

DES, COURAGE, and the Great Debate

May 23, 2007—According to the *EuroPCR Daily* newspaper, one of the key objectives for EuroPCR 2007 (European Paris Course on Revascularization), held in Barcelona, Spain, is the focus on long-term vigilance. The “Great Debate” session on coronary drug-eluting stents (DES) attempted to elucidate the ongoing controversy surrounding long-term prognosis of DES patients, particularly focusing on physicians’ decision making in daily practice. Even with the advances of DES technology, long-term safety issues remain.

Jean Marco, MD, led a discussion, or “Great Debate,” of the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) study results that were presented on March 27 at the American College of Cardiology meeting and published in the *New England Journal of Medicine* (2007;356:1503-1516) by William E. Boden, MD, et al. Dr. Marco began with an historical perspective of percutaneous transluminal interventions (PCI) and declared that a single study may not change current practice. He noted that the COURAGE study aimed to answer the following question: in patients with stable coronary artery disease (stable angina), is an initial management strategy of PCI (almost exclusively with bare metal stents) combined with intensive pharmacologic therapy and lifestyle intervention (optimal medical therapy) superior to optimal medical therapy alone in reducing the risk of cardiovascular events?

Dr. Marco noted that, in COURAGE, there were no significant differences between the PCI group and the medical-therapy group in the composite of death, myocardial infarction, and stroke; hospitalization for acute coronary syndrome; or myocardial infarction. Statistically significant differences were observed in terms of angina-free patients at 1 year (PCI group, 66% vs medical-therapy group, 58%; $P<.001$) and in terms of additional revascularization procedures (21.1% vs 32.6%, $P<.001$). Thus, PCI-treatment benefits in acute coronary syndrome are not necessarily seen in chronic patients, Dr. Marco stated.

Steven Nissen, MD, was invited by EuroPCR to present the noninterventionist’s point-of-view on PCI versus coronary artery bypass graft (CABG) surgery, but he was not in attendance, so the debate was somewhat one-sided. The interventionists’ point of view was presented by Keith D. Dawkins, MD. Dr. Dawkins emphasized that in the COURAGE study, only 6% of the 35,000 patients screened were finally enrolled. In addition, the procedural success rate was low (89%). He concluded that the evidence and guidelines support the use of PCI in ACS (including STEMI and Non-STEMI), and that patients with stable angina may benefit from PCI for symptom relief. As for patients with complex coronary anatomy (left main stem or three-vessel disease), the appropriate revascularization strategy is being explored in the SYNTAX (Taxus Drug-Eluting Stent Versus Coronary Artery Bypass Surgery for the Treatment of Narrowed Arteries), CARDIA (Coronary Artery Revascularization in Diabetes), and FREEDOM (Comparison of Two Treatments for Multivessel Coronary Artery Disease in Individuals With Diabetes) trials.

Next, Laura Mauri, MD, discussed patient and procedural risk factors, emphasizing the importance of understanding the unique features that might delay stent thrombosis. She outlined the questions arising on various DES mechanisms, such as late drug and polymer interaction, increasing mechanical complexity, and the need for greater patient compliance with dual antiplatelet therapy over longer periods of time. Donald Baum, MD, Chief Medical and Scientific Officer at Boston Scientific Corporation (Natick, MA), discussed future developments in the field, noting that randomized data will be available for evaluating stents in currently “off-label” indications. Dr. Marco concluded the session by stating that the key issue remaining to be resolved for DES is the reduction in late stent and very late stent thrombosis rates in the small number of patients at potential risk for these events.

Comprehensive ESC Guidelines for Non-STEMI ACS Presented

May 24, 2007—The European Society of Cardiology’s (ESC) new guidelines for the diagnosis and treatment of non—ST-segment coronary syndromes were presented at the EuroPCR conference in Barcelona, Spain. The official presentation was conducted in recognition of the creation of the EAPCI (European Association of Percutaneous Coronary Interventions), a joint venture between EuroPCR

and the Working Group 10 of the ESC. The guidelines by the ESC Task Force Co-Chairs Jean-Pierre Bassand, MD, and Christopher W. Hamm, et al, are published online by the *European Heart Journal* and can be accessed at the ESC Web site, www.escardio.org. According to the *EuroPCR Daily*, the new guidelines cover issues not previously addressed, including management of complications, such as bleeding, which was considered in the past as a non-event. It has become evident that bleeding is indeed a serious event with a potentially catastrophic impact on outcomes, with a fourfold increase in death and myocardial

infarction at 30 days and long-term. The needs of special populations, such as diabetics, the elderly, anemic patients, and patients suffering from chronic kidney disease, as well as women's related health issues are part of the new guidelines. The ESC guidelines are designed to be a comprehensive guide to practice, addressing all the issues encountered by cardiologists in their daily practice with a focus on user-friendliness, reported the *EuroPCR Daily*.

Conor's COSTAR II Falls Short, Company Halts Marketing

May 23, 2007—At the EuroPCR conference in Barcelona, Spain, Global Co-Principal Investigators, Dean Kereiakes, MD, Mitchell W. Krucoff, MD, and William Wijns, MD, presented the results of the COSTAR II (Cobalt Chromium Stent with Antiproliferative for Restenosis) trial and confirmed that the study failed to meet its primary endpoint. COSTAR II is a pivotal study of the CoStar cobalt chromium paclitaxel-eluting coronary stent (Conor Medsystems, LLC, a subsidiary of Johnson & Johnson, Menlo Park, CA). The COSTAR II trial compared the CoStar stent with the Taxus Express² paclitaxel drug-eluting stent (Boston Scientific Corporation, Natick, MA). The trial was designed to demonstrate noninferiority at 8-month follow-up with respect to major adverse cardiac events (MACE) in patients with multivessel or single-vessel disease. The results showed that the CoStar stent had a significantly higher MACE rate than the Taxus stent (11% vs 6.9%; $P=.005$), largely due to a significantly higher incidence of clinically driven target vessel revascularization (8.1% vs 4.3%; $P=.002$). No significant differences were found in terms of cardiac death or new myocardial infarction, and the protocol-defined stent thrombosis rates were similar.

On May 7, Conor Medsystems announced that the trial failed to meet the endpoints and addressed the company's plans for the CoStar stent. The company cited potentially suboptimal therapeutic dosing of paclitaxel as the cause of the failure. The company said the trial did not identify safety issues, and the overall rates of death, myocardial infarction, and stent thrombosis were consistent with those observed in other clinically relevant drug-eluting stent studies. As a result of these outcomes, the company will terminate clinical trials with the CoStar stent, will not conclude its FDA premarket approval application, and will discontinue sale of the product. The company stated that it continues to be optimistic about the CoStar reservoir platform and developing the use of sirolimus, which may be better adapted for CoStar.

ABSORB Results Presented for Abbott's Bioabsorbable DES

May 22, 2007—At the EuroPCR conference in Barcelona, Spain, Abbott Vascular (Redwood City, CA) announced 9-month results from the first 30 patients enrolled in the ABSORB clinical trial evaluating the safety and performance of a fully bioabsorbable drug-eluting stent platform to treat coronary artery disease. The results demonstrated no stent thrombosis and a low (4%, one patient) rate of major adverse cardiac events (MACE), such as heart attack or repeat interventional medical treatment. Co-Principal Investigator Patrick W. Serruys, MD, presented the results, which confirmed the ABSORB 6-month findings presented at the American College of Cardiology's 56th Annual Scientific Session in March 2007, the company said.

According to the company, the ABSORB trial is a prospective, nonrandomized study designed to enroll up to 60 patients in Belgium, Denmark, France, New Zealand, Poland, and The Netherlands. Key endpoints of the study include assessments of safety, MACE and stent thrombosis rates at 30, 180, and 270 days, with an annual follow-up of up to 5 years, and successful deployment of the bioabsorbable drug-eluting stent. Other key endpoints include follow-up measurements assessed by x-ray angiography, intravascular ultrasound, and other state-of-the-art imaging modalities at 180 days and 2 years. Abbott also unveiled an updated, bioabsorbable stent design with improved radial strength that will be used in the next cohort of patients enrolled in ABSORB.

ARTS II Diabetic Subset Analysis of Cordis Cypher DES Presented

May 29, 2007—Cordis Corporation (a Johnson & Johnson company, Miami, FL) announced that a 3-year follow-up subset analysis of the Arterial Revascularization Therapy Study II (ARTS II) showed that the Cypher sirolimus-eluting coronary stent had results comparable to coronary artery bypass grafting (CABG) and better outcomes than bare metal stents (BMS) in diabetic patients with blockages in two or more coronary arteries. The data were presented as a late-breaking clinical trial at EuroPCR 2007 in Barcelona, Spain. Three-year results from the ARTS II overall population were presented at the American College of Cardiology's 56th Annual Scientific Session on March 26, 2007.

According to Cordis, the Cypher results in the diabetic population of the ARTS II study showed no significant difference in major adverse cardiac and cerebrovascular events (MACCE) compared to the CABG arm of the ARTS I study (27.7% vs 17.7%; $P=.1$). In addition, the analysis showed that the Cypher performed significantly better than ARTS I's BMS arm, in which the MACCE rate was 47.3% after 3 years ($P<.001$). ARTS II's primary endpoint was MACCE and the need for repeat revascularization.

In the diabetic subgroup analysis, investigators compared the findings for the 159 diabetic patients in the ARTS II study to those from the ARTS I study, conducted in 1997, which included 96 diabetic patients treated with CABG and 112 treated with a BMS. The patient risk profile in the ARTS II study was significantly higher than in ARTS I. The investigators reported that the Cypher's definite stent thrombosis rate in the ARTS II diabetic patient population at 30 days after implantation was significantly lower than the rate in the BMS arm of ARTS I (1.3% vs 7.1%; $P=.018$). There were no significant differences in the stent thrombosis rates between the ARTS II diabetic and nondiabetic patients, using the Academic Research Consortium definition, the company stated.

CUSTOM II 6-Month Results Presented for Xtent's DES

May 22, 2007—Xtent, Inc. (Menlo Park, CA) announced that positive 6-month follow-up data from the CUSTOM II clinical trial were presented by Principal Investigator Eberhard Grube, MD, at the EuroPCR conference in Barcelona, Spain. CUSTOM II assessed the safety and efficacy of the company's investigational Custom NX drug-eluting stent system for the treatment of long and multiple lesions in patients with coronary artery disease. The single-arm prospective study evaluated the use of CUSTOM NX in patients with long lesions (defined as >20 mm) and patients with two lesions.

According to the company, CUSTOM II includes a high percentage of patients with complex lesions and a long average lesion length. The average vessel diameter was 2.57 mm, the average lesion length was 28.7 mm, 26% of the enrolled patients were diabetic, and 65.1% of the patients had ACC/AHA lesion grade B2 or C.

Dr. Grube reported that 69 patients were enrolled in the long-lesion arm, and 31 patients were enrolled in the two-lesion arm of the study. Up to two customizable stent deployments of up to 60-mm total length were evaluated in the study. The primary endpoint was major adverse cardiac

events (MACE) at 6 months, with clinical follow-up at 1, 6, and 12 months, then annually for 5 years. Angiographic and intravascular ultrasound (IVUS) follow-up was conducted at 6 months. The anticoagulation regimen was clopidogrel for a minimum of 3 months plus aspirin. The MACE rate was 9% at 6-month follow-up. Early adverse events occurred in five patients, including four myocardial infarctions and one death. At 6 months, four additional patients (4%) underwent target lesion revascularization. Dr. Grube also reported that angiographic and IVUS results indicated that instant late loss was .31 mm, insegment late loss was .22 mm, binary restenosis rate was 7.5%, and neointimal volume was 3.3%.

OrbusNeich's Genous R Stent Compares Favorably to DES

May 23, 2007—OrbusNeich (Fort Lauderdale, FL) announced that the efficacy of its Genous Bio-engineered R stent compares favorably with drug-eluting stents, while the risk of late thrombosis is minimized with the Genous stent. These conclusions from an interim analysis of the Internet-based e-HEALING (Healthy Endothelial Accelerated Lining Inhibits Neointimal Growth) postmarketing data were presented by Co-Principal Investigator Robbert de Winter, MD, at the EuroPCR conference in Barcelona, Spain. According to the company, the antibody-coated Genous captures a patient's endothelial progenitor cells that rapidly form an endothelial layer over the stent to provide protection against thrombus and minimizes restenosis.

e-HEALING is a multicenter, worldwide prospective registry of patients treated with the Genous R stent. The protocol recommends 2 weeks of statin treatment before the procedure and 1 month of clopidogrel after the procedure. The registry's primary outcome is target vessel failure at 12 months. Clinical follow-up takes place at 30 days, 6 months, and 12 months. The follow-up data for patients who received at least one Genous R stent were collected from more than 120 sites in 29 countries. For 2,175 patients at 30 days, the target lesion revascularization rate was .05%, the major adverse cardiac events rate was 1.61%, and the subacute thrombosis rate was .37%. For 1,039 patients at 6 months, the target lesion revascularization rate was 2.89%, the major adverse cardiac events rate was 5.87%, and the thrombosis rate was .88%, Dr. de Winter reported.

SPIRIT FIRST Results Presented

May 22, 2007—Abbott Vascular (Redwood City, CA) announced that 3-year data from the SPIRIT FIRST trial

demonstrated no additional major adverse cardiac events (MACE) and no late stent thrombosis in patients treated with either Abbott's Xience V everolimus-eluting coronary stent system or its Multi-Link Vision metallic coronary stent. Additionally, in data presented from a meta-analysis of the SPIRIT II and SPIRIT III trials at 9 months, Abbott's Xience V compared favorably to the Taxus paclitaxel-eluting coronary stent system (Boston Scientific Corporation, Natick, MA). Abbott supplies a private-labeled version of Xience V to Boston Scientific that is marketed as the Promus. The data were presented at the EuroPCR meeting in Barcelona, Spain.

A meta-analysis of approximately 1,300 patients from the SPIRIT II and SPIRIT III clinical trials indicated that the Xience V system demonstrated superiority over the Taxus stent in angiographic and clinical endpoints, with an excellent safety profile. The data for the Xience V versus the Taxus, respectively were: MACE rate (4% vs 8%; P superior=.004); ischemic target lesion revascularization rate (2.4% vs 5.1%; P superior=.01); in-stent binary restenosis rate (1.9% vs 4.9%; P superior=.02); and in-segment restenosis rate (4.1% vs 7.8%; P superior=.04).

On June 1, Abbott announced it has completed its pre-market approval application to the FDA for its Xience V to treat coronary artery disease based on the safety and efficacy data from the XIENCE V SPIRIT family of clinical trials.

Four-Year Results Presented for Moderate-Release Taxus DES

May 22, 2007—Boston Scientific Corporation (Natick, MA) announced that 4-year follow-up data from its TAXUS VI clinical trial were presented by Co-Principal Investigator Eberhard Grube, MD, at the EuroPCR conference in Barcelona, Spain. TAXUS VI is a randomized, double-blinded, controlled study of 446 patients at 44 international sites. It is designed to assess the Taxus Express moderate-release paclitaxel-eluting coronary stent system in reducing restenosis in high-risk patients, including *de novo* lesions with overlapping stents, lesions of ≥ 26 mm in length, and small vessels. Lesion size ranged from 18-mm to 40-mm lengths and 2.5-mm to 3.75-mm diameters. The data demonstrated that the safety and efficacy benefits associated with a moderate-release formulation of the Taxus Express paclitaxel-eluting stent system were maintained at 4 years with no new stent thrombosis reported after 2 years. The moderate release formulation, which is not commercially available, contains an 8- to 10-fold high-

er *in vitro* dose than the currently marketed slow-release Taxus stent, the company stated.

Dr. Grube reported that the study's 4-year results demonstrate a continued significant reduction in target lesion revascularization (TLR) for the Taxus stent group as compared to the bare-metal-stent control group (12.9% vs 21.4%; P =.0082). Only two TLR events were reported between 3 and 4 years for the Taxus group. The 4-year freedom from TLR rate events was 87.1% for the Taxus group compared to 78.6% for the bare-metal-stent control group. TAXUS VI was the first study to demonstrate the durability of a DES in complex lesions at 4-year follow-up. Follow-up at 4 years included 98% of the enrolled patients. The results supported the long-term safety with the increased levels of paclitaxel in the moderate-release formulation used in the study. No compromise in safety was observed; the Taxus group continues to report no new stent thrombosis after 2 years and a 2.4% cardiac death rate, the company stated.

RESOLUTE 9-Month Results Presented for Medtronic's Next-Generation Endeavor DES

May 22, 2007—Medtronic, Inc. (Minneapolis, MN) announced that positive 9-month results from the RESOLUTE clinical trial were presented by Principal Investigator Ian Meredith, MD, at the EuroPCR conference in Barcelona, Spain. The RESOLUTE data showed a low number of adverse cardiac events and no protocol-defined stent thrombosis with the Endeavor Resolute, the company's next-generation drug-eluting stent system with a Biolinx polymer. The Resolute is designed to address complex medical conditions by matching the duration of drug delivery with the longer healing duration often required by these patients. According to the company, the RESOLUTE 9-month clinical results demonstrated no target lesion revascularization, no target vessel revascularization, and a 7% major adverse cardiac event rate. Of the trial's 130 patients, 129 (99.2%) received clinical follow-up, and 95 patients received angiographic follow-up. In-stent late lumen loss, the study's primary endpoint, was .22 mm, in-segment late loss was .12 mm, in-stent angiographic binary restenosis was 1%, and in-segment angiographic binary restenosis was 2.1%. The average lesion length in the RESOLUTE trial was 15.5 mm, and approximately 82% of enrolled patients were classified as having challenging B2/C lesions. ■