

Coronary Stent Thrombosis

Frederic S. Resnic, MD MSc

March 1, 2008

Percutaneous coronary intervention (PCI) is the most frequent form of revascularization performed worldwide for the treatment of coronary artery disease (CAD) and has been shown to significantly improve anginal symptoms in patients with stable CAD, and to reduce future ischemic events in those patients treated for acute coronary syndromes. Over 95% of patients treated with PCI in the United States today are treated with one or more intra-coronary stents. The commercial introduction of drug eluting stents (DES) in 2003 heralded a new era for interventional cardiology, and rapidly overtook traditional bare metal stent (BMS) procedures as the preferred strategy for PCI given the remarkable efficacy that DES provide in terms of reducing the risk of repeat procedures for stent failure due to restenosis. By 2005, nearly 90% of all patients receiving PCI in the U.S. were receiving at least 1 DES. However, the safety profile of these new devices had not been examined beyond 2 years, and reports began to appear in 2006 of an unexpectedly high rate of late complications with drug eluting stents. The first reports, primarily from European registries, demonstrated higher rates of death and myocardial infarction in patients treated with DES as compared with those treated with BMS. However, confounding factors of device selection and antiplatelet therapy duration clouded the findings of these reports. While the frequency of complications was low, the severity of the complications led to great interest in determining the underlying cause of the problem, if it actually existed.

There are a several hypothetical causes for an increased risk of coronary stent thrombosis for DES as compared with traditional BMS. These include: delayed and incomplete endothelialization of the coronary vessel wall after DES implantation (as compared with BMS), the risk of late stent malapposition due to excessive positive remodeling of the vessel, use of DES in increasingly complex lesions (such as small diameter vessels which independently increase the risk of thrombosis), as well the potential for premature discontinuation of dual antiplatelet therapy. Multiple studies have concluded that the early discontinuation of dual antiplatelet therapy with aspirin and a thienopyridine such as Clopidogrel is the dominant contributant to observed stent thrombosis.

In December 2006, the FDA convened a special panel review of the safety of drug eluting stents and reviewed all available clinical data as well as initial explorations of post-market release registries. The pooled data of all randomized trial patients for each of the approved DES systems was reviewed, and demonstrated no clear increased risk of adverse events or of the specific complication of stent thrombosis for DES as compared with BMS. The study by Mauri and colleagues demonstrated that DES experienced a cumulative risk of stent thrombosis of approximately 0.4% per year which was not significantly different than BMS treated patients [1]. In contrast, a large non-randomized observational registry from Scandinavia demonstrated that DES patients appeared to be suffering from myocardial infarctions and unexplained deaths with a relative risk of 1.20 (95% confidence interval: 1.05-1.37) as compared with bare metal

stent treated patients [2]. The panel concluded that there was no clear evidence of an increased risk of stent thrombosis with DES as compared with BMS for patients treated in accordance with labeled indications. However, the FDA endorsed prolonged dual antiplatelet therapy with aspirin plus a thienopyridine for at least 12 months, if possible, following implantation of a drug eluting stent. Particular attention was paid to the need to educate patients and providers about the importance of continuing uninterrupted dual antiplatelet therapy to avoid the increased risk of stent thrombosis if such therapy is discontinued prematurely.

Since the time of the FDA panel meeting, multiple additional randomized studies and registries have been reported that support the relative equivalence of safety for DES and BMS out to four years following stent implantation. In fact, longer term results from the Scandinavian study and early registries of DES and BMS appear to show reversal of previously reported trends. However, the question of whether DES may carry an increased risk of very late stent thrombosis (> 1 year following implant) relative to BMS, is still unsettled. Newer stent designs, becoming available in the United States over the next 12 months appear to have more biocompatible polymers and may have the potential for reducing rates of stent thrombosis as compared to current technologies. Ongoing clinical trials and registries will continue to expand our understanding of the particular risks of stent thrombosis for existing and yet to be introduced DES platforms.

It is clear that prevention of stent thrombosis is the best approach to reducing the potentially devastating complications of stent thrombosis. The importance of considering patient factors such as the ability to comply with and afford prolonged dual antiplatelet therapy is now a paramount consideration of whether to choose to use DES or BMS in particular patient. In addition, anticipating the potential need to suspend dual antiplatelet therapy for elective surgery must be considered when choosing a stent for a particular patient.

References:

1. Mauri L, Hsieh W, Massaro J et al. Stent thrombosis in randomized clinical trials of drug eluting stents. *N Engl J Med.* March 2007: 1020-1029.
2. Lagerqvist B, James SK, Stenestrand U et al. Long-term outcomes with drug eluting stents versus bare-metal stents in Sweden. *N Engl J Med.* March 2007:1009-1019.