EDITORIAL COMMENT

Drug-Eluting Stent Thrombosis
Increasingly Recognized But Too Frequently Overemphasized*

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After the implantation of drug-eluting stents (DES) (Cypher, Cordis/Johnson and Johnson, Miami Lakes, Florida, or TAXUS, Boston Scientific, Natick, Massachusetts), patients often ask how long they need to continue double antiplatelet therapy. Our answer is frequently to say for one year or, better still, "until you find a physician who tells you that you should stop." This tongue-in-cheek response actually covers up our unspoken uncertainty in the area of prevention of stent thrombosis after the implantation of the two commercially available DES, particularly when they have been used in situations untested in randomized trials. We are well aware that most of the long-term follow-up data from randomized trials have not shown any higher risk of thrombosis with DES compared with bare-metal stents (BMS) (1,2), with most of the patients taking combined clopidogrel and aspirin therapy for three to six months.

Nevertheless, nagging doubts remain with increasing reports of late stent thrombosis in real-world patients, particularly after the discontinuation of double antiplatelet therapy (3–6). Furthermore, new long-term data from TAXUS-II, -IV, and -V and the Basel Stent Cost-Effectiveness Trial (BASKET) studies, recently presented at the American College of Cardiology Scientific Sessions, have shown greater rates of late events in the DES arms (7,8). After 180 days in these TAXUS trials, no thromboses occurred in 1,367 patients with BMS compared with five thromboses in the 1,369 patients with paclitaxel-eluting stents (p = 0.06) (7). In ongoing follow-up of BASKET study patients, the rate of cardiac death and myocardial infarction from 6 to 18 months was almost four times greater in the DES group (4.9% in DES vs. 1.3% in BMS, p = 0.01), which is strongly suggestive of late thromboses in patients with DES (8).

Since the advent of routine dual antiplatelet therapy after BMS implantation, stent thrombosis was no longer perceived as a major problem (9); however, with the introduction of DES, the issue has reared its ugly head again. However, we frequently are reminded that most of the prospectively collected data do not indicate the existence of late DES thrombosis as an entity about which we should be concerned. As most recently shown in the eCYPHER registry, the one-year incidence of stent thrombosis in 15,157 patients treated with sirolimus-eluting stents was 0.19%, with 48.4% of patients taking only aspirin at 12 months (10). How then are we to reconcile this conflicting evidence? Any attempt to deny the existence of the problem would surely be doing as big a disservice to our field as any effort to create undue concerns about its very existence.

In response, we wish to pose a conundrum: the only way you can truly discern from a group of people who are swimming with a lifesaver (double antiplatelet therapy) which ones do not actually need the lifesaver is to remove it from all of them and see who sinks and who swims! Fortunately, perhaps, such an approach is rarely taken after the implantation of DES and, consequently, the question continues to remain unanswered in a satisfactory manner.

A recurring problem when analyzing rates of stent thrombosis (acute, subacute, and late) is the definition of what constitutes a late thrombosis event. Obviously, a patient with angiographic or autopsy evidence of thrombus in a stented segment constitutes an event, but how should we adjudicate the not-uncommon end points of sudden death or target vessel-related myocardial infarction when the patient does not undergo autopsy or angiography?

In this context, the latest work from Joner et al. (11) reported in this issue of the Journal is illuminating because it provides convincing documentation that late stent thrombosis after implantation of DES not only occurs but can cause sudden death and is furthermore associated with histopathological findings, which make sense. From a series of 40 patients who died after DES implantation, 23 patients with 32 DES were identified who had died >30 days after stent implantation. Of this cohort of 23 patients, 14 had histological evidence of late stent thrombosis, which was adjudged to be the cause of death in 13 patients. Somewhat controversially, two patients were adjudicated to have died secondary to in-stent restenosis with neointimal hyperplasia rather than occlusive thrombus, whereas the remaining seven patients died of nonstent-related causes and all of these had patent stents. Eleven patients received sirolimus-eluting Cypher stents and 12 received paclitaxel-eluting Taxus stents. Joner et al. (11) go on to report two comparisons focusing on the inflammatory and healing reactions to the implanted stents, as evidenced by the amount of ongoing fibrin deposition and percent of endothelialization of stent struts. First, all the DES were compared with a control cohort of 36 BMS of similar duration and location of implant, and then the DES with late thrombosis were compared with patent DES. Both Cypher and Taxus stents had significantly greater fibrin scores and decreased endo-

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thelialization as compared with BMS of similar duration of implantation.

Similarly, DES with late thrombosis had higher fibrin scores and decreased endotheialization when compared with patent DES, all of which points to a reduction in healing and endotheialization in DES in addition to the intended suppression of neointimal proliferation. Unsurprisingly, the authors also demonstrate that stent length and mean number of stents per patient were greater in DES with thrombosis versus those without. Worryingly, 7 of the 14 patients with late DES thrombosis were “maintained” on dual antiplatelet therapy, although we are not provided with toxicological confirmation that the patients were actually compliant with their therapy. Two patients were on monotherapy and the remaining five were not receiving any antiplatelet therapy at the time of death, at least raising the possibility that maintenance of dual therapy may have prevented stent thrombosis in these seven cases. In all 14 cases of late DES thrombosis, features of delayed healing were observed. Additionally, in 11 of these patients, the authors were able to identify potential additional pathological risk factors for late thrombosis, including chronic inflammation/hypersensitivity, ostial and/or bifurcational stenting, malapposition, restenosis, and penetration of necrotic core. Of course, in the absence of a substantial control group without stent thrombosis, particularly when one considers that more than 1 million patients have so far been treated with DES worldwide, it is impossible to know whether such pathological features are truly associated with predisposition to late thrombosis in the general DES population or merely represent an incidental finding in this selected cohort. Indeed, this is the main limitation of this study; it is by definition dealing with a highly selected group of patients who have had a fatal event. It would be fascinating to have pathological insights from the patients who have DES implanted and survive, but this is of course impossible to acquire, although angiography can provide some insights into endotheialization and healing in vivo (12).

An intriguing comparison that is, unfortunately, not directly reported is that between patent DES (from the seven patients who died of noncardiac causes) and BMS. From the figures quoted in the report, the difference between these two groups is less marked than the comparisons involving thrombosed DES (fibrin score 1.9 ± 1.1 in patent DES vs. 0.9 ± 0.8 in BMS vs. 3.0 ± 0.9 in thrombosed DES, percentage of endotheialized struts 66.1 ± 25.4% in patent DES vs. 89.8 ± 20.9% in BMS vs. 27.1 ± 25.9% in thrombosed DES). In our minds, although these results are not commented on by the authors, they are in our opinion, one of the most interesting findings of the study, namely that after DES implantation patients fall into one of two groups; those that undergo healing (albeit delayed in comparison with BMS) and, of greater concern, those that exhibit minimal healing and remain at risk of late thrombosis. The challenge now is how to identify and deal with these patients. Is it just a matter of disease complexity such that the greater the number of stents implanted in anatomically challenging situations such as long, calcified, ostial, or bifurcational lesions decreases the chance of healing? Or, is it a complicated interplay of patient-related factors such as genetic control of inflammatory responses or the individual’s response to sirolimus or paclitaxel that governs the healing response? A further consideration is the relative interplay of drug and polymer in the biological responses to DES. It has been postulated that hypersensitivity observed after DES is more likely to be a reaction to the polymer than the drug, particularly for immunosuppressive sirolimus (13). The advent of nonpolymer DES (14) and bioabsorbable polymer DES (15) may help to clarify this issue, but for the time being, the answers to all of these questions remain beyond us. However, with the majority of DES now being implanted in situations that have not been evaluated in major outcome trials (10), this issue is a pressing one.

In light of their results, Joner et al. (11) advocate prolonged dual antiplatelet therapy for patients at high risk of late thrombosis, but how are we to identify these patients? We are currently not confident in our ability to identify patients prone to stent thrombosis and are not optimistic that forthcoming trials will provide the data we need. Perhaps instead the field will take a leap forward with the introduction of new generation DES with improved biocompatibility, better healing, and less late thrombosis. For the time being, we are now in a situation in which we know late thrombosis in DES exists, often with catastrophic consequences for the individual patient but, thankfully, it seems to be a rare event for our patient population as a whole.

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