Clinical Challenges in the Prevention and Treatment of Late and Very Late Stent Thrombosis

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Early (up to 30 days postprocedure) stent thrombosis occurs in about 1.0% of patients who receive either drug-eluting stents (DES) or bare-metal stents (BMS). However, late (between 30 days and 1 year postprocedure) or very late (beyond 1 year postprocedure) DES thrombosis has recently been recognized as a potential complication of DES deployment. Enormous attention has been paid (in both the medical literature and lay press) to this potential adverse event following DES because of the associated high morbidity and mortality. As often occurs with medical reporting in the mass media, the public has been presented with mixed messages comprised largely of sound bites rather than the full information needed to discern the truth. For physicians, the accurate assessment

of risk for stent thrombosis related to DES has been difficult for several reasons. First, the definition of what constitutes stent thrombosis has been the subject of debate. Second, this dreaded event occurs infrequently (fewer than 3 events per 1000 patients treated) and, thus, requires analysis of several thousand patients followed for well beyond a 1-year duration for detection. Third, randomized controlled trials that have adhered to relatively narrow participation criteria and have excluded more complex "real world" patients may under-represent the true magnitude of this problem. Fourth, "very late" stent thrombosis events must be differentiated from the 1% to 2% yearly "background" incidence of death or myocardial infarction observed in patients with coronary artery disease that is attributable to plaque rupture or progression in non-stented coronary segments. Finally, we now appreciate that very late (beyond 1 year) stent thrombosis did occur following BMS deployment (albeit rarely), particularly when all antiplatelet therapy (including aspirin) was discontinued.

In this supplemental issue of *Reviews in Cardiovascular Medicine*, we present an educational series focusing on the scientific and clinical basis for late and very late DES thrombosis. Dr. John J. Young reviews the pathobiology of restenosis and neointimal formation, with an overview of the currently available DES platforms as well as the potential mechanisms that underlie delayed healing. Dr. David R. Holmes, Jr., reviews the prevalence and clinical factors associated with late DES thrombosis. Drs. Paul A. Gurbel and Udaya S. Tantry discuss the role of compliance with, and resistance to, antiplatelet therapies in the pathogenesis of late and very late stent thrombosis, and Dr. Norman E. Lepor addresses strategies for primary and secondary prevention. Dr. Dean J. Kereiakes concludes the supplement with a discussion of innovative DES technologies that may mitigate thrombotic risk. This supplement is meant to complement the recent US Food and Drug Administration (FDA) panel evaluation and recommendations regarding DES thrombosis.

As you know, the FDA panel met on December 7 and 8, 2006, to discuss and analyze recent data concerning late DES thrombosis. After reviewing all available data from industry and following an open public session, the panel has provided the following summary:

1. DES, when used in accordance with their FDA approved and labeled indications, are associated with a numerical excess of late stent thrombosis (after 1 year implantation) compared to BMS; however, the magnitude of this excess is uncertain and additional data are needed.
2. DES are not associated with an increased risk of death or myocardial infarction compared to BMS.
3. DES are not associated with an increased rate of all-cause mortality, but longer-term follow-up and an increased number of patients in future trials was requested.
4. Safety concerns apply equally to both currently approved DES, but do not outweigh their benefits compared to BMS when used according to approved labeling.
5. Antiplatelet therapy after DES implantation should follow the current American College of Cardiology/American Heart Association/Society for Cardiac Angiography and Interventions clinical practice guidelines for percutaneous coronary intervention (at least 12 months of aspirin and clopidogrel therapy for patients at low risk for bleeding complications).
6. The off-label use of DES, like BMS, is associated with increased risk compared with on-label use. Available data were insufficient to identify specific subsets of patients at particularly increased risk for stent thrombosis.
7. There was agreement that the data for off-label use are limited and the panel recommended larger and longer follow-up for post-approval studies, with specific and uniform definitions for stent thrombosis events.
8. The panel also agreed that at least 12 months of dual antiplatelet therapy should be recommended following off-label DES use.

We hope that you will find this supplement to be a valuable resource and adjunct to the US FDA panel recommendations and that the information provided will be useful to you in caring for your patients. ■