Drug-Eluting Stents in Coronary CTOs

Recommendations for treating patients with CTOs using new DES technology.

BY RAJESH M. DAVE, MD, FACC, FSCAI

Coronary chronic total occlusions (CTOs) remain the most challenging subset of patients for coronary interventionists. The primary challenges are the initial safe crossing of the occlusion with a guidewire, short-term recurrence after balloon angioplasty, and bare-metal stent implantation. Historically, CTOs represent 10% to 15% of all percutaneous coronary intervention (PCI) procedures, but this number is on a dramatic rise with the recent availability of specialized wires, support catheters, and CTO crossing technologies—most importantly, the reported significantly improved longer-term PCI outcomes with drug-eluting stents (DESs).

Multicenter and single-center data have demonstrated that successful recanalization of CTOs improve left ventricular function and regional wall motion abnormalities, and results in decreased death and referral for bypass surgeries.[1,2]

Currently, DES use in non-CTO PCI is under great scrutiny with the concern for late stent thrombosis. This concern needs to be carefully weighed against the unequivocal reductions in target lesion revascularization and major adverse cardiac events (MACE) with DES use. In my opinion, the use of off-label DESs in CTOs is justified and can be well defended from published clinical results for the two prominent marketed DESs in the US.

Herein, I present two cases of coronary CTO recanalization with DESs, review the technical fundamentals for a successful procedure, and summarize the current literature on DESs in CTOs. I present my recommendations for treating this important growing subset of patients in the current era.

CASE REPORTS

Case 1

A 45-year-old man with non–insulin-dependent diabetes mellitus and hyperlipidemia was admitted with unstable angina at an outlying facility. Cardiac catheterization demonstrated significant left coronary vessel dis-

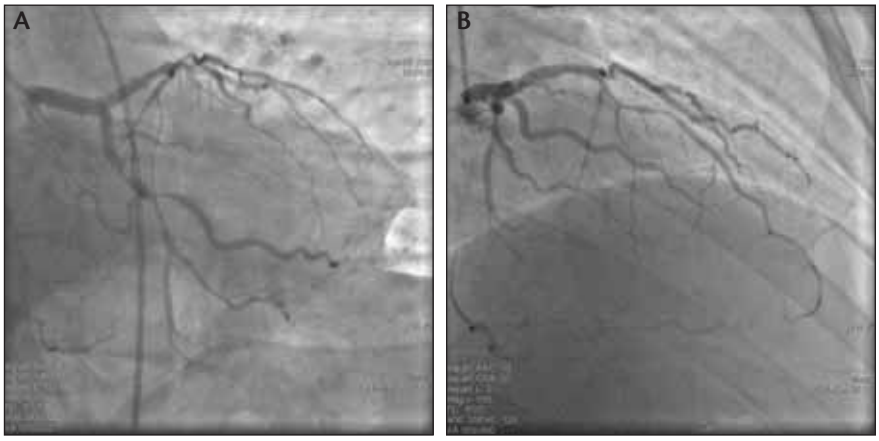

Figure 1. Severe left circumflex coronary artery stenosis (A). Severe left anterior descending (LAD) artery stenosis (B).

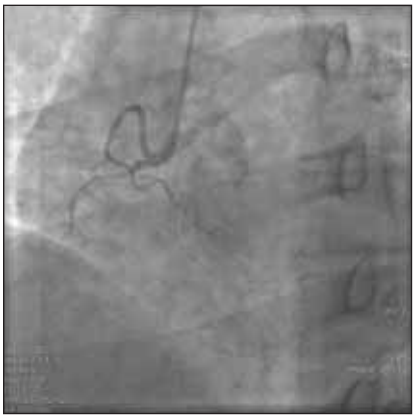

Figure 2. Right coronary artery CTO.

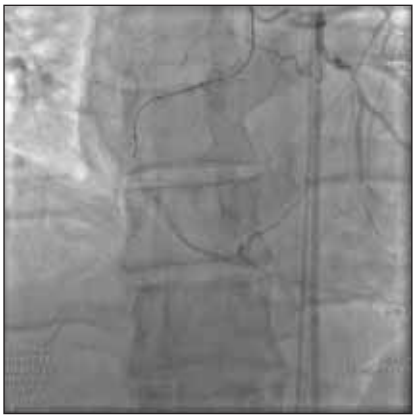

Figure 3. Dual injections from right and left coronary. Miracle Bros 3-g wire in conjunction with a .014-inch Quick-Cross catheter.

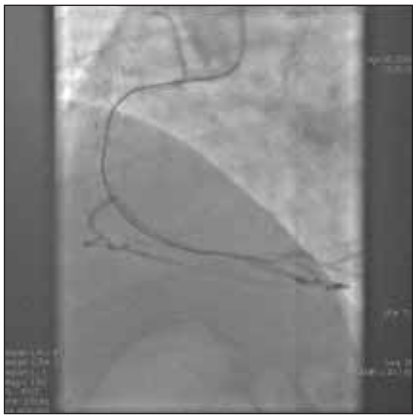

Figure 4. Crossing of a right coronary artery CTO with Miracle Bros 6-g wire.

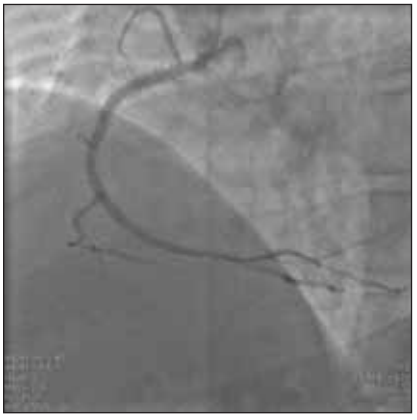

Figure 5. Final result after Cypher stent placement in a right coronary artery.

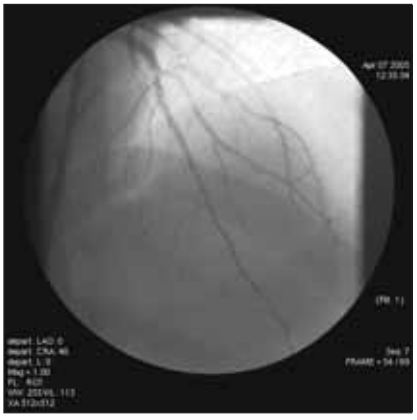

Figure 6. Final result after Taxus stent placement in a LAD artery.

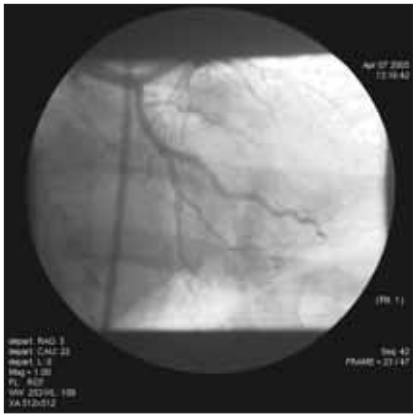

Figure 7. Final result after Taxus stent placement in a left circumflex/obtuse marginal bifurcation.

ease affecting the LAD and left circumflex coronary artery bifurcation (Figure 1). In addition, he had a CTO of the right coronary artery (Figure 2). A coronary artery bypass graft procedure was recommended. However, the patient declined and sought my opinion for an alternative treatment strategy. After reviewing his angiograms, I suggested PCI with DES of the right coronary artery CTO, as well as DES treatment of the left coronary lesions.

A staged procedure was performed first with recanalization of the right coronary artery CTO. A 7-F Amplatz (Abbott Vascular, Santa Clara, CA) right guide catheter was placed in the ostium of the right coronary artery to provide adequate support. Concurrently, a left coronary diagnostic catheter was placed in the left main coronary artery for simultaneous injections to visualize distal right coronary artery lumen filling via left coronary collaterals (Figure 3). Utilizing a .014-inch Quick-Cross (Spectranetics, Colorado Springs, CO) support catheter and Miracle Bros (Abbott Vascular) 3-g and 6-g guidewires, the lesion was crossed (Figure 4). The position of the wire in the distal true lumen was confirmed by contralateral injection and visualization. After balloon angioplasty, two 3-mm X 33-mm Cypher (Cordis Corporation, a Johnson & Johnson company, Miami, FL) stents were implanted (Figure 5). Based on intravascular ultrasound (IVUS), the stents were postdilated to 4 mm to achieve optimal wall apposition.

The LAD and left circumflex coronary artery lesions were treated the next day with 3-mm X 32-mm and 3.5-mm X 16-mm Taxus (Boston Scientific Corporation, Natick, MA) stents deployed in the LAD artery (Figure 6). The left circumflex bifurcation lesion was treated utilizing a modified Culotte technique, using a 3.5-mm X 24-mm Taxus stent in the obtuse marginal and a 3.5-mm X 24-mm Taxus stent in the proximal segment of the left circumflex coronary artery (Figure 7). The patient was sub-

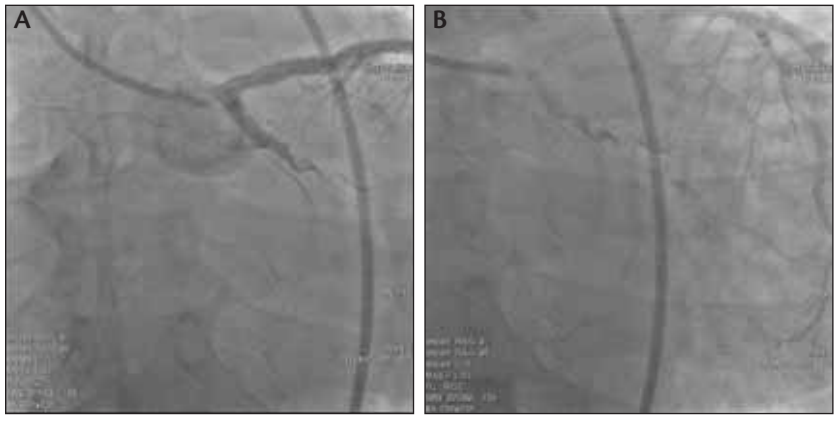

Figure 8. Left circumflex CTO with left to left collaterals.

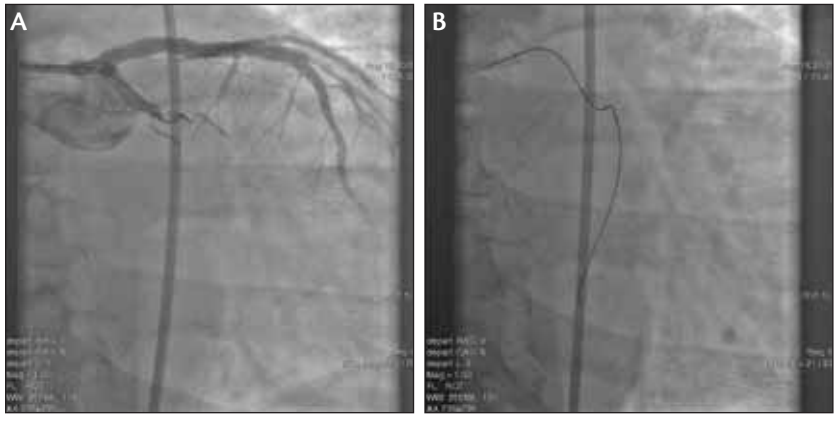

Figure 9. Probing and crossing of a left circumflex tortuous CTO with a Miracle Bros wire and Quick-Cross support catheter.

sequently discharged and placed on indefinite aspirin and clopidogrel bisulfate therapy.

As of January 26, 2007, approximately 2 years after the index procedure, the patient remained MACE-free and without angina. The patient has maintained the dual antiplatelet therapy and was instructed on the importance of medication compliance as part of the follow-up consultation.

Case 2

A 44-year-old man was admitted with angina. He had a history of coronary artery disease with right coronary artery intervention. During angiography, significant disease of the left coronary circulation was identified involving a diagonal branch of the LAD artery and, more importantly, a total occlusion of the left circumflex coronary artery (Figure 8). In addition to significant coronary artery disease, left ventricular function was compromised, with an ejection fraction of 25%. Based on the patient's clinical history, the duration of the left circumflex CTO was estimated at 3 to 6 months.

To recanalize the CTO of the left circumflex coronary artery, an 8-F GL 3.5 guide catheter (Abbott Vascular) was utilized to provide strong support. During angiography, the left circumflex coronary artery demonstrated slight antegrade flow distal to the occlusion from left system collaterals. The lesion was approached with a .014-inch BMW (Abbott Vascular) wire first to navigate through a proximal tortuous segment and allow subsequent placement of the support catheter into the proximal portion of the occlusion to facilitate exchange for a stiffer guidewire. Very carefully, a Miracle Bros 3-g guidewire was navigated through a calcified tortuous occlusion into the atrioventricular groove left circumflex coronary artery (Figure 9).

Balloon angioplasty was then performed to facilitate passage of a second guidewire into the obtuse marginal branch. The initial crossing attempt was made with an Asahi Prowater (Abbott Vascular) guidewire, but this was unsuccessful despite the balloon predilation. However, a Miracle Bros 3-g guidewire was successfully placed in the obtuse marginal branch (Figure 10). Kissing balloon angioplasty was performed next. Subsequently, utilizing bifurcation crush technique stenting, 3-mm X 16-mm and 3.5-mm X 20-mm Taxus stents were deployed in the left circumflex coronary artery, and a 3-mm X 28-mm Taxus stent was placed in the obtuse marginal bifurcation (Figure 11).

A subsequent intervention was scheduled 1 month later, at which time the LAD artery diagonal lesion was stented with a 2.5-mm X 16-mm Taxus stent. The patient returned for evaluation 3 months after the procedure, during which an echocardiogram demonstrated significant improvement in left ventricular function with an estimated ejection fraction of 55% and normal wall motion.

The patient was MACE and symptom free 1.5 years after the procedure. A dual antiplatelet regimen of aspirin and clopidogrel bisulfate has been maintained and will continue indefinitely. Stressing the importance of medication compliance has become standard practice during follow-up with all DES patients.

FUNDAMENTALS OF CTO RECANALIZATION TECHNIQUE

The essential elements of successful CTO intervention include operator experience, patience, and careful patient and lesion selection. The decision to expose catheterization laboratory personnel, operator, and patient to prolonged radiation, higher contrast use, and an increased risk for periprocedural complications, such as perforations, needs to be carefully weighed against potential patient-derived benefit for ischemic symptom relief and functional improvement.

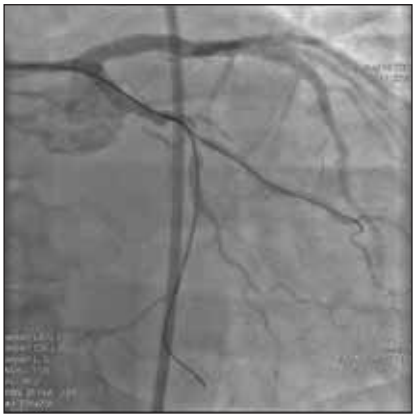

Figure 10. Bifurcation of left circumflex/obtuse marginal branch, both crossed with Miracle wires.

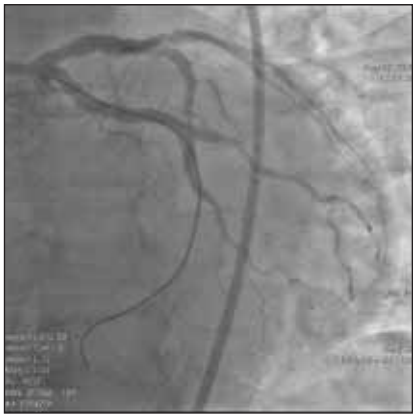

Figure 11. Final result after bifurcation utilizing the crush stent technique with a Taxus stent in the left circumflex/obtuse marginal artery.

First, optimal visualization in multiple views coupled with excellent guide catheter support are critical at the start of any CTO procedure. I strongly recommend visualization of the reconstituted collateralized distal segment with simultaneous contralateral injections as demonstrated in first case. The optimal guide should provide coaxial and safe engagement of coronary ostia, such as the XB (Cordis), Voda and ART (Boston Scientific), GL, or EBU (Medtronic, Inc., Minneapolis, MN) curves for left coronary and the Amplatz for right coronary systems. True lumen guidewire position beyond the occlusion is imperative before balloon angioplasty or atherectomy treatment. Heparin anticoagulation is the preferred option during a CTO procedure to allow for protamine reversal in the event of a significant perforation. A patient presenting with known history for heparin-induced thrombocytopenia may not be an appropriate for CTO intervention.

It is beneficial to use a low-profile support catheter or an over-the-wire balloon catheter in conjunction with a good support guidewire to approach the proximal segment of the CTO lesion. Not only does it provide support, it also allows a safe exchange of wires as the case unfolds without compromising the tip shape of the guidewire.

The principle guidewire technique is to allow safe crossing of CTO microchannels or, occasionally, subintimal tracking and re-entry into the distal true lumen. A variety of guidewire families are available in the market. "Stiff" metal tip or hydrophilic-coated guidewires are utilized in our practice. These include Miracle guidewires with tip weights ranging from 3 g to 12 g, Confianza guidewires (Abbott Vascular), Pilot guidewires (Abbott Vascular), Choice PT guidewires (Boston Scientific), and several others, including tapered tip configurations not mentioned here. There are active guidewires also in use, such as the Safe-Cross RF Total Occlusion Crossing System (Kensey Nash, Exton, PA). Newer devices, such as the Frontrunner (Cordis) catheter and the Crosser (FlowCardia, Sunnyvale, CA) catheter are also available for use. In my practice, the main method of crossing a CTO is guidewire-based, using a good support catheter and slow, carefully directed advancement with optimal angiographic and distal anatomic landmark guidance.

In the presence of pre-existing microchannels, crossing the CTO should require minimal force. Antegrade coaxial force generated by a guidewire is greatest when the wire tip is straight. Hence, aggressive shaping of the tip of a guidewire is not recommended, and extreme care should be exercised to prevent the guidewire tip from becoming deformed (by using an introducer) during insertion through the hemostasis valve or within proximal anatomy leading to the fibrous cap of the CTO. In the case with microchannels, any buckling of the wire means that it is in a wrong channel, or it is at an angle with the channel lumen. In this situation, the guidewire should be gently withdrawn to straighten the tip and then slowly readvanced. An alternative useful technique consists of leaving the noncrossing first guidewire in place and using a buddy wire technique with a second guidewire to gain entry in the true channel. The same principle applies if the first guidewire is in a subintimal plane (so-called parallel-wire technique). The final phase of the procedure is the crossing of the distal fibrous cap of the occlusion and may require the use of an even stiffer guidewire. There are several other techniques and devices, including subintimal tracking and re-entry, and IVUS of the subintimal plane, to identify the location of the true lumen, as well as a retrograde approach.

Having established guidewire placement across the CTO, predilation is recommended, typically using a bal-

loon catheter sized to the adjacent proximal lumen diameter. In heavily calcified lesions, a frequent problem is the inability to place the predilation balloon within the lesion despite the presence of a .014-inch guidewire. For this situation, I would first try a Tornus (Abbott Vascular) support catheter advanced over the .014-inch guidewire with advancement across the proximal cap and through the calcified segment. If this is not successful, other options available today include the use of a .7-mm laser guidewire or a .9-mm laser catheter atherectomy.

DES UTILIZATION FOR CTO DATA

Hoye et al[3] recently published their experience for coronary CTO intervention from 1992 to 2002. In this retrospective analysis, 874 patients with 885 CTO lesions of >1 month duration were analyzed. Mean follow-up was 4.47±2.69 years. Index procedure CTO revascularization was successful in 65.1% of the lesions treated, with bare-metal stent implantation performed in 81% of the lesions treated overall. At 5 years, survival was significantly higher in those patients with successful recanalization (93.5% vs 88%; *P*=.02). In addition, MACE rates were also substantially lower in patients with successful revascularization (63.7% vs 41.7%; *P*<.0001). The majority of MACE events reflected repeat revascularization. Independent predictors for survival, in addition to successful revascularization, were lower age, absence of diabetes, and multivessel disease. The encouraging perspective derived from this pre-DES era study is that with the introduction of DES to the treatment equation for CTO lesions, lower revascularization rates should improve MACE-free survival at 5 years in this large patient population.

Buller et al[4] demonstrated in TOSCA that target vessel revascularization was reduced by bare-metal stent placement compared to percutaneous transluminal coronary angioplasty (PTCA) alone in 410 patients with nonacute occluded coronary arteries. At 6-month follow-up, stenting in 197 patients resulted in 55.2% angiographic restenosis versus 69.3% in the PTCA-group in diabetics as well as nondiabetic patients. The target vessel revascularization rate after stenting was 20% in diabetics and 21.5% in nondiabetics, compared to 31.6% and 30% by PTCA-alone, respectively. Even though stenting was superior to PTCA alone, reintervention rates remained high in CTOs. Other similar CTO studies have reported restenosis rates for bare-metal stenting of 32% (SICCO) and 42% (STOP).[5,6]

Sirolimus-eluting stent implantation in CTO was published by Ge et al[7] and included 122 patients and reported a 6-month binary restenosis rate of 9.2% versus a binary restenosis rate of 33.3% for 259 CTO patients treated with a bare-metal stent before the availability of the sirolimus-eluting stent. In this study, the mean CTO lesion length and stent length were 26.5±13.4 mm and 41.6±19.5 mm, respectively. Similarly, in a series of 56 CTO patients treated with sirolimus-eluting stents published by Hoye et al,[8] the 1-year cumulative MACE-free event rate was 96.4% for the sirolimus-eluting stent patients and 82.8% for a similar CTO patient cohort treated with a bare-metal stent before sirolimus-eluting stent availability.

The safety and efficacy of the paclitaxel-eluting stent have been studied in two prospective, nonrandomized studies and in three real-world registry analyses. In 48 consecutive CTO patients studied by Werner et al,[9] the reported 6-month angiographic restenosis rate at 6 months was 8.3% with paclitaxel-eluting stent implantation compared to a patient population treated with bare-metal stents (51.1%; *P*<.001). For both patient populations, the duration of the CTO was >3 months in 70%, one-third of the patients were diabetic, and the length of occlusion was 18±13 mm and 16±12 mm for the paclitaxel-eluting stent and bare-metal stent groups, respectively. The 1-year MACE rates were 12.5% in the paclitaxel-eluting stent group versus 51.1% in the bare-metal stent group (*P*<.001). In a similarly designed registry, 45 patients were followed up for 6 months, assessing binary angiographic restenosis and late lumen loss.[10] The in-stent restenosis rate was 13.2%, and the in-segment late lumen loss was .13±.58.

Upon approval of the paclitaxel-eluting stent, several real-world registries were conducted to assess the safety and usage patterns of paclitaxel-eluting stents. The first of these registries was the WISDOM registry, presented by Alexandre Abizaid in 2004. Within this registry, 778 patients from 22 sites and nine countries outside of the US were followed up for a period of 1 year. Overall, MACE showed an excellent safety profile and sustained long-term efficacy in high-risk CTOs.

Finally, in the US, the ARRIVE 1 and 2 registries are being conducted. These real-world registries, conducted after approval of the paclitaxel-eluting stent, are following up 7,592 patients from 103 sites that are primarily community centers. Within this population, 65% of the studied patients are considered complex lesion subsets. Overall, 2% of the patients are CTOs (approximately 151 patients). The follow-up is 2 years. Early presentation of the data by John Lasala, MD, PhD, at the Annual Scientific Session of the American College of Cardiology 2005 showed excellent safety and efficacy for the CTO subpopulation with event rates in line with the overall population.

Recently, a retrospective analysis was published by Migliorini et al,[11] in which 6-month follow-up data were reported on 104 CTO lesions treated with sirolimus- or paclitaxel-eluting stents. The results were compared to case-matched control bare-metal stent patients. Stent length was 51±28 mm in the DES group, compared to

40±19 mm in the bare-metal stent group (*P*=.073). The 6-month MACE rate was lower in the DES group compared to that of the bare-metal stent group (9.8% vs 23%; *P*=.072). The angiographic follow-up rates were 80% in the DES arm versus 81% in the bare-metal arm. The 6-month restenosis rates were 19% in the DES group versus 45% in the bare-metal stent group (*P*<.001). By multivariate analysis, the predictors of restenosis were stented vessel segment length and vessel diameter of <2.5 mm, although the only predictor of MACE was a stent length >28 mm. These predictors of angiographic restenosis are similar to SIRIUS and RESEARCH study results. Hence, an important observation from this study is that patients treated with short stents (ie, <28 mm), even in the presence of a CTO, confer similar benefit to patients in randomized controlled trials involving nonocclusive coronary lesions.

Although these small, single-center data have been published, we get a glimpse of off-label DES use in CTO from the national cardiovascular data registry developed by the American College of Cardiology. Out of 206,733 evaluated procedures, 12,311 procedures involved off-label DES use in CTO. The rates of in-hospital adverse events were compared to expected rates calculated from a validated model. The observed in-hospital mortality rate with DESs in CTOs was 2.5% versus the expected rate of 3.3% based on historical control data analysis. The procedural myocardial infarction rate was 1%, and the unplanned coronary artery bypass graft rate was 0.3%. This is a very important observation and suggests that off-label DES use for the treatment of CTO lesions is safe and does not result in an unacceptable higher in-hospital adverse event rate.[12]

CONCLUSION

DES use in CTOs appears safe and results in lower restenosis and revascularization rates, at least in short-to-midterm follow-up. This will be a subject of intense investigation in years to come. How should a practicing clinician address this difficult subset in 2007?

These recommendations are the author's opinion and are not based on level-1 published data. First, appropriate lesion and patient selection are critical toward achieving an event-free hospitalization and index procedure. A careful review of baseline angiography will determine the suitability of the occluded segment to successful recanalization. Favorable features include a reference vessel diameter of at least 3 mm, absence of heavy calcification, no side branch involvement, and a visible segment of artery distal to the occlusion. The foundation anticoagulant should be heparin, when possible, to allow reversal in the event of perforation. All possible guidewires, support catheters, or crossing devices should be readily available during the procedure. Last, and perhaps of greatest importance, is that adequate time must be allocated for procedure setup, diagnostics, and completion; a CTO case cannot be scheduled in the midst of a busy catheterlab schedule because it requires patience and perseverance.

I perform atherectomy—either rotational or laser—in calcified lesions that are long and bulky. This allows for better stent expansion. Also, the use of specialized balloon technology, such as the Cutting Balloon (Boston Scientific) and AngioScore (Fremont, CA) products, may prove beneficial in these subsets for lesion preparation before stent implantation. I routinely use IVUS in the majority of these lesions because, quite often, these arteries appear much smaller than their actual size. I place DESs from normal vessel segment to normal vessel segment to ensure full lesion coverage. Last, the question of antiplatelet therapy still remains unanswered, especially in these patients with multiple DESs. In our practice, we continue dual antiplatelet therapy of aspirin and clopidogrel bisulfate at least for 1 year and, in some cases, if tolerated, even longer, as demonstrated in both presented cases. With next-generation DES technology, improved polymers, and drug-elution kinetics, we hope to see better healing/endothelization of DES after implantation and a reduced need for long-term dual antiplatelet therapy. ■

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