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The Drama of Drug-eluting Stent Thrombosis: Dr. Jekyll and Mr. Hyde

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Long as the introduction of percutaneous coronary intervention (PCI), restenosis has always been the stumbling stone of this innovative therapeutic technology [1-3]. As such, the arrival of drug-eluting stents (DES) in scene has offered what initially seemed to be the long-waited solution to this troublesome sequel of everyday practice. Indeed, very early following FDA approval of first-generation DES in 2003, these devices have convincingly reshaped the landscape of interventional cardiology that the Healthcare Systems took a bold initiative of assigning impressively high reimbursements to account for their extraordinary cost. It was a short halcyon period during which interventional cardiologists were anxious of being deemed guilty if they did not offer their patients the so-called 'smart' stent whenever technically feasible. Then, with the fall of 2006, the winds began to shift with alarming reports raising concerns about disturbingly higher rates of very late (after one year) stent thrombosis associated with the use of DES as compared with bare-metal stents (BMS). The media flashed the red light particularly with some evidence suggesting that relative to other acute coronary syndrome events, DES thrombosis was associated with substantially higher mortality and morbidity. Albeit infrequent, almost all cases developed a myocardial infarction, and one-tenth to one-third of cases died [4]. Soon the FDA assigned an expert panel to review evidence available from an array of sources, and in December 2006, the panel expectedly announced that there was an evidence for a small – though insignificant – increase in stent thrombosis events following DES [5]. However, evidence was far from clear, and intuitively, further evidence was still needed especially given the rare nature of the event that made all the available reports statistically underpowered.

Attempts to quantify such a rare-by-nature event would reasonably require increasing the number of patients, and/or protracting the length of follow-up. Hence, meta-analyses were called into action. One of these, performed by Stone et al, pooled data from 9 randomized trials (5261 patients) comparing DES versus BMS [6]. They demonstrated the incidence of stent thrombosis to be almost identical between the two stent types during the first year of follow-up (0.6%), nevertheless, between 1 and 4 years, that incidence was much higher with DES (0.5% versus 0.1%). Published in the same year 2007, Mauri et al provided a meta-analysis of 8 of these same trials; this time adjudication of events from patient-level data was based on the newly introduced Academic Research Consortium classification of stent thrombosis [7]. Ultimately, they concluded that the 4-year incidence of definite or probable stent thrombosis was similar for sirolimus-eluting stents as compared with BMS (1.5% versus 1.7% respectively) as well as for paclitaxel-eluting stents versus BMS (1.8% versus 1.4% respectively). Interestingly, almost one-half of these events occurred very late with DES in comparison with around one-third such events following BMS. Yet, evidence of the aforementioned meta-analyses stems from randomized controlled trials performed under the heavy constraint of long lists of exclusion criteria which might have not actually reflected real-life practice. In this regard, registry data would work well. Daemen et al reported a large-scale real-world registry from two high-volume centers with an average follow-up of 1.7 years [8]. In this, the cumulative rate of definite stent thrombosis was 1.1% early following the procedure (within one month), whereas thereafter, it occurred at a constant annual rate of 0.6% per year.

On the other frontier, the key advantage of DES is significant reduction of restenosis, translated clinically into major reduction of target vessel revascularization (TVR). Weighted evidence from randomized trials demonstrated TVR rates to be cut-off by one-half to two-thirds with DES as compared with BMS at 5 years follow-up, amounting to roughly 10-15% need for TVR following DES at long-term [6,9]. Whether one can accept the trade of extra non-fatal TVR for a much smaller risk of stent thrombosis that could result in death of myocardial infarction was the theme of a decision-analytic model by Garg et al. [10] comparing DES with BMS in terms of quality-adjusted life expectancy. Eventually, they concluded that the threshold excess risk of very late stent thrombosis with DES versus BMS, above which BMS would be the preferred strategy, is only 0.14% per year (over 4 years follow-up). However, two important parameters stand out as chief determinants of the outcome of their model: the incidence of TVR following BMS and the length of time over which DES continues to pose an excess risk of stent thrombosis. Therefore, one should be more ready to accept higher levels of risk of very late stent thrombosis offended by DES in patients with a higher risk of restenosis and subsequent TVR. Conversely, the longer we believe that the risk of very late stent thrombosis will persist, the higher the impetus to favor the use of BMS. It is noteworthy that this model did not consider the possibility that extended use of dual anti-platelet therapy beyond one year after PCI might help protect against the excess risk of stent thrombosis associate with DES, albeit at the cost of extra major bleeding events [11]. Obviously, this latter has 'pushed' the world's foremost authorities of guidelines to extend the duration of dual anti-platelet therapy following the implantation of first-generation DES up to one year, and might ultimately 'push' the guidelines' committees to recommend continuing the 'drug-dependant' state, indefinitely. Under these circumstances, surgery needing discontinuation of this therapy would pose an imminent risk of a 'hard endpoint'. Do patients then comply with extended prescriptions of dual anti-platelet therapy? A recently reported randomized study employing DES has shown that the proportion of patients receiving dual anti-platelet therapy at 24-months follow-up was 59.4% and 63.9%, for everolimus eluting and paclitaxel eluting stents, respectively [12].

At the end of the day, the patient, the ultimate 'client' of this market, should be actively indulged in the decision-making process. Do we honestly supply our patients with comprehensive and up-to-date information about our 'product', DES? Do all patients who receive DES on elective basis have a clear background on the small but long-lasting risk of stent thrombosis, and probability of having a 'serious event' as a result? Are they regularly made aware of the pros and cons of what they will 'hold inside'? And what about the safety and efficacy profile of new-generation DES already 'in duty'? Make no mistake,

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arguments of clinical equipoise between the available drug-devices will remain, and undoubtedly, will continue to provide a potential venue for future research.

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