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A forerunner in research initiatives, Dr. Dave discusses the COURAGE trial, the C3 Conference, and his experience at one of the largest-volume interventional practices in the US.



The results of the COURAGE trial were recently released at the American College of Cardiology annual meeting. What is your take on the results, and how do you think they will affect practice of percutaneous coronary interventions (PCIs)? Before the release of the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) data, the jungle drums indicated the results would be “blockbuster,” “landmark,” and would “shake the foundation of interventional cardiology.” However, when the results became public, they fell right in line with five previous studies (RITA-2, ACME, MASS, AVERT, and MASS II) in showing that death and myocardial infarction rates were no different between the two therapies, and angina relief was greater in favor of PCI. Thus, the COURAGE data are as expected. The controversy is in the fact that the investigators believed that PCI was being overutilized in patients with stable coronary disease, and perhaps medical therapy should be more frequently prescribed as a first approach to treating this patient population.

The investigators concluded that as many as 80% of PCIs would be affected. However, interventional cardiologists are actually treating patients with acute and unstable conditions and a minority of patients with stable angina. This is demonstrated in a 2006 CDC survey of 15 million coronary artery disease (CAD) patients, which showed that only 30% of PCI patients were stable. Physicians most likely discussed both treatment options with these patients, and patient preference for angina relief resulted in the decision to proceed with PCI.

The COURAGE trial was designed to assess angina relief by using an intention-to-treat analysis. Careful

review of the two study groups indicates that 32.6% of medical therapy patients crossed over into the PCI arm to obtain angina relief, despite receiving what was considered optimal medical therapy. These crossover patients were analyzed as part of the medical therapy arm, despite the fact that they underwent PCI. The study protocol anticipated a 7% crossover rate—significantly less than what actually occurred during the trial.

When one looks at the lack of significance in angina relief at 5 years, the two groups are similar. However, a per protocol analysis largely favors a PCI approach to achieve satisfactory angina relief. Eligibility criteria were met for 3,071 patients out of 35,539 who were screened for enrollment into the COURAGE trial, so the results might actually apply to <9% of the PCI population. My impression is that the trial results will have a minor impact on the way patients with stable angina are treated by interventional cardiologists and might raise awareness of the importance of maintaining patients on good medical therapy. In addition to optimal medical therapy, each patient must be educated about the importance of compliance with prescription medications and lifestyle modifications (eg, weight loss, increased exercise, and smoking cessation), and as cardiologists, we routinely stress these points during preprocedure and follow-up office visits.

Which areas in CAD need the most attention from physicians and industry in upcoming years? Currently, we focus on whether to use a Taxus (Boston Scientific Corporation, Natick, MA), a Cypher (Cordis Corporation a Johnson & Johnson Company, Miami, FL), or a bare-metal stent. We really need to focus on how to use the current stents properly and in what subgroups. Recent data show that extended clopidogrel use is essential for reducing stent thrombosis, yet many patients slip through the cracks and do not take the medication for the minimum 12 months. In addition, recent data show that procedural lack of intravascular ultrasound use is the greatest predictor of stent thrombosis, yet only 8% of cases use intravascular ultrasound. If stronger efforts were made to ensure use of drug-eluting stents (DESs) for the labeled indications, good deployment technique, and patient compliance with medications, the small amount of stent thrombosis could be avoided. Education at both the physician and patient levels needs to be addressed.

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Boston Scientific should be commended for initiating a \$40 million program directed solely at educating DES patients. The evolution of stents that have inert biodegradable polymers may be an exciting new chapter in DES as a safe and effective treatment for CAD. Finally, stents for complex anatomies, especially bifurcations, will be a welcome addition to the current technologies, and I predict these stents will be available in the US within the next 3 years.

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What are the differences between the PCI technologies available in the US and those in Europe? The technologies are basically the same. The major difference is that Europe does not have the rigorous review of the FDA, which gives Europe access to 15 DESs. For better or for worse, in Europe a DES does not necessarily need to be proven safe and effective. To obtain a CE mark, the company must demonstrate the safety of the device or technology typically through clinical evaluation, and the company must demonstrate that a quality system is in place to ensure the product meets performance specifications. The concept of efficacy or benefit to the patient is not required. A prime example of this would be the historical gold-coated stent (NIR Royale, formerly manufactured by Boston Scientific Corporation), which had a significantly higher restenosis rate despite receiving CE mark approval. One of my concerns is that industry resources are going abroad because they face extremely difficult FDA requirements to initiate phase I and II trials. However, this is changing.

Recently, an FDA panel addressed the issue of late-stent thrombosis, and Congress is reviewing industry DES practices. What is your take on these developments?

Unfortunately, the data have not caught up with how DESs are used in the real world, which places stent manufacturers in a difficult situation. Their product—in this case, a DES—has been used according to the approved labeling in approximately 35% of procedures. Unfortunately, physicians, believing that the DES is safe and effective regardless of the instructions for use (IFU) have used the DES in an off-label manner approximately 65% of the time.

The data used to gain marketing clearance by the FDA demonstrated DESs as safe and effective when used according to the IFU; however, the IFU have not been followed in too many cases, and the results have given DESs an unfortunate reputation in the eyes of the general public and an aggressive press. Stent manufacturers have always promoted the technology within the IFU, and physicians have more recently become educated about the importance of careful lesion selection and patient compliance with the requisite dual platelet inhibition therapy and therapy duration.

In December 2006, the FDA held a rigorous 2-day meeting consisting of approximately 18 hours of testimony, conducted by several dozen physicians, industry representatives, and lay individuals. A panel of 21 experts in the field reviewed the information. A consensus document is available at www.fda.gov/cdrh/news/091406.html and was recently updated at www.fda.gov/cdrh/news/010407.html. A condensed-version white paper was also published by the Society of Cardiac Angiography and Intervention. Formal guidance after review from this meeting was given at the Cardiovascular Revascularization Therapies meeting and the American College of Cardiology (ACC) i2 meeting, both held in March 2007. In addition, the FDA scheduled a town hall meeting to be held in May 2007 to review recommendations. A congressional inquiry has also been called that asked industry to disclose any and all preclinical and clinical data pertaining to the DES technology. I do not expect any more information will be gathered that has not already been reviewed.

What can you tell us about your practice and what you have established at the Central Pennsylvania Cardiovascular Research Institute? I came to Harrisburg in 2001 and joined the superb group of cardiologists within Associated Cardiologists. Before my arrival, the practice had already excelled in treating cardiovascular disease in central Pennsylvania. Since my arrival, the practice has reached several milestones. To encourage and obtain research within the practice, I founded the Central Pennsylvania Cardiovascular Research Institute to attract industry-sponsored clinical research initiatives and to comply with good clinical practice guidelines for conducting clinical research. To that end, Associated Cardiologists and the Research Institute have a full-time, five-person staff dedicated to clinical trial recruitment and management.

With the objective of promoting education within the practice and community, 3 years ago, we hosted the first Capitol Cardiovascular Conference (C3) as a forum for teaching and promoting the latest technologies for the treatment of ischemic coronary, carotid,

and lower-extremity peripheral vascular disease. The practice is one of the largest-volume interventional practices in the country. My focus during the last 6 years has been to promote good patient care with the best-available technology and to help others learn how best to treat the multitude of vascular diseases presented to us on a routine basis.

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What can we look forward to at the C3 meeting this year? C3, held from September 9 to 12, is a perfect time to enjoy the beauty of the fall in central Pennsylvania. The meeting focuses on technical aspects of advanced cardiovascular interventions in a very rapidly changing field. This conference complements great academic meetings such as TCT, SCAI, and ACC. Today's cardiovascular interventionist wants to know and learn “how to” rather than “when to” do a particular procedure, especially those involving the newest technology.

This year's program is greatly enhanced with eight live transmission sites across the world emphasizing complex intervention in peripheral and coronary arteries. We have invited more than 60 world-renowned faculty. In addition to the live cases, satellite symposia will discuss carotid artery stenting, lower-limb atherectomy and stenting, chronic myocardial ischemia and chronic total occlusion, and percutaneous heart valve and DES as related to current developments, which we all know are constantly changing.

The meeting has been expanded from 2.5 days to 3.5 days. The first day is devoted to in-depth scientific symposiums on carotid, SFA, and below-the-knee disease, which will provide an excellent review of all current controversies and will supplement the live case sessions presented on the following days.

Since I came to Harrisburg, I have trained more than 300 physicians in endovascular and complex coronary interventions. I have always welcomed and encouraged collaboration, and I truly enjoy teaching my professional colleagues new and evolving technologies. The C3 meeting serves as a venue for me to share my passion for research and teaching. This year will be the third C3 meeting, and I hope it will continue to increase in attendance. ■