Late drug-eluting stent thrombosis in unprotected left main coronary artery lesions—sometimes possible, but rarely definite or probable

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Online publish-ahead-of-print 28 July 2008

This editorial refers to ‘Late and very late stent thrombosis following drug-eluting stent implantation in unprotected left main coronary artery: a multicentre registry’ by A. Chieffo et al., on page 2108

Beyond relieving angina, revascularization strategies for coronary artery disease (CAD) have focused on the subsequent occurrence of death, myocardial infarction, repeat revascularization, and, more recently, stent thrombosis. Numerous trials comparing percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) have shown the long-term rates of death and myocardial infarction to be similar between these strategies, largely independently of the extent and location of CAD. The main outcome gap between percutaneous and surgical approaches has been the higher rate of repeat revascularization procedures for those initially undergoing PCI. At 5-year follow-up in the Bypass Angioplasty Revascularization Investigation (BARI) trial, 54% of patients initially undergoing multivessel balloon angioplasty required a repeat procedure vs. 8% among those assigned to bypass surgery. With the introduction of bare-metal stents (BMS), this gap between PCI and CABG was narrowed. The 5-year follow-up from the Arterial Revascularization Therapies Study (ARTS) trial demonstrated the need for repeat target vessel revascularization (TVR) for those undergoing multivessel stent placements vs. CABG to be 30 and 9%, respectively. Most recently, drug-eluting stents (DES) have reshaped the landscape of interventional cardiology by substantially reducing rates of restenosis, and this intuitively should narrow the repeat TVR gap between PCI and bypass surgery further. In particular, the 5-year data from randomized trials comparing BMS and DES have shown TVR rates to be additionally reduced by one-half to two-thirds with DES, such that the ~10–15% need for repeat revascularization for the DES cohort at long-term follow-up should be nearing that associated with bypass surgery.

Several important CAD subsets, such as chronic total occlusions, complex bifurcation lesions, and stenoses of unprotected left main coronary arteries (ULMCA), have been considered unattractive or ‘verboten’ for PCI, but are being increasingly considered with the availability of DES. Large-scale trials comparing revascularization strategies have specifically excluded those with ULMCA since such cases are known to be at particularly high risk for adverse events and are clearly benefited by CABG vs. medical therapy. Likewise, DES have not been without their own peril as concerns of an increased occurrence of stent thrombosis surfaced with more widespread and ‘off-label’ use and longer-term follow-up. While stent thrombosis is infrequent, it almost always results in a myocardial infarction, and in one-tenth to one-third of cases death occurs. Therefore, to quantify adverse events more accurately, including the occurrence and the timing of stent thrombosis, Stone et al. pooled data from nine trials which randomized 5261 patients to BMS or DES. They reported the frequency of stent thrombosis, defined according to each study’s protocol, to be low (0.6%) and identical for BMS and DES groups during the first year of follow-up. Between 1 and 4 years after the procedure, numerically more stent thrombosis events occurred in the DES group (0.5% vs. 0.1%), producing a similar 4-year cumulative event rate (1.2% vs. 0.7%).

Mauri et al. performed further analyses on eight of these same stent trials using patient-level data, readjudicating events, and applying a hierarchical classification for stent thrombosis set by the Academic Research Consortium. This stent thrombosis classification scheme includes three degrees of certainty (definite, probable, and possible) and three periods of time following the procedure [early (0–30 days), late (31–360 days), and very late (>360 days)].
Definite stent thrombosis requires an acute coronary syndrome with angiographic or autopsy evidence of thrombotic target-vessel occlusion. Probable stent thrombosis requires early unexplained death or acute myocardial infarction involving the target vessel without angiographic confirmation. Possible stent thrombosis includes all unexplained deaths occurring late or very late after stent placement. Considering a composite of definite or probable stent thrombosis and using Kaplan–Meier estimates, Mauri et al. reported 4-year event rates to be similar for sirolimus-eluting stents vs. BMS (1.5% vs. 1.7%) and paclitaxel-eluting vs. BMS (1.8% vs. 1.4%). Roughly one-half of these events, however, occurred very late in DES-treated patients, while one-third of events occurred very late in BMS-treated patients.

Real-world, large-scale registry data with less restricted or unrestricted DES use have also provided an element of concern for higher than anticipated rates of late and very late stent thrombosis. Daemen et al. reported on 8146 consecutive DES patients enrolled at two medical centres and followed for an average of 1.7 years. The cumulative incidence of definite stent thrombosis was 1.1% early after implantation, and between 30 days and 3 years occurred at a consistent rate of 0.6% per year. The 3-year cumulative rate was 2.9%. There was no BMS control group, and data beyond 2 years were very limited. Regardless, events occurred late in 16% of cases and very late (median 451 days) in 24% of cases. This somewhat unpredictable occurrence of late and very late stent thrombosis has been unsettling. Daemen et al. and others have identified several factors to be associated with stent thrombosis, including diabetes, acute coronary syndrome during the index procedure, bifurcation lesions, stent under expansion, residual dissection, and low ejection fraction.

Putting these observations and concerns together, the approach to revascularize patients with ULMCAD percutaneously has been cautious and controversial. It could certainly be expected that patients with stent thrombosis of the left main coronary artery, whether early, late, or very late, would have a particularly high risk of dying. Chieffo and colleagues importantly add to the literature by reporting the frequency and timing of stent thrombosis in their experience with DES for ULMCAD. Data were collected from five centres’ prospective registries and entered into a common data set retrospectively. During a 4-year interval, 731 consecutive patients undergoing elective DES-PCI for de novo ULMCAD were included. The registry did not include patients who had a myocardial infarction as the procedural indication, although 46% had unstable angina. PCI was considered instead of surgery because of patient preference, a high (≥6) EuroSCORE, or failure of all previously placed bypass graft conduits. Patients were systematically followed for 30 ± 13 months, and dual antiplatelet therapy was given for a median duration of 9 months (interquartile range, 6–21).

There are many noteworthy findings from this registry, particularly in the context of prior reports on stent thrombosis not associated with ULMCAD. The first is that Chieffo et al. observed definite or probable stent thrombosis in 0.9% of the cohort at 2.5 years, and this is remarkably low yet directly in line with the Kaplan–Meier curves from Stone et al. and Mauri et al. The second impressive finding is that of the four patients with definite stent thrombosis, all survived. This is a powerful testament to the skills and care provided by these centres. Considering the timing of events, the number of definite stent thrombosis cases is too small to make certain conclusions, though it is important to know that three of the events occurred early, and only one occurred late. Probable stent thrombosis occurred in three patients, and all these events occurred early. Therefore, the third noteworthy observation is that no case of definite or probable stent thrombosis occurred after 4 months, and, as such, all events occurred while taking dual antiplatelet therapy. Fourthly, possible stent thrombosis occurred in 2.7% of patients, and this is also consistent with previous reports. Fifthly, TVR at long-term follow-up was 13%. Finally, cardiac-related mortality occurred in 4.2% of the cohort, and this should not be different from the mortality expected had these patients undergone CABG since the median EuroSCORE was 3 and more than one-third of patients had a score ≥6.

These impressive results are the consequence of careful planning and expert care. Others hoping to replicate these outcomes or design prospective studies should note that the majority of patients appropriately had preserved left ventricular ejection fraction, a low or intermediate EuroSCORE, and stable CAD. Indeed, Chieffo et al. found that unstable angina, ejection fraction, and EuroSCORE each was correlated with cardiac death on logistic analysis. Likewise, intravascular ultrasound guidance was utilized in roughly half of the cases, and angiographic follow-up was scheduled between 4 and 9 months and was performed in 75% of patients. At this juncture, prospective randomized data to assess the use of specific DES for ULMCAD would be of interest, and a number of head-to-head DES trials are underway. Similarly, data directly comparing DES vs. CABG for patients with a ULMCAD are awaited. The Synergy Between PCI with TAXUS and Cardiac Surgery (SYNTAX) trial, which randomized 1800 to DES or CABG, included 710 patients revascularized for left main coronary artery disease. Initial results are anticipated for presentation during the 2008 European Society of Cardiology Congress.

In summary, while the controversies surrounding PCI for ULMCAD will remain and arguments of clinical equipoise between revascularization strategies will continue, the findings of Chieffo et al. and related registries are nonetheless showing that acceptable outcomes with DES-PCI are possible. Whether large-scale trial data will be as attractive and whether these results can be widely replicated among other centres is unknown. Make no mistake, stent thrombosis in ULMCAD-treated lesions is certainly possible and understandably catastrophic—but in this respectable and sizeable registry its occurrence was rarely definite or probable.

Conflict of interest: H.H. reports no conflict of interest. D.J.M. reports having received past honoraria for serving as a member of Data and Safety Monitoring Committees for stent manufacturers including Boston Scientific and Guidant.

References


The above article uses a new reference style being piloted by the EHJ that shall soon be used for all articles.