Editorial

Shedding light on stent thrombosis

Tawfiq Choudhury[1,2], Rodrigo Bagur[1,2], Ashlay A. Huitema[1,2], Amir Solomonica[1,2], Shahar Lavi[1,2]

[1]Department of Medicine, Western University, London, ON, Canada; [2]Division of Cardiology, London Health Sciences Centre, London, ON, Canada

Correspondence to: Shahar Lavi, MD. Department of Medicine, Western University, 339 Windermere Road, London, ON N6A 5A5, Canada.
Email: shahar.lavi@lhsc.on.ca.

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Stent thrombosis (ST) is a less commonly seen complication of percutaneous coronary intervention (PCI) with the current use of second generation drug eluting stents (DES), compared to previous stent platforms (1). It is likely to be multifactorial and includes patient related, lesion related, procedural and post-procedural factors. The importance of the various contributing factors to ST is variable depending on the time interval between the initial stent implantation and the occurrence of ST. Parallel to the improvements in new generation DES platforms, including thinner struts and more biocompatible polymers, the incidence of early and late ST has fallen. However, patients are exposed indefinitely to risk of very late ST with all stent platforms (1). Some platforms, such as first generation paclitaxel eluting stents display uncovered stents years after implantation, which increase this risk further (2). This highlights the temporal variance in causative factors in relation to occurrence of ST and the fact that stent design is likely to be only part of the solution. Although patient-related factors can be difficult to influence, a lot of attention has focused on ways in which procedural (i.e., stent implantation technique) and post-procedural factors can be modified to reduce the incidence of ST.

The cumulative incidence of definite ST at 3 years was 1.5% with bare metal stents (BMS), 2.2% with first generation DES and 1.0% with second generation DES (3). The mortality from ST is high and ranges from 11–42% according to various studies (4). In the PROTECT (Patient Related Outcomes with Endeavor versus Cypher Stenting Trial) pooled analysis, cumulative incidence of cardiac death at 4 years in patients with ST following implantation of a DES was 32.1% (5). When considering the total number of PCI performed worldwide, including the high number of BMS and 1st generation DES implantations in the past, the number of patients at risk is not negligible. But do we understand the mechanism behind this dangerous sequela of PCI?

Intracoronary imaging, particularly with optical coherence tomography (OCT), which has a higher resolution than intravascular ultrasound (IVUS), provides detailed mechanistic insights into the possible causative factors of ST. Due to the low current incidence of ST, recent studies using intracoronary imaging in ST patients have been small. Furthermore, a large proportion of patients with ST, present with ST elevation myocardial infarction (STEMI), and therefore intracoronary imaging is sometimes challenging to perform due to haemodynamic instability, time of presentation, or other factors. Conducting international, multicentre trials can also be difficult due to the lack of widespread availability of OCT. Bearing in mind the above limitations, there have been several observations over the recent years in patients with early [EST—ST occurring within 30 days and consisting of acute ST (AST)—ST <24 h and sub-acute ST (SAST)—ST >24 h but within 30 days], late (LST—>30 days and up to 1 year) and very late (VLST—beyond 1 year) ST

using OCT. The results have been varied. In a very small case control study the incidence of stent underexpansion was higher in patients with ST compared to patients without ST whether AST or SAST (6). In the PESTO registry, consisting of 120 patients with ST undergoing OCT at a median of 4 days after presentation, stent malapposition was observed in 48% and stent underexpansion in 26% of patients presenting with early ST (7). Thus, technical factors related to stent deployment are likely to be relevant to ST in the early phase post-stent implantation. In LST and VLST, previous studies have suggested neoatherosclerotic plaque rupture and malapposition as the most common findings in patients presenting with VLST (8,9). In the PESTO registry, ruptured neoatherosclerotic plaques were more common in BMS than in DES. It should be noted, that when malapposition is detected late, beyond 1 year it may be acquired due to positive remodelling possibly related to an inflammatory process and not due to suboptimal stent deployment (10).

Adriaenssens and colleagues (11) from the PRESTIGE group investigators recently published the results of OCT analyses of 217 patients presenting with definite ST. This is the largest case series on OCT in ST to date, performed in 14 European centres, and is the subject of this editorial. OCT was performed at the time of the acute presentation and analysed in a core lab in a blinded fashion. The PRESTIGE group are to be commended for undertaking such a rigorous study design. The OCT criteria used were in accordance with the agreed international working group consensus criteria (12). The majority of patients presenting to the registry were LST/VLST (71%) as compared to AST/SAST (29%). In either group, the main presentation was as STEMI (79% in AST/SAST and 72% in LST/VLST). The index procedure was undertaken in the context of acute coronary syndrome (ACS) in the majority (78.4%) of patients and notably, nearly two-third of patients had DES implanted and half the patients had newer generation DES implanted. A small number of patients with bioresorbable scaffolds (BRS) also presented with early ST. A quarter of patients (25.8%) in the EST group were not on dual antiplatelet therapy (DAPT). There was a higher incidence of diabetics in the EST groups compared to the LST and VLST groups. The dominant OCT findings in each group were as follows: AST—uncovered struts; SAST—uncovered struts and underexpansion; LST—uncovered struts and severe restenosis and VLST—neoatherosclerosis and uncovered struts. The prevalent theme in AST, SAST and LST were uncovered struts with a third of patients in the LST found to have persistent uncovered struts. Underexpansion was a major finding in the SAST group (25.5%) with a stent expansion index <0.8 in 65.8% of patients. Apart from uncovered struts, severe restenosis was the other dominant finding in the LST group (19.1%). In the VLST group, the major findings were varied according to stent type. In the BMS group, neoatherosclerosis was the dominant finding whereas, in DES, the major findings were uncovered struts and underexpansion in first generation DES and uncovered struts and malapposition in second generation DES.

The observation that uncovered struts were the dominant finding in AST and SAST, is not surprising as stents are not expected to be completely covered early following implantation. The finding of uncovered struts in the LST and VLST groups is likely secondary to delayed endothelialisation with DES. Patients with VLST or LST and uncovered struts on OCT might warrant an extended period of antiplatelet therapy beyond the standard six months or 1 year period of DAPT.

The other key observation in all groups was malapposition. This observation is in keeping with the results of the PESTO registry and other previously reported studies, including IVUS studies (6,13). Results from an autopsy study suggest incomplete stent apposition as an independent predictor of ST in EST (14). In the same autopsy series, the extent of intrastent necrotic core prolapse and medial tear were also independent risk factors for early ST. The majority of patients in the AST and SAST group were recent ACS patients. A recent *in vitro* study, using a malapposition stent model and porcine blood, showed a significantly higher rate of ST in the malapposed segment compared to the well apposed stent segment (15). Thus, along with adequate antiplatelet therapy, these findings suggest that optimisation of stent deployment and plaque coverage are essential in the acute setting. In the LST and VLST group, the occurrence of malapposition can be either late acquired or persistent (16). If acquired, it cannot be influenced by optimisation of stent deployment during the index procedure. Performing intravascular imaging during the index procedure and later assists in the differentiation between persistent and late acquired malapposition. With the low numbers of OCT at the time of index procedure in the study, it is unknown how many were late acquired.

Detecting malapposition on OCT during the presentation with ST can help optimize stent apposition at the time using balloon dilatation and avoiding further stent

implantation. However, one of the caveats of OCT, with its higher resolution, is that minor, non-clinically important malapposition is detected. Thus using standardised OCT criteria, as in the PRESTIGE group study, to detect and measure malapposition is essential to avoid heterogeneity in outcomes and over or under reporting. In the current study, malapposition was considered present when the axial distance between the luminal surface of the strut to the lumen contour was greater than the strut thickness (including polymer, if present) including a correction factor to account for strut blooming artefact. However, despite detecting malapposition, and albeit using strictly defined criteria, not all detected malapposition is likely to be clinically relevant. Is identifying any strut with malapposition clinically meaningful? Or is the length of malapposition and the malapposition distance likely to be more relevant? What degree of malapposition requires optimisation of stent apposition and influences patient outcomes? The answers to these questions remain unclear.

Although late acquired malapposition cannot be prevented at the time of index PCI, the OCT observation that 44% of patients had underexpanded stents, suggests that further optimization of stents implantation could have been performed. This is in agreement with other studies using OCT in post-PCI patients. In the DOCTORS (Does Optical Coherence Tomography Optimize Results of Stenting) multicentre, randomised study, 42% of patients had underexpanded stents post PCI in NSTE-ACS patients (17). Thus, underexpansion as detected by OCT appears to have a high prevalence post-angiographically guided PCI. Again, whether all OCT detected underexpansion is clinically relevant to ST is unclear. However, previous studies using intravascular imaging show better stent optimisation with both IVUS and OCT with the potential for lower definite ST at 1 year with intravascular imaging guided PCI (18,19). Thus, better stent optimisation using more intracoronary imaging during index PCI procedures is necessary. In the current study, only about 5% of patients underwent intravascular imaging during the index procedure. The low use of index-procedure OCT in the current, multicentre study which was conducted across several centres in Europe is likely to be representative of OCT use during routine PCI in real-world practice. Although, it is unknown if further imaging would have resulted in better outcome, it would likely result in further optimization of PCI technique. In the TOTAL-OCT study, OCT imaging post stenting in patients presenting with STEMI led to further intervention such as balloon dilatation or stent implantation in 42.5% of patients due to findings of significant edge dissection, stent malapposition, stent underexpansion, and significant residual disease (20). This resulted in larger final in-stent minimum lumen diameter, without affecting clinical outcomes (20). However, the sample size of this sub-study was underpowered to detect an effect on outcomes.

The VLST group had the largest number of patients, which reflects the persistent risk of VLST with all types of stents and related to the time from stent implantation. The lack of BRS in this group is likely due to the shorter duration from implantation. The finding of neoatherosclerosis in the VLST group using OCT demonstrates yet another application of OCT. Neoatherosclerosis is *de-novo* atherosclerosis within the implanted stent. The underlying pathophysiology is unclear but likely to be multifactorial including the lack of a fully functional endothelium within the stented segment (21). Neoatherosclerosis occurs earlier and more frequently in DES than BMS, but is present in both stent types and is an important substrate for VLST in both. Risk factors for neoatherosclerosis from observational data include smoking, chronic kidney disease, LDL cholesterol, lack of angiotensin converting enzyme inhibitor use and duration of implantation (22,23). Thus, aggressive secondary risk factor management in post-PCI patients and research in further modifications in stent design to reduce this unwanted pathological process are essential. Where patients present with ST, detection of neoatherosclerosis on OCT could guide management by indicating the need for further stent implantation where feasible.

The study by Adriaenssens *et al.* provides further insight into the mechanisms behind the rare yet dangerous complication of ST. The OCT observations can, however, only be taken as an association rather than a direct cause-effect inference. The general consensus appears to be that stent malapposition, underexpansion, uncovered struts, stent restenosis and neoatherosclerosis are the predominant mechanisms associated with ST. There are a few limitations of this study, which have already been alluded to by the authors.

To optimize results, the use of OCT imaging should, ideally, be more often performed during the initial PCI procedure. However, use of OCT is associated with further cost, time and potential adverse effects related to higher contrast use and prolonged procedure time (20). Further studies are required to investigate whether OCT-guided PCI alters not only the PCI technique, but also the incidence of adverse events, such as ST. In the meantime,

it is important to recognize that with the high sensitivity of OCT in detecting subtle, clinically irrelevant findings along with relevant ones, clinical discretion should be used at all times.

We highly recommend that OCT is performed in every case of ST to shed light on the mechanism of ST and guide potential therapy.

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Footnote

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