Insights From The Portland DES Symposium

Part II: Culprit lesion PCI for unstable angina in the era of the drug-eluting stent.

BY ANDREW J. CARTER, DO, ON BEHALF OF THE FACULTY MEMBERS*

This article is the second 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 with the DES. In the first article of this three-part series, the application of the DES for the management of bifurcation lesions was discussed.[1] The technical and clinical trial summaries for the CYPHER (Cordis Corporation, a Johnson & Johnson company, Miami, FL) and the TAXUS (Boston Scientific Corporation, Natick, MA) stents were also provided. This second part of the series reviews the fundamental clinical aspects related to the management of patients with acute coronary syndromes (ACS) undergoing culprit lesion PCI in the era of the DES. A detailed discussion of pharmacological management of patients with ACS is beyond the scope of this article but is available to the reader for review.[2-6]

CURRENT RESEARCH

The majority of published data regarding the DES pertains to clinical application of this technology in relatively low-risk, noncomplex patient and coronary lesion subsets. These low-risk patient subsets represent only a minority of the types of challenging cases faced in the routine daily practice of interventional cardiology. In the SIRIUS and TAXUS IV trials, approximately 30% to 50% of the enrolled patients underwent placement of a DES for unstable angina.[7,8] Importantly, this population of unstable angina patients had similar early and long-term clinical outcomes compared to patients with stable angina. The unstable angina patients eligible for enrollment in

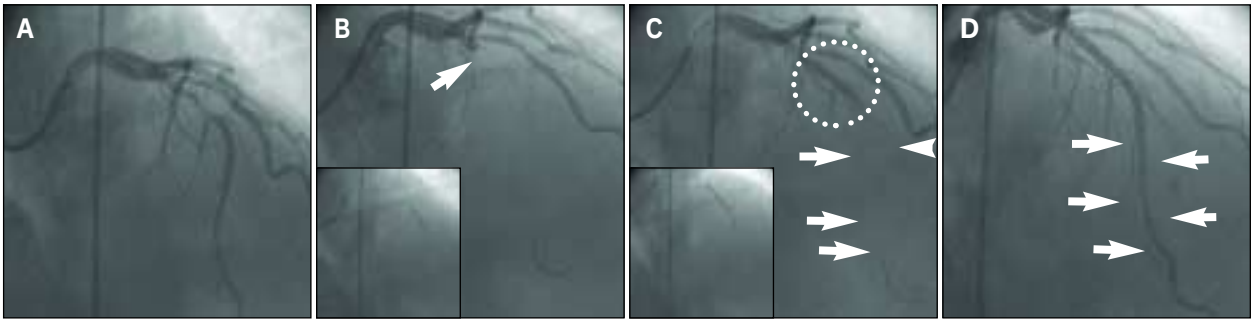

Figure 1. A complex, noncalcified ulcerated 70% stenosis of the mid-left anterior descending coronary artery in an AP cranial projection (A). Unfractionated heparin (50 U/kg) and eptifibatide (180 µg/kg bolus followed by infusion of 2 µg • kg^{-1} • min^{-1}) was administered intravenously, achieving an ACT of 390 seconds. A 6-F, XB 3.5 guiding catheter was selected to provide optimal support for delivery of a 3.5-mm diameter, 23-mm length CYPHER stent. Transient acute closure (arrow) of the vessel occurred despite predilation at a low pressure and with an undersized (2.5-mm diameter, 15-mm length, see insert) balloon (B). A low residual stenosis is noted within the lesion after deployment of the CYPHER stent (insert demonstrates deployment of the CYPHER stent; region within circle) (C). Distal coronary flow, however, was abnormal (TIMI-1) due to no-reflow that was likely secondary to embolization of atherothrombotic material in the microvascular bed of the distal LAD (arrows). Adenosine was administered intracoronary in boluses of 24 to 40 µg (8 µg/mL) via the guide catheter and the central lumen of an infusion catheter positioned in the distal aspect of the LAD. The final angiographic result (AP cranial projection) demonstrates an excellent result with less than 5% residual stenosis (D).

SIRIUS and TAXUS IV, however, likely represent a lower-risk subset because these trials excluded patients with positive cardiac enzymes within 48 to 72 hours of the DES procedure. Recently, data from large single- and multicenter registry trials of the DES (e-CYPHER, RESEARCH, WISDOM) have provided clinical outcome data for higher-risk patients with unstable angina, non–ST-segment, and ST-segment elevation myocardial infarction (Table 1).

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" day-to-day practice of interventional cardiology.[9,10] The RESEARCH registry was implemented in April 2002, after CE Mark 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 patient who received bare metal stents immediately before the RESEARCH study. The patients in the sirolimus-eluting stent group more frequently had multivessel disease, more type C lesions, received more stents, and had more bifurcation stenting. At 1 year, the cumulative rate of cardiac death, myocardial infarction, or target vessel revascularization was 9.7% in the sirolimus-eluting stent group

TABLE 1. SUMMARY OF DES CLINICAL TRIALS INCLUDING PATIENTS WITH ACS

	SIRIUS[3] (n = 533)	TAXUS IV[5] (n = 588)	RESEARCH[9] (n = 508)	WISDOM[16] (n = 778)
Unstable Angina	53%	25%	38%	34%
Myocardial Infarction	NA	NA	17%	18%
Glycoprotein IIb/IIIa Inhibitor	54%	58%	19%	21.9
Death	0.9%	1.2%	3.4% (12 mo)	2.4% (30 d)
SAT	0.4%	0.6%	0.4% (12 mo)	0.1% (30 d)
TLR	4.9% (12 mo)	3% (9 mo)	3.7% (12 mo)	Pending

TABLE 2. CLINICAL USE OF SELECTED ANTITHROMBOTIC AGENTS FOR MANAGEMENT OF ACS[2]

ORAL ANTIPLATELET	
Aspirin	Initial dose of 162 to 325 mg, soluble nonenteric; 75 to 160 mg/d
Clopidogrel	Initial dose of 300 to 600 mg preferably >6 hours prior to PCI; 75 mg/d
Ticlopidine	Initial dose of 500 mg before PCI; 250 mg b.i.d.
HEPARINS	
Dalteparin	120 IU/kg SQ every 12 h (max dose 10,000 IU b.i.d.)
Enoxaparin	1 mg/kg SQ b.i.d. every 12 h; initial 30 mg IV bolus
Heparin (UFH)	Initial bolus 60 to 70 U/kg (maximum 5,000 U) IV followed by infusion of 12 to 15 $U \cdot kg^{-1} \cdot h^{-1}$ (maximum 1,000 U/h) titrated to aPTT 1.5 to 2.5 times control
ANTITHROMBINS	
Bivalirudin	0.75-mg/kg bolus plus 1.75 mg/kg per hour for the duration of PCI
INTRAVENOUS ANTIPLATELET THERAPY	
Abciximab	0.25 mg/kg bolus followed by infusion of 0.125 $\mu g \cdot kg^{-1} \cdot min^{-1}$ (maximum of 10 µg/min) for 12 to 24 h
Eptifibatide	180 µg/kg bolus followed by infusion of 2 $\mu g \cdot kg^{-1} \cdot min^{-1}$ for 18 h (up to 72 to 96 h if pre-PCI, or conservative medical therapy)
Tirofiban	0.4 µg/kg min for 30 min followed by infusion of 0.1 $\mu g \cdot kg^{-1} \cdot h^{-1}$ for 18 h (up to 48 to 96 h if initiated pre-PCI or conservative medical therapy)

TABLE 3. SELECTED CLINICAL CONSIDERATIONS FOR PCI OR CABG IN MANAGEMENT OF PATIENTS WITH ACUTE CORONARY SYNDROMES

	PCI	CABG
Single-Vessel Disease	• Recommended	
Two-Vessel Disease	• Discrete lesions, nonproximal LAD	• With proximal LAD lesion and/or impaired LV systolic function (EF <40%) • Diabetic
Multivessel Disease	• Nondiabetic, nonproximal LAD, LVEF >40%	• Diabetic, LVEF <40%
Left Main Disease	• Nonsurgical candidates, protected left main	• *de novo* lesions
Failed PCI or CABG	• Failed SVG • Brachytherapy for ISR bare metal stents • DES for ISR bare metal stents investigational • DES for failed brachytherapy investigational	• Failed PCI with multivessel or left main disease • Failed brachytherapy • Failed DES

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-eluting stent group and 10.9% in the control group. Fifty-three percent of the sirolimus-eluting stent group and 55% of the control group had unstable angina or acute myocardial infarction. The frequency of stent thrombosis at 30 days tended to be lower for the sirolimus-eluting stent group (0.4%) as compared to the control group (1.6%; $P = .1$), despite significantly lower rates of administration of glycoprotein IIb/IIIa inhibitors (19% sirolimus vs 33% control; $P < .01$). A detailed analysis of 30-day clinical outcomes was reported on the patients with ACS from the RESEARCH registry.

In the ACS subset of the RESEARCH registry, the majority of patients treated with sirolimus-eluting stents had rest angina with electrocardiographic abnormality or acute myocardial infarction.[10] The 30-day major adverse cardiac event (death, myocardial infarction, subacute stent thrombosis) rate was similar between sirolimus (6.1%) and control (6.6%) patients. In multivariate analysis, sirolimus-eluting stent utilization did not influence the incidence of major adverse cardiac events. The investigators concluded that sirolimus-eluting stent implantation for a patient with ACS is safe, with early outcomes comparable with bare metal stents.

DISCUSSION

Throughout the course of the Portland DES Symposium, several panel members discussed aspects of managing patients with ACS and potential clinical indications for DESs. The faculty emphasized the limited current data for DES use in patients with ST-segment elevation myocardial infarction. At present, the clinical application of DESs appears justifiable for the management of patients with unstable angina and non–ST-segment elevation myocardial infarction and coronary anatomy suitable for PCI. The clinical management of patients with ACS necessitates pharmacologic interventions targeting acute thrombus passivation to prevent myonecrosis as a result of arterial thrombosis and procedure-related atheroembolic events, as well as chronic plaque stabilization therapies for the secondary preven-

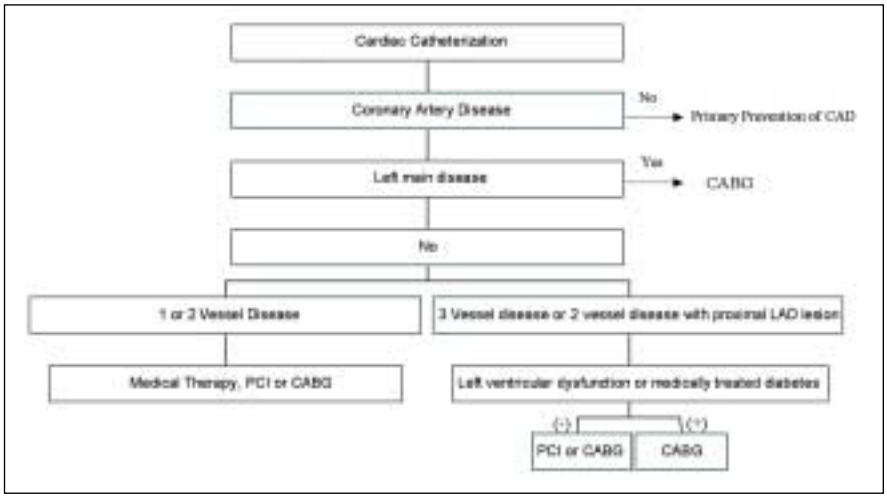

Figure 2. A simplified scheme of recommended percutaneous and surgical revascularization strategies for managing patients with ACS.

TABLE 4. CRITICAL ASPECTS OF CASE MANAGEMENT

THERAPEUTIC OPTIONS	PCI versus surgical revascularization (Figure 2)
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 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 ACT 250 to 300 s with glycoprotein IIb/IIIa inhibitor[4] or 350 to 400 s without glycoprotein IIb/IIIa inhibitor[6]) or direct thrombin inhibitor (bivalirudin, 0.75-mg/kg bolus plus 1.75 mg/kg per hour for the duration of PCI, with provisional Gp IIb/IIIa inhibition[11])
	Glycoprotein IIb/IIIa inhibitor: Preprocedural versus procedural administration; eptifibatide bolus and infusion; abciximab bolus and infusion; tirofiban bolus and infusion (refer to Table 2 for specific dosing guidelines)
DEVICE SELECTION	**Guiding catheter:** 6F, XB 3.5 (Cordis) or EBU (Medtronic) for extra support
	Guide wire: 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: Consider direct stenting for less critical lesions in noncalcified, nonangulated coronary segments.[12] 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 a noncompliant balloon at an 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.

tion of subsequent cardiac events. Guidelines for the use of antithrombotic therapy are outlined in Table 2.

The coronary angiograms depicted in Figure 1 demonstrate a noncalcified, ulcerated, mid-left anterior descending lesion in a patient who presented with chest pain, transient ST-segment elevation, and a troponin I of 0.4 ng/mL. The patient's ischemic symptoms and ST-segment elevation promptly resolved after the administration of aspirin, sublingual and intravenous nitroglycerin, and fractionated heparin (enoxaparin 30 mg IV, then 1 mg/kg SQ q 12 h). Approximately 8 hours after presentation and the administration of clopidogrel (300 mg loading dose) and a beta-blocker, coronary angiography was conducted to determine coronary anatomy, identify the culprit lesion, and to define a revascularization strategy. Coronary angiography revealed a complex, ulcerated lesion of the mid-left anterior descending coronary artery (Figure 1). Percutaneous catheter-based treatment of a culprit coronary lesion unstable angina necessitates that the operator address several critical aspects of case management (Tables 3 and 4).

This case highlights some of the unexpected challenges faced while conducting PCI, acute vessel closure, and no-reflow. These procedure-related events are more likely to occur in patients with ACS due to lesion morphology. The unstable coronary lesion contains more active inflammation (monocyte/macrophage infiltration) and morphologic features, such as a thin cap fibroatheroma with a large lipid core, fissured/ruptured plaque, and endothelial denudation with superficial platelet aggregation and thrombus formation.[13,14] Despite an aggressive systemic antithrombotic pharmacologic regimen and the selection and technical application of devices to minimize arterial trauma, this patient developed acute vessel closure after predilation and no-reflow after stent placement. Acute vessel clo-

sure is most often due to barotrauma-induced arterial dissection or intramural hematoma. Acute vessel closure was effectively managed with placement of the DES, and no-reflow is the result of atheroembolic debris and microvascular dysfunction. Coronary angiography excluded a contributing mechanical factor for the abnormal coronary blood flow. The Society of Cardiac Angiography and Interventions recently developed guidelines for the management of no-reflow.[15] In this case, we effectively utilized repeated intracoronary bolus injections of adenosine (24 to 40 µg) via an infusion catheter to restore normal or TIMI-3 coronary flow. This case illustrates some of the more common mechanical and physiological complications inherent to PCI that are not specifically addressed by first-generation DESs. The clinical outcome in this case depended on prompt recognition and effective management of no-reflow by the interventional cardiologist.

CONCLUSION

In the era of the DES, managing patients with ACS requires a comprehensive assessment of clinical syndromes to determine prognosis, selection of immediate and chronic pharmacological therapies, as well as proper timing for percutaneous or surgical revascularization to yield optimal long-term patient management via 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. Further clinical trials will be necessary to determine safety and efficacy of the DES in managing patients with acute ST-segment elevation myocardial infarction. The interactions of the DES with specific antiplatelet or antithrombotic therapies should be investigated to determine additional incremental benefits on acute and long-term clinical outcomes, in particular for patients with diabetes. In the future, the characterization of coronary anatomy in high-risk patients (multiple cardiac risk factors, genetic predisposition, elevated C-reactive protein) with high-resolution, noninvasive imaging procedures, such as cardiac MRI, may enable identification of a vulnerable plaque and the potential to combine stent-based local drug delivery with systemic therapies for the prevention of myocardial infarction. ■

Andrew J. Carter, DO, is Medical Director, Cardiovascular Research, Providence Heart and Vascular Institute, Providence St. Vincent Medical Center, Portland, Oregon. He has disclosed that he is a consultant to and receives research grants from Boston Scientific, Cordis, Guidant, and Medtronic. Dr. Carter may be reached at (503) 216-5206; acarter@providence.org.

**Maurice Buchbinder, MD, Scripps Memorial Hospital, San Diego, CA; Tim A. Fischell, MD, Heart Institute at Borgess Medical Center, Kalamazoo, MI; Phillip Au, MD, Director, Interventional Cardiology, Northwest Kaiser Healthcare, Portland, OR; Peter Banitt, MD, Legacy Good Samaritan Hospital, Portland, OR; Douglas Dawley, MD, Oregon Clinic, Providence Portland Medical Center, Portland, OR; Bradley Titus, MD, Legacy Good Samaritan Hospital, Portland, OR; Michael Wilson, MD, Providence St. Vincent Medical Center, Portland, OR.*

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