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EDITORIAL

Drug-Eluting Stent Thrombosis: An oversensationalized but unresolved problem?

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Bare metal stent (BMS) restenosis was the 'Achilles Heel' of percutaneous coronary intervention (PCI) and when drug-eluting stent (DES) trials showed dramatic reductions in restenosis and target-lesion revascularisation, they were widely embraced [1-4]. Interventional cardiologists now had a therapy that could provide patients with a durable percutaneous revascularisation option and DES were enthusiastically adopted and soon used in 80% of PCIs in the US and some European Centres [5, 6]. Consequently, the indications for stenting were pushed further and further into uncharted territories. Patients and lesions that were previously considered the realm of cardiac surgery soon became daily practice for interventional cardiologists. Significant improvements in short- and mid-term outcomes compared to BMS have continued to be observed in real world experiences [7-9]. As the penetration of DES continued into patient and lesion subsets not formally tested in randomised trials, an entity characterized by sudden occlusion of the drug-eluting stent with an associated acute clinical syndrome was occasionally detected. The term late stent thrombosis was introduced to define this relatively new phenomenon, sometimes described with BMS as well. The absolute risk of stent thrombosis appears to be less than 2% throughout the first 3 years after stent implantation [6]. DES thrombosis has provided us with a moment for pause to reconsider how to best use these new devices and what to expect from future ones.

Stent thrombosis had been well recognised as a complication in the first 2 weeks after BMS implantation but as extremely rare after the first month. Double antiplatelet therapy (i.e. aspirin plus clopidogrel or ticlopidine) was shown to be extremely effective in reducing BMS thrombosis [10, 11]. Even though the individual randomised trials did not show an increase risk of stent thrombosis, death or myocardial infarction up to 1 year after implantation, sporadic reports were increasing seen in the literature of late stent thrombosis occurring even 1 to 2 years after DES implantation. The initial fervour for DES was suddenly dampened last year by the publication of a relatively small randomised trial (BASKET-LATE) and the presentation of a meta-analysis at the European Society of Cardiology meeting in Barcelona, both of which suggested an increase in the risk of death and myocardial infarction with DES compared to BMS [12, 13]. This has stirred up considerable debate and controversy about the safety of DES to such an extent that an entire issue of The New England Journal of Medicine (March 8, 2007; Volume 356, Number 10) and numerous sessions at every recent cardiology conference have been dedicated to the subject.

The studies suggesting that DES may be associated with an increased risk of late thrombosis and death have been limited by: small sample sizes thus making them underpowered to detect differences in a rare event; absence of concurrent controls; and inadequate follow-up periods. In addition there are doubts concerning the methodology used in some studies such as the BASKET-LATE and the SCAAR Study Group report [12, 14]. In both studies there were no overall differences in event rates at the end of the follow-up period and significant differences were only detected when the analysis was limited to the events occurring after 6 months. Furthermore, some of the information which grabbed headline attention was limited by a lack of access to the original source data, thus relying on limited published results, abstracts and online information. Another difficulty in interpreting the literature has been the lack of a uniform definition of stent thrombosis. As a result of these shortcomings, 2 new independent patient-level meta-analyses of the four pivotal randomised sirolimus-eluting stents (SES, Cypher, Cordis, Miami Lakes, Fla) trials and the five pivotal randomised paclitaxel-eluting stents (PES, Taxus, Boston Scientific, Natick, Mass) stent trials have been performed and recently published [15, 16]. The analysis performed by Stone *et al*. [15] demonstrated that, the overall incidence of stent thrombosis at 4 years does not differ significantly between.

DES & BMS (1.2% with the SES vs. 0.6% with BMS, p=0.20; 1.3% with PES vs. 0.9% with BMS, p=0.30). However, the time distribution of these thrombotic events appears to differ and both SES and PES are associated with a small but significant increase in the incidence of late stent thrombosis between 1 and 4 years after implantation (0.6% with SES vs. 0% with BMS, p=0.025; 0.7% with PES vs. 0.2% with BMS, p=0.028). It is uncertain why these increased rates of stent thrombosis seen more than 1 year after implantation did not translate into higher rates of death or myocardial infarction in the randomised studies, especially considering that stent thrombosis is associated with higher rates of morbidity and mortality. It may be that the sample size in these studies was not large enough to detect small differences between the treatment groups in a rela-

tively rare event such as stent thrombosis. An additional and somewhat overlooked alternative explanation may be that the increased rates of death or myocardial infarction due to DES thrombosis may have been offset by a reduction in adverse events associated with in-stent restenosis and repeat revascularisation [6]. There is increasing evidence that in-stent restenosis is not as benign a process, as previously thought, and may present as an acute myocardial infarction in up to 10% of cases [17, 18]. It also important to note that the protocol definition of stent thrombosis in most trials censored thrombotic events that occurred after target-vessel revascularisation. Since patients with BMS are more likely to require re-intervention for restenosis, thromboses occurring in these patients are censored more frequently, thus lowering the thrombosis rate after BMS implantation, and introducing a bias against DES. The second patient-level pooled analysis by Mauri *et al*. [16] included the thrombotic events occurring after the treatment of restenosis, and found no differences in the overall incidence of stent thrombosis between DES and BMS during 4 years of follow-up.

Stent thrombosis definition

A major difficulty in interpreting, comparing and collating published reports of stent thrombosis has been the lack of a uniform definition. The current debate around stent thrombosis has resulted for the first time in a widely accepted definition, as proposed by the Academic Research Consortium (ARC) [16, 19]. Stent thrombosis is classified by the ARC definition as definite, probable, or possible and as acute (within 24 hr), subacute (24 hr to 30 days), late (31 to 360 days), or very late (>360 days) (See table). The main limitation of the ARC definition arises when DES are implanted in multiple vessels. In patients who receive a DES in all major coronary arteries, any subsequent myocardial infarction during the follow-up period will be labelled as "probable late thrombosis".

Antiplatelet therapy following DES implantation

A major part of the controversy and uncertainty around DES thrombosis has been on the role and duration of dual antiplatelet therapy in preventing it. Current product labelling recommends dual antiplatelet therapy for 3 months after SES and 6 months after PES implantation. Although premature discontinuation of such therapy is associated with an increased risk of stent thrombosis, the optimal duration of double antiplatelet has not yet been precisely determined. Thus current guidelines recommend that after DES implantation, dual antiplatelet should be continued for at least 12 months in patients who are not at high risk of bleeding, and aspirin be continued life-long [19-21]. Nevertheless, DES thrombosis may occur despite continued double antiplatelet therapy and currently a large amount of research is being conducted into studying if aspirin and clopidogrel resistance may play a part, and if a point-of-care assay for clopidogrel resistance would decrease some of these events.

Different DES: not all the DES are equal

There are currently at least 6 DES platforms with CE mark approval. These stents have varying efficacies and possibly also varying risks of stent thrombosis after implantation. Operators have to decide not only between whether to implant a DES or BMS, but also which DES to choose as it appears that not all DES are created equally. Although, the underlying concept of a DES is that it elutes an active substance which has antiproliferative and/or cytostatic effect, these drugs have different mechanisms of actions and in vivo efficacy. In addition these drugs are applied to different stent designs and are combined with different polymers to control their release. Thus, we will not only have to know the efficacy of each of these DES but we will also need to know the risk of late and very late thrombosis with each of them. It may be feasible, in a particular patient or lesion, to choose a DES which may not have the best efficacy in reducing late loss, but

Table - Academic Research Consortium (ARC) Proposed Definitions of Coronary Stent Thrombosis

- **Definite**
  - Acute coronary syndrome AND

  Either
  - Angiographic confirmation of stent thrombosis or occlusion

  Or
  - Pathologic confirmation of acute stent thrombosis
- **Probable**
  - Acute myocardial infarction involving the target-vessel territory without angiographic confirmation of thrombosis or other identified culprit lesion
  - Unexplained death within 30 days
- **Possible**
  - Unexplained death after 30 days

that has a lower risk of thrombosis or requires a shorter course of dual antiplatelet therapy. A current example is the Endeavor zotarolimus-eluting stent (Medtronic Vascular Inc., Santa Rosa, California) for which only 3 months of dual antiplatelet therapy is currently recommended. In a head-to-head comparison with SES, the Endeavor stent was associated with greater late lumen loss and angiographic restenosis [22]. However, in a recent combined safety analysis of the Endeavor clinical trial program, presented by Dr J Fadajet at the American College of Cardiology Scientific Sessions 2007, there have been no cases of late stent thrombosis (using the protocol definition) in over 1000 patients up to 2 years after implantation of the Endeavor zotarolimus-eluting stent.

It is imperative that clinicians consider the risk:benefit ratio of a DES over BMS for each individual patient (i.e. an assessment of the balance between the risk of restenosis versus the risk of thrombosis). However, correct patient selection for DES not only involves assessing whether a patient has an indication for DES but also if a contra-indication to DES implantation exists. In light of DES thrombosis, this involves assessing the patient's ability to comply with 12 months of dual antiplatelet therapy. Factors contributing to dual antiplatelet therapy discontinuation that need to be considered include: risk of future bleeding, need for a surgical or invasive procedure within 12 months of receiving a DES, and socio-economic factors (such as education level, costs of thienopyiridines, understanding of instructions, and mis-information from healthcare professionals).

Mechanisms and Risk Factors of Late Stent Thrombosis

The mechanisms of late stent thrombosis are not completely understood and involve a complex interplay of procedure-related, patient-related, lesion-related, and stent-related factors [23]. Potential causes include delayed or incomplete endothelialisation, late polymer reactions, strut fractures, positive remodelling with stent malapposition, and new plaque rupture either adjacent to or within the stented site, among others [15, 23] Registry studies have identified a number of patient and lesion characteristics that are associated with an increased risk of DES thrombosis [19, 21]: a) Patient-related risk factors: dual antiplatelet therapy discontinuation, diabetes, acute coronary syndrome/myocardial infarction, low ejection fraction, renal failure, prior brachytherapy; b) Lesion-related risk factors: bifurcations (one or two stents), longer stent length, small vessels and small stent diameters, suboptimal stent results (residual dissection, stent underexpansion, stent malapposition). These factors may also have a differential risk of stent thrombosis at different time periods after DES implantation [23]. From this list of risk factors it is clearly apparent that there are at least 2 factors which are potentially correctable, i.e. the stent implantation technique and discontinuation of dual antiplatelet therapy. It has become more important now than ever before that meticulous attention is paid to DES implantation technique, especially in complex lesions. Premature discontinuation of dual antiplatelet therapy appears to be the most powerful of these risk factors, although there is considerable uncertainty as to what constitutes premature discontinuation. Our data, presented at the Transcatheter Cardiovascular Therapeutics Conference (TCT 2006) in Washington DC last year, suggests that the risk of developing a thrombotic event associated with discontinuation diminishes after 6 months from DES implantation. However, we continue to advise 12 months of dual antiplatelet therapy in our patients [24]. Even though these factors are useful when assessing the risk:benefit ratio of DES in an individual patient, there are no data currently to suggest that prolonged or life-long double antiplatelet therapy is beneficial in preventing DES thrombosis in these 'high risk' patients. Also it is important to recognize that the same subgroups of lesions and patients who may be at a higher risk of stent thrombosis (e.g. long lesions, small vessels, diabetes, bifurcations) are also at a higher risk of restenosis and thus may have the greatest benefit from DES. Furthermore, it is worth noting that while we may be able to identify patient and lesion characteristics associated with a higher risk of subacute thrombosis (within 30 days), we are currently unable to effectively identify any specific characteristic associated with a higher risk of late stent thrombosis after 6 months.

The issue of late stent thrombosis after DES implantation has been oversensationalized with attention grabbing headlines in the lay press. Thus, it is important to re-emphasise that while very late (>1 year) stent thrombosis rates are probably higher with DES, the risk of having this event is quite low (0.6%-0.7%) [15]. Also overall death and myocardial infarction rates have been similar to those of BMS in the pivotal randomised trials up to 4 years after implantation. However, there remain a number of unresolved issues as regards to DES thrombosis, i.e. mechanisms of ST, identifying high risk patients, duration of dual antiplatelet therapy and prevention of stent thrombosis. Furthermore, the randomised trials studied DES in discrete, previously untreated lesions in native coronary arteries. Currently, about 60% of DES use is in lesions more complex than studied in the initial randomised trials and there is some concern that this "off-label" use may be associated with an increased risk of stent thrombosis. On the contrary, we should not let the current debate overshadow the benefits of this technological advancement and its persistent reduction in target-lesion revascularisation as compared with BMS, even in the most complex of coronary lesions. However, DES thrombosis has identified a shortcoming of the first generation DES platforms and currently a number of second generation DES are being studied. The current concerns about stent thrombosis have also affected how future DES will be judged and how future DES trials will be conducted. For a new DES platform to gain worldwide acceptance, it will no longer be sufficient to show improvement in efficacy endpoints, especially of surrogate end points such as late loss, but future studies will have to focus on safety endpoints and show no increase risk of death and myocardial infarction.

Until we develop new DES that do not carry the risk of thrombosis, it will require the collective effort not only of interventional cardiologists implanting DES but also importantly of physicians, dentists, surgeons and other healthcare professionals involved in the care of patients implanted with DES. Thus, in conclusion, we would like to offer some practical advice [5, 6, 19, 21].

1. The most important advice is recognition that DES thrombosis is a potentially devastating condition when it occurs and should be always be considered in patients with DES presenting with acute myocardial infarction in the territory of a DES implanted up to 4 years previously.
2. The correct management of suspected stent thrombosis is referral for urgent coronary angiography and percutaneous coronary intervention.
3. Stent thrombosis is often related to stopping of dual antiplatelet therapy prior to an invasive, dental or surgical procedure.
4. Encourage compliance with 12 months of dual antiplatelet therapy and keep patients informed of risks of stopping. Don't stop antiplatelet therapy prematurely without first discussing with the patient's cardiologist.
5. Many invasive procedures can be performed safely without interruption of double antiplatelet therapy.
6. Elective procedures that carry an increased risk of bleeding should be delayed until a month after the ideal course of dual antiplatelet therapy (12 months post DES implantation; 1 month post BMS implantation).
7. DES recipients requiring urgent or elective procedures mandating cessation of dual antiplatelet therapy should continue on aspirin if at all possible, with the thienopyridine restarted as soon as possible after the procedure. There are no data currently for "bridging therapy" while dual antiplatelet therapy is temporarily suspended. Some experts have suggested using short-acting intravenous glycoprotein IIb/IIIa inhibitors or enoxaparin peri-operatively when the patient is not protected by clopidogrel.
8. There is no evidence to suggest that patients who have received a DES and have completed and discontinued their course of dual antiplatelet therapy without incident should restart a thienopyridine. These patients should remain on aspirin indefinitely for secondary prevention.

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