

## EDITORIAL COMMENT

# Do We Know What Causes Very Late Drug-Eluting Stent Thrombosis?\*

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The Academic Research Consortium (ARC) divides stent thrombosis (ST) into early (within 30 days), late (30 days to 1 year), and very late (beyond 1 year). Intravascular imaging studies, to date mostly using intravascular ultrasound (IVUS), have provided clues with regard to the causes of ST—primarily by focusing on either early or very late ST, although each study usually includes a small number of patients with events between 30 days and 1 year. In this issue of *JACC: Cardiovascular Interventions*, the current study is similar in that 15 of 18 patients have very late ST with only 3 patients presenting earlier than 1 year (and those 3 at least 172 days) after implantation (1).

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The distinction between patients with early versus very late ST is important, especially after drug-eluting stent (DES) implantation. Studies should not combine these 2 groups of patients, because their fundamental mechanisms seem to be different.

The IVUS-identified causes or predictors of early ST are mechanical and procedure-related—primarily stent under-expansion and, secondarily, inflow/outflow problems, including a larger plaque burden, a small lumen area, and/or a large dissection at either stent edge. Notably, despite the lack of supporting evidence, many physicians still believe that acute malapposition is an important cause of early ST.

Conversely, intravascular imaging findings in patients with very late ST after DES implantation are: 1) large areas of late stent malapposition primarily from positive remodeling or frank aneurysm formation (2–4); 2) vessel wall inflammation—inferred from intracoronary aspirates (5);

3) in-stent neo-atherosclerosis with plaque rupture (6); and 4) strut fracture (7). With optical coherence tomography (OCT) Guagliumi et al. (1) add to this list by showing that very late ST is associated with uncovered DES with 12.3% uncovered struts/patient and 72% of patients having at least 1 cross-section with >30% of the struts uncovered with neointima, the metric established by histopathology to separate late/very late ST from control subjects (8).

It seems that the influence of mechanical and procedure-related factors decreases over time, comparing studies of early/late versus late/very late ST, whereas biologic mechanisms begin to emerge during the late ST period. To this end, studies show that the minimum DES area in very late ST patients is no different from matched control subjects (it important to use the absolute minimum stent area rather than stent expansion—defined as minimum stent area divided by the reference lumen area—because the latter ratio can be influenced by positive remodeling extending from the stent where it causes late malapposition into adjacent reference segments). The exact transition from mechanical to biologic causes of ST is difficult to pinpoint, because patients with ST between 30 days and 1 year are poorly represented in all studies of DES thrombosis and have never been studied separately.

Are there multiple causes of very late ST or are these findings inter-related? Strut fracture is more common in aneurysms (7,9), possibly the result of excessive motion and destabilization of stent strut geometry within the aneurysm. Late stent malapposition area correlates with total eosinophil count and eosinophil fraction, with an average increase of 5.4 eosinophils (2.6%)/1-mm<sup>2</sup> increase in malapposition area (5). Patients with ST and in-stent neo-atherosclerosis rupture also have late malapposition (6). Multiple IVUS and/or OCT findings are also seen in the 18 patients reported by Guagliumi et al. (1) and in 18 patients studied by Ko et al. (10) with OCT alone, and so on. Therefore, a plausible argument can be made that some of these findings are inter-related, that they are not causes but either markers of or at most contributing factors to ST, and that the main culprit is poor healing or inflammation within the DES-treated lesion that manifests itself as malapposition, lack of stent strut coverage, and so forth at 1 end of the spectrum and ST at the extreme other end of the spectrum.

Most ST patients do not undergo intravascular imaging to understand the underlying causes. Each of the cited (as well as other unlisted) studies reports only a modest number of patients studied with different protocols on the basis of different underlying hypotheses, inevitably leading to a range of findings and conclusions. Thus, there is a need for a global registry of ST patients studied under a unified protocol to better understand this phenomenon. Although second-generation DES are safer, millions of patients have received first-generation DES, and they seem to be at ongoing risk for very late ST.

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Is it necessary to do both OCT and IVUS to assess ST? Guagliumi et al. (1) are to be congratulated in using both OCT and IVUS in their study. However, this is expensive and not always practical—especially in the setting of an acutely ill patient with ST. Although IVUS is clearly superior to angiography because angiography lacks the resolution to assess mechanisms of stent failure, OCT is as good or better than IVUS in assessing potential mechanisms of late stent complications—both ST and restenosis. Optical coherence tomography can detect and quantify malapposition and measure minimum stent area, although the absolute numbers might differ from IVUS (1), detect in-stent neo-atherosclerosis and plaque rupture (11), assess and quantify stent strut neointimal coverage (1), and identify red and white thrombi (12). The 1 area in which IVUS is superior to OCT is in the assessment of vessel wall remodeling. Although the remodeling index by IVUS is an independent predictor of ST in an exploratory multivariable analysis in the Guagliumi study (1), it is not clear how much this adds to the understanding of very late ST or whether it is worth the cost, because positive remodeling is associated with >30% uncovered struts.

What does this mean for patients? This is the most relevant question, because there is growing evidence of the unacceptable rate of complications associated with excessive prolongation of dual antiplatelet therapy. When detected incidentally in prospective studies with routine follow-up, abnormalities seen in patients studied at the time of very late ST have not always been associated with an increased frequency of subsequent ST. For example, late stent malapposition is consistently seen at the time of very late DES thrombosis (1–7). Conversely, incidentally detected late stent malapposition during routine follow-up studies of DES-treated patients is not associated with an increased frequency of subsequent adverse events (13–16). Finally and as acknowledged by the authors, current OCT cannot determine the histopathologic composition of neointimal tissue; and the type of tissue might be as important as the presence or absence of tissue. However, even if the presence of at least 1 cross-section with >30% of the struts uncovered with neointima does not predict subsequent ST in prospective studies, the study of Guagliumi suggests that the negative predictive value of full stent strut coverage—as well as the absence of other abnormal imaging findings—might, in and of itself, be important and reassuring.

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