Drug-Eluting Stents
Dual Antiplatelet Therapy for Every Survivor?

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No recent pharmaceutical or medical device has generated as much ongoing and expanding attention as drug-eluting stents (DES). In fact there has been an explosion of published reports on the topic within cardiology, medical, surgical and subspecialty journals. The device industry has repeatedly sent their own summaries of information directly to physicians, while mainstream media has kept the consumer and Wall Street appraised of safety concerns, often with sensational headlines. The Food and Drug Administration has also taken notice by convening a meeting on DES in late 2006. What have we learned through all this dissemination of data?

The introduction of DES was greeted with intense enthusiasm in a “perfect storm” sort of way. Device representatives were eager to promote this new product that could dramatically reduce restenosis. Patients expected to be treated with this new and “better” technology. Lastly, cardiologists had a potent new tool at their disposal that they increasingly incorporated into practice until it became the default revascularization device instead of bare-metal stents in many parts of the world. This quick and widespread adoption in DES resulted in its frequent use in relatively untested and off-label indications. At the Cleveland Clinic, the use of DES mirrored the community and many interventional practices throughout the world, where the penetration of this device peaked at >90%.

While DES use was increasing, McFadden and colleagues sounded an alarm with the publication of a report on 4 patients who experienced late stent thrombosis. Although this could have been a chance finding, DES were systematically shown to confer an increased risk of late thrombosis relative to bare-metal stents. This safety issue has been confirmed by several independent analyses with patient-level data from the pivotal randomized trials.

Stent thrombosis is uncommon, although when it occurs it often results in myocardial infarction or death. However, at a broader population level, no excess in hard end points has been observed. One explanation for this conundrum is that restenosis can culminate as an acute coronary syndrome, and DES decrease restenosis as well as the accompanying acute coronary syndromes that would have resulted from this process.

Because late stent thrombosis appears to occur with inadequate antiplatelet therapy, operators have frequently increased the duration of dual antiplatelet therapy beyond 6 months. Registry data support that extension of dual antiplatelet therapy to 1 year can attenuate the risks associated with DES. It is unknown what the optimal duration of dual antiplatelet therapy should be; however, on the basis of available data it is currently recommended that patients receive at least 12 months of uninterrupted therapy. The need for prolonged dual antiplatelet therapy has made some patients unattractive candidates for DES. Examples include patients with known bleeding abnormalities, conditions that require life-long anticoagulation therapy such as atrial fibrillation or a mechanical heart valve, medical noncompliance, or an upcoming surgical procedure that might prompt interruption of antiplatelet therapy. Currently at our institution, where operators are left to their own discretion as to when to use a DES versus a bare-metal stent, the proportionate use of this device has fallen to ~50%. It is unknown what the optimal prevalence of DES utilization should be; however, we are reminded that the intent of this device was to prevent restenosis, which occurs in a minority of patients with modern-generation bare-metal stents, even in relatively complex lesions in referral populations.

Within this mountain of DES data, numerous studies have tried to determine the incidence and predictors for late stent thrombosis. Such data might be used to determine who would be a good candidate for a DES, or alternatively who would be better served by a bare-metal stent or by coronary artery bypass graft surgery (Figure). Moreover, these data could potentially be used to identify patients who would need heightened surveillance or adjunctive treatment upon termination of antiplatelet therapy, such as during the perioperative period. With this backdrop in mind, Airoldi and colleagues provide an important piece of the puzzle through their research on the incidence and predictors of DES thrombosis upon termination of thienopyridine therapy. The authors studied 3021 patients who received a paclitaxel-eluting stent or a sirolimus-eluting stent at 4 institutions and were followed for 18 months. There are 4 main findings from this study that we will discuss in detail.

First, the overall incidence of stent thrombosis was 1.9% at 18 months. The authors acknowledge that this incidence is higher than expected from randomized clinical trials. A likely explanation for this higher incidence of stent thrombosis is...
Algorithm to optimize stent safety and efficacy. ACS indicates acute coronary syndromes; BMS, bare-metal stent; CABG, coronary artery bypass graft surgery; DES, drug-eluting stent; IVUS, intravascular ultrasound; and STEMI, ST-elevation myocardial infarction.

...that 67% of their patients received DES for off-label indications. Patients with myocardial infarction were excluded and an off-label bare-metal stent group was unavailable for comparison. Analysis of on-label use of DES with 4 years of follow-up documented a cumulative incidence of stent thrombosis of 1.3%. Despite the lower incidence of late DES thrombosis with on-label use, it is still several-fold higher than the incidence of late bare-metal stent thrombosis, which is virtually nonexistent. Unlike the lower-risk clinical trial population where no excess mortality has been observed, the real-world use of DES has been associated with increased mortality. Accordingly, we should continue to be cautious about the off-label use of DES until further data are accumulated.

Second, half of the observed stent thromboses occurred within 30 days of stent implantation. Since the bare-metal stent era, we have known that there is a relatively high incidence of early stent thrombosis that is largely related to technical aspects of stent deployment. Residual dissection, persistent slow coronary flow, and stent underexpansion are at least as important today with DES as they were with bare-metal stents. DES are unique in that they confer a low yet persistent risk for late thrombosis. A crucial finding from the study by Airoldi et al published in this issue of Circulation is that higher final pressure at stent implantation was protective against stent thrombosis, presumably by ensuring good stent expansion and apposition. While we focus on understanding the late safety issues of DES, we should continue to optimize stent deployment regardless of the stent type in an effort to prevent early and late thrombotic events. Adjunctive technologies such as intravascular ultrasound to maximize stent apposition and fractional flow reserve to minimize bifurcation stenting of jailed side-branches may also improve safety. More intense antiplatelet therapy during the first month after the stent procedure may also prove to provide additional protection, although this needs further study.

Third, the strongest predictor of stent thrombosis within 6 months was the termination of clopidogrel. Indeed, several studies have identified premature termination of antiplatelet therapy as the most potent predictor of stent thrombosis. This crystallizes the idea that patients need to have a firm understanding of the importance of long-term and uninterrupted dual antiplatelet therapy before DES implantation. This may be difficult to do during the urgent nature of an acute myocardial infarction, where early termination of clopidogrel and increased mortality have been observed. Even when a patient contends that there has been complete medication compliance, point-of-care platelet function monitoring may reveal the opposite.

Fourth, the risk of stent thrombosis after discontinuation of thienopyridine treatment after 6 months, if present, seems to be small. On the basis of this conclusion, some readers may assume that it is safe to stop clopidogrel at 6 months; however, this could put patients at unnecessary risk. Several points in support of our concern deserve comment. First, the authors only documented 16 stent thromboses after 6 months, which corresponds to an incidence of 0.3% among patients who remained on dual antiplatelet therapy and 0.2% among patients who stopped clopidogrel. Such a rare event makes it difficult to firmly document an association. A common statistical error is to claim equivalence between 2 exposure groups, when all that can be stated is that no association was found. It is unknown whether a larger group of patients with longer follow-up would have revealed an association between late termination of clopidogrel and stent thrombosis. Second, patients were not randomized to stop clopidogrel at 6 months. Rather, this decision was determined on an individual basis. We know from this study that patients who remained on long-term clopidogrel were more frequently treated with prior brachytherapy and more often had a history of myocardial infarction, percutaneous coronary intervention, or coronary artery bypass graft surgery. These and other unknown confounding variables could have strongly influenced the incidence of late stent thrombosis. Third, analysis of 4 pivotal paclitaxel trials, which confirmed an increased risk for late DES thrombosis, also revealed that nearly 90% of these events occurred after clopidogrel had been discontinued. Even more concerning is that late stent thrombosis has been documented to occur in up to 23% to 36% of patients who remain on dual antiplatelet therapy. Although early termination of dual antiplatelet therapy can result in stent thrombosis within a matter of days, late termination more...
frequently results in stent thrombosis weeks or even many months later. Unfortunately, this makes late stent thrombosis idiosyncratic in nature and difficult to predict.

In summary, DES are complex coronary devices that effectively reduce restenosis; however, a small but significant number of patients may suffer from late stent thrombosis. It is our duty to determine each patient’s candidacy for a DES and to minimize complications for those who receive this device (Figure). Accordingly, patients should understand and be willing to remain on long-term dual antiplatelet therapy. The body of available data supports at least 12 months of uninterrupted clopidogrel in addition to aspirin. In patients who have not had bleeding problems during the preceding year of treatment, dual antiplatelet therapy does not appear to be associated with significant excess bleeding compared with aspirin alone, although there are obvious cost implications if such a strategy were to be applied broadly. Hopefully, the next generation of DES will not come with this rare yet serious complication of late thrombosis. Until then, DES should mean “Dual anti-platelet therapy for Every Survivor” (for at least 12 months, if not longer).

Disclosures

Dr Bavry has received honoraria for consulting from Genesis Associates, The Frankel Group, HRA, Protaggale Pharma, and Hagen/Sinclair Research Recruiting. Dr Bhatt has served on the speaker’s bureaus of Bristol-Myers Squibb, Sanofi Aventis, and The Medicines Company; he has received honoraria (currently donated to nonprofit organizations) from AstraZeneca, Bristol Myers Squibb, Centocor, Eisai, Eli Lilly, GlaxoSmithKline, Millennium, Parke-Davis, Pfizer, Sanofi Aventis, Schering Plough, The Medicines Company, and tns Healthcare. He has served as a consultant to or on the advisory boards of (compensation currently donated to nonprofit organizations) AstraZeneca, Bayer, Bristol-Myers Squibb, Cardax, Centocor, Cogenus, Daiichi-Sankyo, Eisai, Eli Lilly, GlaxoSmithKline, Johnson & Johnson, McNeil, Medtronic, Millennium, Otsuka, Paraxigen, PDL, Sanofi Aventis, Schering Plough, Scios, The Medicines Company, tns Healthcare, and Vertex. He provided expert witness testimony regarding antithrombotic therapy (compensation donated to a nonprofit organization >1 year ago).

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