STENT THROMBOSIS AFTER DRUG ELUTING STENTS: MECHANISMS AND PREVENTION

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First-generation drug-eluting stents (DES), which release an antiproliferative compound via nonbioerodable polymers, reduce the incidence of angiographic in-stent restenosis and repeat revascularization [1-12]. Since the publication of the first randomized trial comparing a DES with a bare-metal stent (BMS) in highly selected patients and lesions [1], the use of DES in clinical practice has expanded to include most coronary lesion subsets and high-risk patients (e.g. with multivessel disease or diabetes) [4-5,9-12] and, more recently, to primary percutaneous coronary intervention (PCI) for ST-segment elevation acute myocardial infarction (MI) [13,14]. Simultaneously, late stent thrombosis (LST), although rare, started to be described in case reports as causing acute MI or death [15-18], and emerged as a cause for concern with first-generation DES [19]. Subsequent randomized trials, pooled analyses, and registries reported an increased incidence of late (>1 year) clinical events (MI and death) in the overall population and in subgroups treated with DES versus BMS [19-24], whereas other pooled analyses found no such significant differences [25-27].

In view of these diverging results, many databases have been scrutinized retrospectively for the incidence of stent thrombosis, MI, and death. According to the original protocol definition of LST (occurring >30 days after the index procedure, angiographically confirmed, and after exclusion of target-lesion-related re-intervention), an increased incidence of LST was observed [25-28].

Subsequently, new definitions were introduced by the Academic Research Consortium (ARC), an informal collaboration between academic research organizations in the United States and Europe, to (re)define stent thrombosis with the objective of capturing all events and to encourage use of uniform terminologies. This definition includes three temporal categories: acute (<30 days), late (30 days to 1 year), and very late (>1 year); and three levels of evidence: definite, probable, and possible [29]. Further, the inclusion of all target-lesion-related re-interventions was proposed [29]. Within the defined criteria, MI

was considered as a "probable" manifestation of stent thrombosis, while unexpected death (>30 days after the index procedure) was considered as a "possible" manifestation of stent thrombosis [29]. The combination of "definite" and "probable" has been recommended as the best way to characterize DES safety [29]. Revisiting a pooled analysis [20] using the ARC definitions resulted in an overall increase in rates of stent thrombosis, with a nearly identical combined incidence in DES and BMS, and a trend towards more very LST with DES [30].

Independently of the definition changes of stent thrombosis and the debate concerning its clinical consequences, the goal of this presentation will be to focus on the primary mechanism leading the vascular substrate for LST.

BMS or 'light' DES systems may not differ acutely in their vascular reaction as compared to 'potent' DES, so called 'first' generation DES. However, on the long term they will allow a quietscent healing response. On the contrary, as documented also in the literature, 'potent' DES appear to induce a long term site-specific inflammatory reaction after DES deployment [16,18]. This site-specific vascular response, in the presence of systemic triggers, can activate local pathophysiologic mechanisms responsible for LST [19] (see Figure 1).

The understanding of the similarities of the acute phase after any intravascular intervention and the dissimilarity of the long term phase in accordance to the used device is the key to understand the difference among BMS and DES as well as the difference among different DES types (light versus potent).

The potential ways to avoid or to palliate for this novel, iatrogenic clinical entity will focus on two issues: stent related and antiplatelet related issues.

Concerning different DES systems, one can clinically observe that potent DES systems have shown strong antiproliferative properties in various lesion/patient subsets, associated with marked reductions in restenosis and revascularization rates [1-5]. However, there may be an incremental risk of (very) LST with SES [20], likely associated with delayed or incomplete healing [31], potentially raising longer-term safety concerns [19]. Conversely, the light DES systems appear not to be associated with any excess in LST compared with BMS [32], yet its efficacy and performance relative to other DES as measured

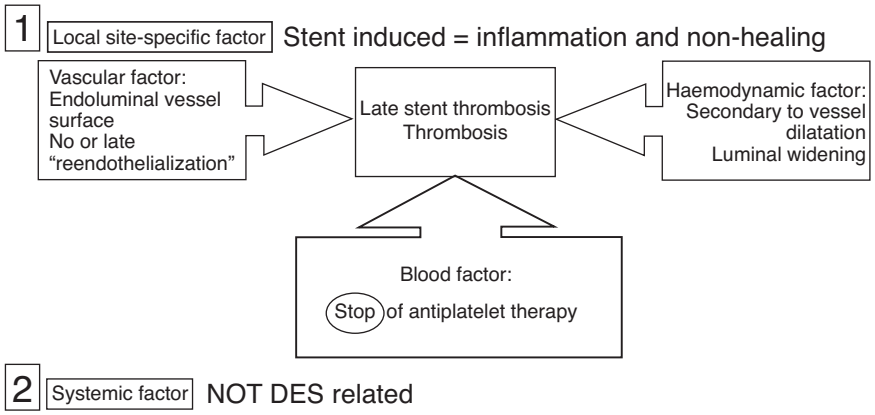

Fig. 1. Stent related and systemic mechanisms inducing late stent thrombosis.

by angiographic metrics, particularly in lesion/patient subsets with a high propensity for restenosis, has been questioned [33].

A further manner to modulate long-term outcome will be the selection, titration and duration of the antiplatelet therapy.

Pros and cons of the different strategies will be discussed.

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