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EDITORIAL COMMENT

Drug-Eluting Stents: Safe But Not Sufficient*

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Drug-eluting stents (DES) were quickly adopted into clinical practice after they were demonstrated to reduce restenosis and repeat target lesion revascularization (TLR) compared with bare-metal stents (BMS) (1,2). Concern soon surfaced over reports of late stent thrombosis with DES (3), leading to the release of 2 Federal Drug Agency advisories in 2006. Protracted dual antiplatelet therapy is now advised after DES implantation. Differences in antiplatelet therapy given to patients receiving DES and BMS complicate the interpretation of the relative long-term benefit of stent type. We are now nearing the end of the DES versus BMS debate, with recent studies documenting the safety of current DES (4). Our major concern should now shift back to the underlying problem beyond the target lesion, namely progressive coronary atherosclerosis.

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In this issue of *JACC Cardiovascular Interventions*, 2 reports categorize the source of late events after DES placement. Chacko et al. (5) report 5-year data from the SIRIUS (Sirolimus-Eluting Stent in De Novo Native Coronary Lesions) study, a sirolimus-eluting stent (SES) versus BMS randomized trial in 1,057 subjects at high risk for restenosis (1). The initial 9-month benefit of SES over BMS in reducing TLR was maintained at 5 years (12.5% vs. 28.8%, $p < 0.001$). No significant differences were observed between the SES and BMS cohorts in myocardial infarction or revascularization at sites within the target vessel remote from the target lesion or in nontarget vessels, although a trend was observed for decreased revascularization with SES within the target vessel remote from the target lesion. Overall death and myocardial infarction were not different between the 2 stent cohorts.

Also in this issue, Leon et al. (6) report pooled 5-year data from 4 paclitaxel-eluting stent (PES) versus BMS trials of 2,797 subjects with both simple and complex de novo coronary lesions. The initial reduction in TLR was maintained long-term, as with the SES data, and death or myocardial infarction was not different between the PES and BMS cohorts, although myocardial infarction trended (hazard ratio: 1.59, 95% confidence interval: 0.99 to 2.55, $p = 0.054$) more frequent in the PES cohort during years 2 to 5.

It important to document that DES deployment does not have remote effects on the coronary vasculature for 2 reasons. Restenosis can potentially lead to remote revascularization and hence altered clinical outcome due to increased angiographic surveillance after recurrent symptoms. Moreover, in 1987, our group demonstrated that angioplasty-induced medial injury but not endothelial denudation has adverse vasoactive effects in both the intervened and remote coronary vessels, potentially affecting atherogenesis (7). These effects seem to be mitigated by antiplatelet therapy. Similar adverse remote vasoactive effects have been reported with SES (8).

Although the current studies demonstrate no difference in remote atherogenesis between DES and BMS placement, they cannot evaluate whether either angioplasty or stent placement themselves affect remote disease progression. A second limitation of the current studies is their failure to record antiplatelet and other medication use during the extended follow-up period. Long-term clopidogrel use in the DES cohorts could have mitigated adverse effects. Another limitation of the current SES study is its use of a composite end point, which included death, myocardial infarction, and revascularization. As acknowledged by the authors, these end points are not apples and oranges; they are watermelons and grapes. No number of uneventful interventions can be equated with 1 death. Composite end points including events in addition to death, myocardial infarction, and stroke cloud rather than clarify clinical results.

The current reports emphasize that although events originating beyond the target lesion occurred equally in the 2 cohorts they occurred frequently. This finding is consistent with the original observation of Cutlip et al. (9) who pooled data from 1,228 subjects in 3 second-generation coronary stent trials over 5 years. After the initial year of follow-up, the average annual hazard rate was 1.7% for events related to the target lesion but 6.3% for nontarget-lesion vessels. In this study, diabetes mellitus and multivessel disease were independently associated with increased risk for remote events. These data underscore the need for aggressive medical management of all patients undergoing any type of percutaneous coronary intervention.

We are probably nearing the end of the DES versus BMS debate, at least in terms of clinical safety. Douglas et al. (4) recently analyzed the data from 262,700 elderly patients undergoing stent placement at 650 sites during a 3-year period beginning in 2004 within the American College of

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Cardiology's National Cardiovascular Data Registry (NCDR). Of these nonrandomized patients, 83% received a DES and 17% a BMS. Data from the NCDR were linked to Medicare claims through a unique probabilistic matching technique, which resulted in 76% being correctly matched. After adjustment for differences in baseline characteristics, death and myocardial infarction occurred less frequently in the DES than in the BMS cohort (hazard ratio: 0.75 and 0.77, respectively). Repeat revascularization also occurred less frequently in the DES group, although the hazard ratio was 0.91. Possible incomplete adjustment for group differences and uncontrolled medication use limit the results from this very large observational study from certifying the safety and efficacy of DES. More valuable information could be derived from such large databases if our medical information systems were less encumbered by excessive concerns for patient privacy (10).

Ultimately, however, the current study provides no information on the relative clinical value of stent placement compared with accompanying medical management. To this end, the COURAGE (Clinical Outcomes Utilizing Revascularization and Aggressive Drug Evaluation) trial provides a useful comparison (11). In this trial of optimal medical management with or without percutaneous coronary intervention, death, myocardial infarction, and other major events occurred at similar rates. In fact, the 4.6-year all-cause death or nonfatal myocardial infarction rates were 19.0% and 18.5% for the intervention and nonintervention groups, respectively, which compare favorably with a 21.0% rate at 4.8 years for the SES cohort and approximated 17.2% for the PES cohort in the current studies. This finding is especially remarkable in view of the fact that DES were not introduced until the final 6 months of the COURAGE trial. Both the high event rates due to disease remote from the target lesion in the current study and the excellent outcomes with aggressive medical management in the COURAGE trial suggest that the greatest opportunity to improve clinical outcomes lies in managing the underlying atherosclerosis. It should be remembered that in the COURAGE trial optimal medical management in the interventional cohort at year 5 had achieved mean values for blood pressure of 124/70 mm Hg, low-density lipoprotein cholesterol of 71 mg/dl, and glycated hemoglobin of 7.1% in patients with diabetes mellitus.

Interventions do not cure atherosclerosis, and interventionalists need to be familiar with all the medical details of each patient. As an example, I have encountered several DES-treated patients who were known to require noncardiac surgery within months of their intervention, unnecessarily complicating antiplatelet therapy. A good stent is necessary, but having a good physician is even more important.

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