Current Issues in DES Care

Cardiac Interventions Today engages Rajesh M. Dave, MD, FACC, FSCAI, and Samin K. Sharma, MD, in a discussion about DES safety concerns, patient management, off-label use, and the impact of media coverage.

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Cardiac Interventions Today: There is much buzz in the media about drug-eluting stents (DESs) and their safety, as well as the concerns that were raised at the European Society of Cardiology meeting, a further data analysis done by CRF that was presented at TCT, and a subsequent FDA Panel Meeting. It is clear now that there are some safety concerns about DESs. What are your thoughts about this, and what would you recommend to the readers about how they should utilize this available information?

Dr. Sharma: Once the DES revolution started, a DES was being used in more than 90% of cases. In some of those cases, a DES was chosen based on the scientific data; in other cases, DESs were just used in complex cases. Although DESs had not been tested in complex cases, they became the mainstay of coronary interventions, replacing bare metal stents in treating most coronary lesions. Clinical restenosis (target lesion revascularization) decreased to approximately <5%. In some institutions, the actual volume of PCI procedures decreased because restenosis almost became a non-issue. Data then started to appear last year showing that after discontinuation of clopidogrel, DES patients started developing very late stent thrombosis. Although it was a very small incidence, it was clearly a signal—0.2% per year after 1 year and up to 0.6% at 3 to 4 years difference in very late stent thrombosis between bare-metal stents and sirolimus-eluting stents. The same difference (.6% absolute difference) was also observed between bare-metal stents and the Taxus stent (Boston Scientific Corporation, Natick, MA) in the TAXUS trials. Therefore, the issue of somewhat higher late stent thrombosis is a real concern. In my opinion, stent thrombosis was not seen until 1 year, because of the routine use of clopidogrel up to 1 year as per the routine recommendation based on the CREDO and CURE trials at that time.

Dr. Dave: A meta-analysis of 14 randomized clinical trials and 6,675 patients, which appeared in the December 2006 issue of the American Journal of Cardiology,[1] demonstrated similar findings that there was definitely a potential for late stent thrombosis, especially when antiplatelet therapy was discontinued. We accept that there is a small increase in the very late stent thrombosis in patients with DESs. This was confirmed by an independent analysis performed by Cardiovascular Research Foundation on four Taxus trials (TAXUS II, IV, V, and VI) in approximately 3,500 patients and

the Cypher (Cordis Corporation, a Johnson & Johnson company, Miami, FL) trials (RAVEL, SIRIUS, E-SIRIUS, and C-SIRIUS) in approximately 1,750 patients. Both the Cypher and Taxus data were available up to 4 years. There are also some data available on the Endeavor stent (Medtronic, Inc., Minneapolis, MN) up to 3 years, and there might potentially be some increase in late stent thrombosis. In addition, Renu Virmani, MD, presented autopsy data on patients with DESs, which demonstrated decreased endothelialization on the stents out to 40 months.

The question is, even though there is very late stent thrombosis in some patients with DESs, should we stop placing DESs and should we change our treatment therapy to bare-metal stents? In my opinion, although there is a potential small price to pay when giving patients DESs, the benefits of significant reduction in target vessel revascularization ultimately result in a decreased incidence of myocardial infarction (MI) and, potentially, death. These benefits outweigh the risks associated with placing DESs given that bare-metal stents are certainly associated with higher target vessel revascularization, especially in complex patients.

There are no current data available regarding late stent thrombosis in complex patients who have DESs placed (ie, bifurcation, chronic total occlusion [CTO], and multivessel stenting), and they may have an even higher rate of very late stent thrombosis.

In our practice, we continue antiplatelet therapy for a longer period of time. Even though there is the potential for very late stent thrombosis associated with the use of DESs, we should continue to use the majority of DESs when appropriate. We do not believe that the increase in death and MI is substantial enough to warrant a change to bare-metal stents in our practice at this time.

Dr. Sharma: I absolutely agree. The major change is that the patients who are scheduled for surgery within 1 year are the patients who are now getting bare-metal stents, otherwise everyone else is receiving DESs. We now continue clopidogrel for a long period of time—up to 3 years or maybe longer.

Cardiac Interventions Today: The standard of care, based on the BARI data and the ARTS data, is that patients with multivessel disease, especially diabetics, should have coronary artery bypass grafting. However, there is significant off-label use of DESs in patients with multivessel disease. How do you approach patients with multivessel disease, and what do you think about the role of DESs in multivessel stenting?

Dr. Sharma: Patients with multivessel disease are high-risk patients if you decide to intervene. The results of the two major randomized trials (SYNTAX and FREEDOM) comparing DES versus CABG in complex multivessel disease will not be available for 2 to 4 years. We learned from the randomized trials of stents versus CABG (such as ARTS I, ERACI II) that the only difference was in terms of higher repeat revascularization after bare metal stents. There was no difference in mortality or MI. Given that information, if the decision is made to intervene in multivessel disease, DESs are being used preferentially over CABG in these patients.

Dr. Dave: Our position on treating multivessel disease using DESs is based on several important aspects. First, there is no level-1 evidence for multivessel DES use until the results of SYNTAX and FREEDOM are available, although there are some data available from the RESEARCH and T-SEARCH registries in multivessel coronary artery disease, which have very encouraging results.

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What do operators do today when we encounter patients with multivessel disease? One of the things that we take into consideration is patient preference; patient preference really drives our decision making at this time. Many patients do not want to have surgery. Couple that decision with whether patients are going to be compliant with dual antiplatelet therapy, their surgical risk, the angiographic characteristics of the coronary arteries (ie, whether multivessel stenting will be feasible), left ventricular function, and other comorbid issues (eg, diabetes), all of which must be taken into consideration when we use DESs for multivessel disease.

Potentially, improved DESs will be available in the US, perhaps with better bioabsorbable polymers that will reduce the need for prolonged antiplatelet therapy. They may also drive DES treatment of multivessel disease even further. Also, more trackable DESs, such as the Xience (Abbott Vascular, Santa Clara, CA), which is receiving very encouraging reviews in Europe, may also improve our ability to treat some of the complex distal disease that we may not currently be able to treat.

The availability of percutaneous hemodynamic support devices will allow a change in the treatment paradigm of patients who are considered to be too high-risk, as well as those who need to undergo treatment for multivessel disease.

I think it is important to mention the ARTS II dataset, which compared the results of multivessel stenting with DESs to historical outcomes with bare-metal stents in bypass surgery from ARTS I and revealed favorable results, with an 89.5% event-free outcome at 1 year. Similarly, the ERACI-III study revealed an increased need for revascularization compared to CABG in ERACI-II for the DES group, but it had a lower mortality rate. The RESEARCH and T-SEARCH data, when coupled with that of ARTS II, and the patient-related factors mentioned earlier, make a good decision tree that dictates whether patients should be treated with DESs in multivessel disease.

Cardiac Interventions Today: While we were speaking about multivessel disease, there are particular subsets of patients in which great differences exist between different operators regarding technique and perceived outcomes. Let us first discuss the role of DESs in bifurcation lesions.

Dr. Dave: It has been demonstrated in a variety of studies that bifurcation lesions increase MACE rates, as well as restenosis rates. The restenosis rate is mainly related to the side branch ostium. Especially with a DES, the inability to fully scaffold the side branch ostium without causing significant stent deformation may lead to restenosis.

Although conventional wisdom suggests that provisional stenting of the side branch be performed whenever possible, in my experience, in the majority of instances in which a true bifurcation lesion exists with a >2.5-mm side branch and severe stenosis at the branch ostium, a two-stent approach is required. There are many techniques that I use, including crush, Culotte, modified Culotte, and, less often, T stenting. In my opinion, and at least in our practice, we have seen very encouraging results with optimal deployment of two stents—and I emphasize optimal deployment. What I mean by optimal deployment is to perform IVUS examination of both vessels after kissing balloon angioplasty to accurately size the vessel for state placement. It is mandatory to perform kissing balloon angioplasty again after stenting. In addition, liberal use of atherectomy and/or plaque modification devices makes a difference, leading to better stent expansion and higher final mean luminal diameter.

We have seen significant improvement in restenosis rates with DESs compared to bare-metal stents. Despite this improvement, a 10% recurrence rate would not be unexpected in coronary bifurcation lesions. This is consistent with reported 9.5% target lesion revascularization rate with DESs in bifurcation lesions.[2] The recently presented Nordic bifurcation study did not demonstrate any statistical difference in target lesion revascularization between the two arms of the study, which include main branch stenting only with balloon angioplasty of the side branch versus main and side branches both stented at 6-month follow-up. However, there were more cardiac enzyme leaks with side branch stenting. I expect that there is a higher level of radiation and contrast use, as well as a prolonged procedure when both branches need to be stented with DESs.

> Dr. Sharma: "In my opinion, CTO is the next frontier in interventional cardiology, and we all have to retrain ourselves to achieve success >90% in CTO revascularization."

In summary, I almost always use DESs, unless in special circumstances, such as noncompliance with dual antiplatelet therapy, pending surgery, and a few others. It is important to note that I almost never use bare-metal stents in both branches. In selected patients, if I have to use a bare-metal stent, main vessel treatment with stenting only and balloon angioplasty of the side branch is the preferred approach.

Newer advances in bifurcation devices, such as those by Devax (Irvine, CA) and Invatec (Roncadelle, Italy), may substantially improve the long-term outcome in these patients. However, vigorous studies are required to prove any additional benefit of these dedicated devices.

Dr. Sharma: The simultaneous kissing stents (SKS) technique is quite simple and involves placing two DESs (one in the main vessel and one in the side branch), covering the entire part of the lesion in both branches, and overlapping proximally in the main vessel. Both stents are then inflated and deflated simultaneously, giving excellent angiographic results. Our data have shown target lesion revascularization of 5% at 1 year after the SKS technique.

Cardiac Interventions Today: Let us turn our attention to CTOs. With newly available specialty wires and techniques, such as retrograde recanalization, we are finding ourselves implanting multiple and longer DESs. What are your thoughts about DESs in CTO treatment?

Dr. Dave: First, I do not offer treatment of CTO in coronary arteries if the patient is not a candidate for DES. Given the procedural risks and higher rates of restenosis, bare-metal stents are suboptimal in the treatment of these lesions. At the same time, I do recognize that placement of multiple long DESs increases the likelihood of late thrombotic events. This was demonstrated in published data from Migliorini et al,[3] in which one of the predictors of MACE events was stent length >28 mm. In our practice, I strongly

emphasize the importance of optimal stent deployment with IVUS guidance and prolonged antiplatelet therapy for best results.

There are many studies, including the ARRIVE registry, WISDOM, and SITCO, which have demonstrated very good results in these patients, indicating an average 13% to 19% restenosis rate with DESs.

The main fundamental issue that still remains is the operator's ability to place a wire across the lesion. As we all know, this requires operator experience, patience, and perseverance. With CTO treatment mostly abandoned by many operators, especially in the US because of poor results with bare-metal stents, a fair amount of retraining will be required to make this field mainstream once again. Meetings, such as The Chronic Total Occlusion Summit by Drs. Martin B. Leon and Jeffrey W. Moses, provide an excellent opportunity for such retraining. No doubt, with benefits such as less long-term referral to CABG, improved left ventricular function, and improved angina, this technique needs to be encouraged. We do need more vigorous studies with, hopefully, next-generation DESs, but before that, we must retrain ourselves to ensure that these studies reflect real life in a variety of centers, rather than select operators and hospitals.

Dr. Sharma: In my opinion, CTO is the next frontier in interventional cardiology, and we all have to retrain ourselves to achieve success >90% in CTO revascularization. The success rate of CTO will increase by specialty wires, such as Confianza Pro (Abbott Vascular), MiracleBro (Abbott Vascular), and CrossIt (Abbott Vascular). Other new devices, such as Frontrunner (Cordis) and Safe-Cross (Kensey Nash, Exton, PA), have failed to improve the success of CTO recanalization. After successful recanalization, DESs are routinely placed and have shown to be superior to bare-metal stents in randomized trials (PRISON II).

Cardiac Interventions Today: Unprotected left main treatment still remains very controversial in the absence of randomized clinical data. Who should we offer this treatment to, and should we only utilize DESs?

Dr. Dave: In our practice, we do not routinely perform left main intervention. Currently, I offer left main intervention to a select group of patients, such as patients who are not candidates for surgery, who have isolated left main disease, rare but strong patient preference for percutaneous coronary intervention over surgery if suitable anatomy, and failed bypass grafts patients in need for left main intervention.

As we all are well aware, the results of bare-metal stent placement are very poor in this lesion subset. In addition, in the US, we are limited by DES sizes. This raises an important dilemma, especially for vessels larger than 4.5 mm. Although event rates are low at large vessel diameters, any event in the left main may result in significant morbidity and mortality. With hemodynamic support using either the TandemHeart PTVA device (Cardiac Assist Inc., Pittsburgh, PA) or intra-aortic balloon pump, this intervention can be life-saving in a patient with cardiogenic shock and in need of urgent left main revascularization.

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In the run-in phase of SYNTAX, patients with three-vessel disease and left main disease had a significantly higher chance of going for CABG than percutaneous coronary intervention in North America compared to Europe. I suspect that the regional standard of practice and the medicolegal issues in the US drives this trend. But certainly, this randomized clinical trial will provide critical insight into this issue, which will determine whether this treatment will be extended to normal-risk (for CABG) patients. Dr. Park from Korea reported an approximate 80% MACE-free survival in these types of normal-risk patients for CABG for left main DES placement at 5 years. Many reported studies have varying rates of target lesion revascularization, ranging from 1.8% to 29%. Again, I suspect that factors such as left main bifurcation treatment versus main trunk stenting play a role in future target lesion revascularization. The main target lesion revascularization site has been the ostial left circumflex artery. Newer treatment strategy, such as the Axxess stent (Devax Inc.) may improve this issue.

Dr. Sharma: In our practice also, unprotected left main interventions are largely performed in patients at high risk for CABG due to comorbid medical conditions such as age >80 years, COPD, CVA, etc. In these cases, DES is a viable alternative to CABG and provides excellent acute and mid-term results. The target lesion revascularization rate is approximately 10% in bifurcation left main and approximately 0% to 1% in ostial or mid-left main lesions. All of these patients are recommended to undergo angiography at 4 to 6 months routinely, as per ACC/AHA guidelines.

Cardiac Interventions Today: What has been the impact of the media coverage regarding DESs on your current clinical practice?

Dr. Dave: I believe the media is a double-edged sword. It does increase awareness, but its premature reporting without thorough study of the literature may have a deleterious impact on clinical practice. As an example, we all have seen the advertisements on TV urging patients to call lawyers if they have a DES.

As you know, the FDA has an oversight on advertisements by industry. Why should there not be an oversight on media before reporting major clinical issues?

Dr. Sharma: It is true that the media has really heightened and highlighted this issue, but now, with the recent *New England Journal of Medicine* publication, the public fear has been alleviated, and the importance of taking clopidogrel has taken the center stage.

Cardiac Interventions Today: How long do you use dual antiplatelet therapy in your DES patients?

Dr. Dave: In our practice, for FDA-approved indications or for simple lesions, we recommend 1 year of dual antiplatelet treatment; thereafter, we suggest indefinite aspirin therapy. However, we find that the lion's share of procedures we perform are procedures in which DESs are used off-label. With the likelihood of late stent thrombosis, which may even be higher in complex patients, proper patient understanding and teaching are very important. Especially in lesions such as left main, bifurcation, dual DES, and CTO along with many others, I use even longer dual antiplatelet therapy, if tolerated. In some select patients, I recommend lifelong therapy. However, it is important to recognize that these are off-label uses of these drugs, and more clinical trials are needed to further clarify this issue. I applaud the joint AHA/SCAI/ACC advisory statement highlighting this issue.

Dr. Sharma: As of July 2006, all patients undergoing DES placement at Mount Sinai Hospital, unless there are bleeding issues, receive clopidogrel for 3 years, along with 81 mg of aspirin daily. In my opinion, this combination will significantly reduce the incidence of very late stent thrombosis and hopefully will not increase the bleeding incidence.

Cardiac Interventions Today: What do you think about the new DES contenders in US market? How will they impact the US market for DESs?

Dr. Dave: There are three main DES contenders, Xience (Abbott Vascular), Endeavor (Medtronic), and Costar (Cordis), for future US commercialization. I am impressed with the penetration of the Xience V in the European markets. Anecdotally, I have heard very encouraging results with this stent, with its flexibility and profile. In the SPIRIT II study performed in Europe, the Xience V in-stent late-loss and target lesion revascularization numbers compared to the Taxus stent late-loss number numbers were 0.11 compared to 0.36 and 2.7% versus 6.5%, respectively, demonstrating noninferiority to Taxus. We are awaiting SPIRIT III and COSTAR II data.

> Dr. Sharma: "In 4 to 5 years, we will be using a DES with bioabsorbable polymer so that after . . . the DES has done its job of eliminating intimal hyperplasia, it will become a bare-metal stent."

With multiple off-label DES use in the US, the cost of stents will remain a major factor in a bidding war among industry vendors. The greater competition in the DES market will help drive the price lower and fuel further research in improving this technology. This ultimately will be good for our patients. However, I would like to see lower profiles, improved trackability, and superior or equivalent results from these newer platforms, as opposed to lower cost.

Newer technologies using bioabsorbable polymers or nonpolymer technologies are being investigated. Stents, such as the BioMatrix (Biosensors International Group, Singapore), Nobori (Terumo Medical Corporation, Somerset, NJ), Axxion (Biosensors), and Custom 1 (Xtent Inc., Menlo Park, CA) are being investigated outside the US. Abbott Vascular, Igaki Tamai (Igaki Medical Planning Company, Kyoto-City, Japan), Reva Medical (San Diego, CA), and Biotronic (Ann Arbor, MI) have biodegradable DES programs. These platforms, if successful, have the potential to revolutionize how we will treat arterial obstructions in the future.

Dr. Sharma: Among the newer stents, Xience V has the most promise. Endeavor may do OK, but it will have a high target lesion revascularization rate, especially in small vessels, due to higher late loss. Still, I think it is a safe stent from a stent thrombosis point of view, even very late stent thrombosis. In my opinion, in 4 to 5 years, we will be using a DES with bioabsorbable polymer so that after 6 to 8 months, after the DES has done its job of eliminating intimal hyperplasia, it will become a bare-metal stent. ■

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