need for 1-year

clinically driven target vessel revascularization (Hazard ratio, 0.47; 95% CI, 0.25–0.88; P=.02). In recently reported angiographic substudy of the RESEARCH registry, the treatment of in-stent restenosis (Hazard ratio, 4.16; 95% CI, 1.63–11.01; P<.01), ostial location (Hazard ratio, 4.84; 95% CI, 1.81–12.07; P<.01), diabetes mellitus (Hazard ratio, 2.63; 95% CI, 1.14–6.31; P=.02), and total stented length (per 10-mm increase) (Hazard ratio, 1.42; 95% CI, 1.21–1.68; P<.01) were identified as independent predictors for in-segment restenosis after sirolimus-eluting stent implantation.[11]

The investigators concluded that restenosis after sirolimus-eluting stent implantation in complex patients is an infrequent event, occurring mainly in association with local, lesion-based characteristics and diabetes mellitus. Thus, anatomic and metabolic factors seem more important predictors of restenosis after sirolimus stent implantation than the number or length of implanted stents.

DISCUSSION

Throughout the course of the Portland DES Symposium, several panel members discussed aspects of managing patients with multivessel coronary artery disease and potential clinical indications for DES-PCI. The faculty emphasized the limited current data for DESs in patients with multivessel coronary artery disease. At present, the clinical application of DESs appears justifiable for the management of patients with focal two- or three-vessel coronary artery disease and coronary anatomy suitable for PCI with >95% probability for procedural success consistent with ACC/AHA guidelines.[3] The faculty acknowledged the known limitations of bare metal stent PCI in patients with diabetes mellitus and the limited data available on DESs in this patient population.

The issue of restenosis in the diabetic patient is complicated by the atherosclerotic burden, vessel wall mechanics, and numerous biologic aberrations induced by hyperglycemia, dyslipidemia, and insulin on clotting factors, platelet function, fibrinolytic systems, cytokines, and growth factors together promoting excessive neointimal hyperplasia after coronary stent placement.[12] Diabetes results in increased circulating serum glucose levels. Hyperglycemia is potentially related to many steps in the process of restenosis; however, no consistent data implicate hyperglycemia and restenosis.[13] Insulin has several biological properties, which may be related to the process of restenosis. In fact, some argue that insulin resistance, rather than diabetes, is a more important predictor of restenosis.[14]

Diabetes and hyperglycemia alone have not been implicated in processes of cell cycle regulation. Insulin,

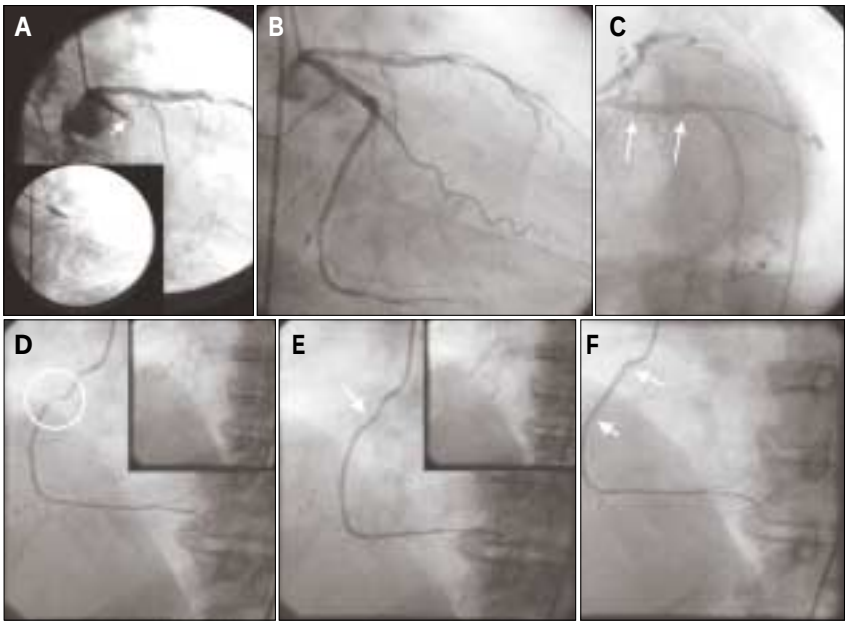

Figure 1. A 100% occlusion of the proximal left circumflex coronary artery in an AP caudal projection (A). Unfractionated heparin (50 U/kg) and eptifibatide (180 µg/kg bolus followed by infusion of 2 µg • kg^{-1} • min^{-1}) was administered intravenously prior to cardiac catheterization. An additional bolus of unfractionated heparin was administered to achieve an ACT >300 seconds. A 6-F XB 3.5 guiding catheter (Cordis) was selected to provide optimal support for delivery of a 3.5-mm-diameter, 15-mm-length Multi-Link Zeta (Guidant Corporation, Indianapolis, IN) stent. A low residual stenosis is noted within the lesion (arrows) after deployment of the Multi-Link Zeta with normal coronary flow (B,C). An irregular high-grade lesion of the mid right coronary artery (LAO projection) (D). The vessel was engaged with a 6-F JR 4.0 (Zuma, Medtronic, Inc., Santa Rosa, CA) guiding catheter with side holes. The lesion was crossed with a 0.014-inch hydrophilic polymer tip-coated guidewire. The lesion was predilated with a 2.5-mm-diameter, 15-mm-length semicompliant balloon (E). After predilation, a 2.5-mm-diameter, 28-mm-length Cypher stent was implanted at 16 atm. The final angiographic result (LAO projection) demonstrates an excellent result with less than 5% residual stenosis within the DES (arrows) and normal distal myocardial blood flow (F).

however, has been recognized as a key regulator of protein synthesis.[15] Insulin causes an increase in translation initiation factors, and activates mTOR by promoting phosphorylation of the protein via an intracellular signaling pathway. In theory, these data identify a mechanism by which insulin promotes neointimal hyperplasia and may interact with potent, site-specific, stent-based therapies such as sirolimus. An improved biological characterization of the process of restenosis in diabetic patients will allow selection of optimal drug, dosage, and possible synergistic systemic or local therapies for the prevention of restenosis.

In the pre-stent era, the BARI and EAST trials suggested a mortality benefit in favor of CABG with utilization of a LIMA-LAD graft as compared with PTCA in patients with diabetes mellitus at 5 or 8 years.[16-18] In subsequent studies evaluating stent placement versus CABG for patients with multivessel disease, such as the Arterial Revascularization Therapy Study (ARTS), the mortality benefit of surgical revascularization in diabetic patients was not confirmed in comparison with bare metal stenting.[19] Repeat revascularization procedures, however, were more frequent after stenting in comparison with CABG, in particular for patients with diabetes mellitus. These data from the PTCA and stent era underscore the necessity for the completion of randomized clinical trials to document the efficacy of DESs versus CABG for multivessel coronary artery disease. The ARTS II (CABG versus sirolimus-eluting stent) and FREEDOM trials (CABG versus sirolimus stent in patients with diabetes mellitus) will provide a better understanding of the clinical application of sirolimus-eluting stents for the management of patients with multivessel coronary artery disease amenable to PCI or CABG (Table 2).

The coronary angiograms depicted in Figure 1 demonstrate complete occlusion of the proximal left circumflex coronary artery and a noncalcified ulcerated mid-right coronary artery lesion in a 50-year-old, diet-controlled, diabetic patient who presented with chest pain, transient ST segment depression, and a troponin I of 0.4 ng/mL. The patient's ischemic symptoms and ST segment depression promptly resolved after administration of aspirin, sublingual and intravenous nitroglycerin, beta-blocker, unfractionated heparin (50 U/kg intravenous), and the glycoprotein IIb/IIIa inhibitor eptifibatide (180 µg/kg bolus plus infusion 2 µg/kg/min). The patient underwent urgent diagnostic coronary angiography and left ventriculography shortly after admission to the coronary care unit of the hospital to determine coronary anatomy, identify the culprit lesion, and to define a revascularization strategy. Left ventriculography demonstrated an ejection fraction of 53%, with inferior-lateral hypokinesis. Percutaneous catheter-based treatment of the culprit left circumflex coronary lesion and a critical nonculprit stenosis of the right coronary artery necessitates that the operator address several aspects of case management, as outlined below.

TABLE 1. SELECTED CLINICAL CONSIDERATIONS FOR PCI OR CABG IN THE MANAGEMENT OF PATIENTS WITH MULTIVESSEL CORONARY ARTERY DISEASE

	PCI	CABG
Clinical Factors		
Diabetes Mellitus	Diet-controlled, noninsulin requiring with focal lesion(s) amenable to PCI with glycoprotein IIb/IIIa inhibitor[23]	Diabetes requiring insulin therapy
LVEF <40%	Focal non-LAD lesion(s), poor distal targets	Two-vessel disease with proximal LAD lesion or three-vessel disease
Other	Comorbid disease, prohibitively high risk post-CABG mortality	Multivessel disease with failed brachytherapy or DES
Anatomic Factors	Focal (covered with 1 or 2 DES/lesion), nonostial lesions with high probability for lesion/procedure success	Left mainstem obstruction Diffuse disease, ostial lesions and CTO with low probability for lesion/procedure success

TABLE 2. SUMMARY OF PLANNED DES CLINICAL TRIALS COMPARING MULTIVESSEL DES-PCI WITH CABG FOR PATIENTS WITH TWO- OR THREE-VESSEL CORONARY ARTERY DISEASE

	Patient Population	Trial Design	Primary Endpoint	Status
ARTS II	Patients with two- or three-vessel CAD amenable to PCI or CABG	RCT DES versus CABG	1-year MACE	Active, enrollment phase
FREEDOM	Diabetic patients with two- or three-vessel CAD amenable to PCI or CABG	2,600 patient RCT FDA approved DES versus CABG	5-year cardiac mortality	Planned, Q3 2004

Therapeutic Options

• Multivessel PCI with or without DES versus surgical revascularization (Table 1).

Adjunctive Therapies

• Oral antiplatelet agents: ASA 325 mg daily, clopidogrel 75 mg daily for 12 months or longer after loading dose of 300 to 600 mg.

• Antithrombin therapy: Preprocedural anticoagulation with fractionated heparin (enoxaparin 30 mg intravenous [IV], then 1 mg/kg SQ q 12 h); procedural anticoagulation with fractionated heparin (30 mg IV), unfractionated heparin (50 U/kg IV with glycoprotein IIb/IIIa; adjust dose to achieve an ACT of 250 to 300 seconds with glycoprotein IIb/IIIa inhibitor[20] or 350 to 400 seconds without glycoprotein IIb/IIIa inhibitor[21]) or direct thrombin inhibitor (bivalirudin, 0.75-mg/kg bolus plus 1.75 mg/kg per hour for the duration of PCI, with provisional glycoprotein IIb/IIIa inhibition[22]).

• Glycoprotein IIb/IIIa inhibitor: Preprocedural versus procedural administration; eptifibatide bolus and infusion; abciximab bolus and infusion; tirofiban bolus and infusion (refer to part II of this series for dosing guidelines).

Device Selection

Left Circumflex

• Guiding catheter: 6-F, XB 3.5 (Cordis) or EBU (Medtronic) for extra support.

• Guidewire: 0.014-inch solid core-tip, hydrophilic guidewire (Choice PT or PT2, Boston Scientific; Whisper, Guidant); 0.014-inch floppy-type spring coil tip (HTF, Guidant).

• Lesion preparation for bare metal stent: Predilation at lowest pressure to achieve uniform "full" inflation of balloon (no waist) and dilate entire diseased segment.

• Stenting technique: Bare metal stent or DES. Bare metal stent, select a diameter and length suitable for optimal (<10% residual stenosis) focal stenting of the thrombotic lesion without "jailing" the branch vessel, and minimize stent length to reduce probability for restenosis.

Right Coronary Artery

• Guiding catheter: 6-F, JR 4.0 with side holes (Medtronic) to allow adequate support, maintain distal myocardial blood flow.

• Guidewire: 0.014-inch solid core-tip, hydrophilic guidewire (Choice PT or PT2, Boston Scientific; Whisper, Guidant); 0.014-inch floppy-type spring coil tip (HTF, Guidant.).

• Lesion preparation for DES: Consider direct stenting for less critical lesions in noncalcified, nonangulated coronary segments.[23]

• Predilation: At lowest pressure to achieve uniform inflation with undersized balloon, length shorter than planned length of DES to reduce zone of vessel wall injury.

• Stenting technique: DES should extend beyond proximal and distal margins of the lesion and segments of the artery treated with PTCA.

• Deployment of DES: At nominal inflation pressure (11 atm, Cypher; 9 atm, Taxus) or higher inflation pressure, typically 12 to 14 atm.

• Postdilation: Is recommended with noncompliant balloon at inflation pressure of 12 to 18 atm to achieve less than 10% residual stenosis.

• Additional DES: For inadequate lesion coverage, edge dissection or intramural hematoma to reduce probability of stent thrombosis.

CONCLUSION

The case described in this article highlights some aspects of clinical decision-making in the era of DES, in particular selection of a revascularization strategy and utilization of DESs versus bare metal stents. This patient was an ideal candidate for PCI given the presenting clinical syndrome, focal nature of coronary disease, left ventricular function, and age. The operator selected a bare metal stent to treat the left circumflex lesion because of probable recent thrombotic occlusion of the artery and limited availability of data regarding the application of DES for this indication at the time of the PCI.

In the era of the DES, the management of patients with multivessel coronary artery disease requires a comprehensive assessment of anatomic location and lesion characteristics, as well as associated clinical syndromes to determine the optimal method of revascularization (PCI or CABG) to yield optimal long-term relief from anginal symptoms and reduction in risk for subsequent major adverse cardiac events. The DES provides potential incremental therapeutic benefit by reducing the need for repeat revascularization procedures and may allow expanded indications for PCI in selected patient subsets previously referred for CABG, such as multivessel coronary artery disease. The results of ARTS II and other planned clinical trials will be necessary to determine long-term efficacy of the DES in management of patients with multivessel coronary artery disease. ■

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1. Carter AJ. Insights from the Portland DES Symposium: part I: treating complex coronary bifurcation lesions in the era of the drug-eluting stent requires careful planning and a strong knowledge base of the technology, components, and techniques. *Endovasc Today.* 2004;(1)31-33.

2. Carter AJ. Insights from The Portland DES Symposium: part II: culprit lesion PCI for unstable angina in the era of the drug-eluting stent. *Endovasc Today.* 2004(2)36-41.

3. Smith SC, Dove JT, Jacobs AK, et al. A Report of the American College of Cardiology/American Heart Association Task Force on Practice Guidelines (Committee to Revise the 1993 Guidelines for Percutaneous Transluminal Coronary Angioplasty) Endorsed by the Society for Cardiac Angiography and Interventions. *Circulation.* 2001;103:3019-3041.

4. Bhatt DL, Topol EJ. Debate: PCI or CABG for multivessel disease? Viewpoint: No clear winner in an unfair fight. *Curr Control Trials Cardiovasc Med.* 2001;2:260-262.

5. Rihal CS, Raco DL, Gersh BJ, et al. Indications for coronary artery bypass surgery and percutaneous coronary intervention in chronic stable angina: review of the evidence and methodological considerations. *Circulation.* 2003;108:2439-2445.

6. Moses JW, Leon MB, Popma JJ, et al. Sirolimus-eluting stents versus standard stents in patients with stenosis in a native coronary artery. *N Engl J Med.* 2003;349:1315-1323.

7. Stone GW, Ellis SG, Cox DA, et al. TAXUS-IV Investigators. A polymer-based, paclitaxel-eluting stent in patients with coronary artery disease. *N Engl J Med.* 2004;350:221-231.

8. Abizaid A. Update on the WISDOM Registry. www.tctmd.com. Accessed 8 Jan 04.

9. Lemos P, Serruys PW, van Domburg RT, et al. Unrestricted utilization of sirolimus-eluting stents compared with conventional bare stent implantation in the "Real World": The Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH Registry). *Circulation.* 2004;109:190-195.

10. Lemos P, Lee CH, Degertekin M, et al. Early outcome after sirolimus-eluting stent implantation in patients with acute coronary syndromes: Insights from the Rapamycin-Eluting Stent Evaluated at Rotterdam Cardiology Hospital (RESEARCH Registry). *J Am Coll Cardiol.* 2003;41:2093-2099.

11. Lemos P, Hoye A, Goedhart D, et al. Clinical, angiographic, and procedural predictors of angiographic restenosis after sirolimus-eluting stent implantation in complex patients. An evaluation from the rapamycin-eluting stent evaluated at Rotterdam Cardiology Hospital (RESEARCH) study. *Circulation.* 2004;109 (rapid access publication, accessed online 1 March 04, www.circulationaha.org)

12. Carter AJ. TOR of the cell cycle: Are there important implications in the era of drug-eluting stent. *Cathet Cardiovasc Intervent.* 2004;61:233-236.

13. Sobel BD. Acceleration of restenosis by diabetes. *Circulation.* 2001;103:1185-1187.

14. Babalik E, Gurmen T, Orhan L, et al. Increased secretion of insulin during oral glucose tolerance test can be a predictor of stent restenosis in nondiabetic patients. *Cathet Cardiovasc Intervent.* 2002;58:306-312.

15. Davis TA, Fiorotto ML, Beckett PR, et al. Differential effects of insulin on peripheral and visceral tissue protein synthesis in neonatal pigs. *Am J Physiol Endocrinol Metab.* 2001;280:E770-E779.

16. Comparison of coronary bypass surgery with angioplasty in patients with multivessel disease. The Bypass Angioplasty Revascularization Investigation (BARI) Investigators. *N Engl J Med.* 1996;335:217–225.

17. Influence of diabetes on 5-year mortality and morbidity in a randomized trial comparing CABG and PTCA in patients with multivessel disease: the Bypass Angioplasty Revascularization Investigation (BARI). *Circulation.* 1997;96:1761 –1769.

18. King SB, III, Kosinski AS, Guyton RA, et al. Eight-year mortality in the Emory Angioplasty versus Surgery Trial (EAST). *J Am Coll Cardiol.* 2000;35:1116-1121.

19. Serruys PW, Unger F, Sousa JE, et al. Comparison of coronary-artery bypass surgery and stenting for the treatment of multivessel disease. *N Engl J Med.* 2001;344:1117-1124.

20. Kereiakes DJ, Montalescot G, Antman EM, et al. Low-molecular-weight-heparin therapy for non-ST-elevation acute coronary syndromes and during percutaneous coronary intervention: an expert consensus. *Am Heart J.* 2002;144:615-624.

21. Chew DP, Bhatt DL, Lincoff AM, et al. Defining the optimal activated clotting time during percutaneous coronary intervention: aggregate results from 6 randomized, controlled trials. *Circulation.* 2001;103:961-966.

22. Lincoff AM, Bittl JA, Harrington RA, et al. for the REPLACE-2 Investigators. Bivalirudin and provisional glycoprotein IIb/IIIa blockade compared with heparin and planned glycoprotein IIb/IIIa blockade during percutaneous coronary intervention: REPLACE-2 randomized trial. *JAMA.* 2003;289:853-863.

23. Schofer J, Schluter M, Gershlick AH, et al. Sirolimus-eluting stents for treatment of patients with long atherosclerotic lesions in small coronary arteries: double-blind, randomised controlled trial (E-SIRIUS). *Lancet.* 2003;362:1093-1099.

24. Marso SP, Lincoff AM, Ellis SG, et al. Optimizing the percutaneous interventional outcomes for patients with diabetes mellitus: results of the EPISTENT (Evaluation of Platelet IIb/IIIa Inhibitor for Stenting Trial) diabetic substudy. *Circulation.* 1999;100:2477-2484.