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EDITORIAL COMMENT

Stent Thrombosis

The Effect of Intention on Perception*

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Since the presentation of meta-analyses by Camenzind et al. (1), Nordmain et al. (2), and the BASKET-LATE (Basel Stent Kosten Effeckivitats Trial–Late Thrombotic Events Trial) study and registry (3) at the European Society of Cardiology (ESC) meeting in 2006 (popularly known as the "ESC firestorm"), the world has been increasingly aware of the potential for late stent thrombosis (LST [30 days to 1 year]) or very late stent thrombosis (VLST [>1 year]) with drug-eluting stent (DES) implantation, and the possibility that said entity can present as an acute myocardial infarction (4,5). In the interest of sober reflection, it may be useful to briefly reconsider the history leading up to and from that sentinel event (the ESC, not LST or VLST).

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When balloon angioplasty (percutaneous transluminal coronary angiography) was in its infancy (late 1970s and 1980s), it was applied to ~5% of ischemic patients, with expected success rates of 60% to 65%. Success was a <50% angiographic residual. Acute occlusive syndromes led to ~5% emergency coronary artery bypass graft (CABG) procedures, and surgical standby was universal. Early repeat trips to the laboratory occurred in 5% to 10% of cases; and restenosis over the first 6 months occurred in upward of one-third of cases (6).

Bare-metal stents (BMS) did not (as is often implied from the simplistic reading of randomized trials) simply lead to the reduction of restenosis from approximately one-third to one-fourth or one-fifth of cases (depending upon patient selection and technique, among other factors). The BMS provided a means of treating most acute occlusive syndromes (dissection flaps, spasm, and recoil), virtually eliminating emergency CABG and surgical standby (accordingly, to say stents have never been shown to reduce mortality is analogous to arguing that parachutes have never been demonstrated to reduce mortality for sky divers). The BMS also provided major improvement in acute success (<20% vs. <50% residual) quickly (decreased X-ray dye and X-ray exposure), allowed for more aggressive lesion anatomy selection (broadening the scope of percutaneous coronary intervention), and reduced restenosis (7).

However, BMS were initially associated with stent thrombosis of 3% to 10%, until operators learned of the benefits of high-pressure inflation, intravascular ultrasound control, and dual-antiplatelet therapy (meaning, aspirin plus thienopyridine, especially as opposed to the use of dextran and coumadin) (7–11).

Since the ESC firestorm, the Swedish media's reference to "ticking time bombs" in patient's chests, and cardiac surgeons' claims that 6,500 preventable deaths per year could be attributed to application of percutaneous coronary intervention to patients who should receive CABG, 2,200 preventable deaths per year derived from LST, and $7 billion per year being spent in 2006 on thienopyridines (dual-antiplatelet therapy) "whose only rationale was the prevention of an iatrogenic disease" (LST), the world first learned of the subtle differences between patient based meta-analyses and -regression (from published mean data). It turned out that the available evidence did not support an increase in long-term mortality from the use of DES rather than BMS (12–14).

Additionally, clinicians began to recognize acute infarctions in patient with LST, from BMS implantation (15). Some actually recalled treating acute infarctions in patients with both early and late occlusion of bypass grafts.

Others came to recognize that in addition to cessation of prescribed antiplatelet agents, and the "usual anatomic, and clinical suspects" (long lesions, small vessels, inadequate acute results, diabetes mellitus), patient behaviors such as continued tobacco use or cocaine use or failure to comply with statins seemed to pop up among patients needing a late-night treatment for LST (16).

In this issue of the *Journal*, Lee et al. (17), operators from a high-volume center in South Korea, reported 30 cases of very late (>1 year) stent thrombosis that accumulated over a 5-year period, and all presented as acute myocardial infarctions (17). This important complication occurred with both BMS (7 cases) and DES (23 cases). Unfortunately, we are not given the denominators of patients treated during this period with BMS or DES, or potential selection biases and/or methodological differences, which might allow any meaningful comparison of the rates. The accompanying intravascular ultrasound data support mechanistic differences; specifically, late stent malapposition only occurred among the 23 cases of DES-associated VLST, not the 7 cases associated with BMS (17).

Limitations of this study derive from the fact that it is a retrospective registry; as such, it is subject to potential selection biases, information biases, and confounding (18). Additionally, it comes from a single, albeit large and busy, center. It is possible to set up prospective registries with

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pre-defined patient selection and well-defined outcomes, and the Food and Drug Administration has "encouraged" such registry development as part of the conditions for approval of new DES. Alternatively, some form of long-term registry is the only practical means of assessing a relatively infrequent complication. In other words, the advantages of reduction/elimination of the impact of known and unknown confounders, which derive from a well-done randomized allocation, is not practical for the kinds of numbers needed to track a late and infrequent adverse outcome.

How you will read these data will be influenced by what you want to do with them. I read them to mean that both BMS and DES, with or without dual-antiplatelet therapy, are subject to potential late thrombosis. I would hasten to point out that so can saphenous vein grafts and arterial bypass conduits. It is important for us to remember that every tentative step we take to help patients necessarily involves potential risks to harm them.

To paraphrase my late mentor, J. Ward Kennedy, this proves what I have always said: Caregivers should consider "medically refractory" ischemia as the primary reason to consider revascularization, generically (19). Interventionists and noninvasive cardiologists should consider the CABG alternative, including consideration of its morbidity (20). The importance of optimal medical therapy before and after either revascularization strategy is re-emphasized (20). Optimal PCI technique, including the appropriate use of intravascular ultrasound and adjunctive pharmacology (which continues to improve daily), is also emphasized by the recognition of late complications (21). Nothing, nothing, nothing—not statins, not angiotensin-receptor blockers, not beta-blockers, and most assuredly, neither BMS nor DES nor bypass grafts—constitutes either a cure for coronary artery disease or is risk free (20,21).

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