Editorial

Malapposed, uncovered, underexpanded—intravascular imaging lessons on coronary stent thrombosis

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Introduction

Three decades after the first stent implantation in a coronary artery, contemporary percutaneous interventional techniques have reached very high levels of efficacy and safety. Successive iterations in stent design—from bare-metal stents (BMS) to first and second-generation drug-eluting stents (DES)—have seen a progressive decline in the rate of stent associated complications. Albeit increasingly rare, stent thrombosis (ST) remains a catastrophic complication associated with severe morbidity and mortality. While overall rates of early and late DES-thrombosis have been halved from 3.0% to 1.5% due to advances in pharmacotherapy and stent design (1-3), in-hospital mortalities of patients suffering from ST still range from 3.6%, for very late ST, to 7.9% for acute and subacute ST (4). As a result, ST has received substantial attention in clinical practice and research.

Beside advances in stent-design and improved pharmacotherapy, pathological studies have advanced our understanding of the mechanisms underlying ST. Human pathology examination has improved the understanding of associations between various morphologic and histologic findings within the stented segment and ST. Nevertheless, the causes of ST are undoubtedly multifactorial and numbers of patients used in these types of analysis are limited. Accordingly, it remains unclear how significant these findings are in "real world" clinical practice. Given the complex interplay between patient and stent-related factors, understanding of the underlying conditions in the stented segment at the time of the ST event remains an important clinical need.

By providing near histology-level images, intravascular optical coherence tomography (OCT) has been used to describe vascular responses following PCI. Subsequently, OCT has been introduced to assess stent coverage and apposition, and detailed characterization of neointimal tissue and vessel wall pathology (5). Therefore, OCT imaging may be the best modality to determine specific underlying mechanisms in real time evaluation of ST events. The number of OCT-imaging studies in the specific setting of ST, however, is limited (6-9). Taking this into consideration, the results of an additional critical appraisal in this field, the report of the PRESTIGE Consortium (Prevention of Late Stent Thrombosis by an Interdisciplinary Global European Effort) in *Circulation* 2017, should be highlighted (10). Adriaenssens *et al.* present results from a prospective registry evaluating OCT imaging findings in patients presenting with ST in several centers in Europe.

The current study

The PRESTIGE registry represents the largest available series of patients with OCT imaging during ST presentation, including 231 cases. Patients presented with

early-, late- and very late ST. The majority, however, 71.4% of patients presented with late and very late ST, while 28.6% of patients presented with early ST. The underlying stent type was a new generation DES in 50% of cases. The predominant OCT findings were: underexpansion, uncovered stent struts, malapposition, and neoatherosclerosis. The frequency of observations varied according to the timing of ST, accordingly in patients presenting with early, late and very late ST. The rate of stent underexpansion was highest in patients with early (subacute) ST. As expected, uncovered struts were most frequently found in patients with early ST. Although, the proportion of uncovered struts decreased over time, uncovered struts still were reported in every fifth patient presenting with very late ST. Malapposition was a frequent finding in early ST, however was also reported in 14% of patients presenting with very late ST. Neoatherosclerosis was a relatively frequent finding in patients with very late ST, observed in almost one third of patients. The authors summarize: stent underexpansion and uncovered struts were most frequently observed in early ST and neoatherosclerosis was the predominant findings in patients presenting with very late ST.

Before considering potential implications of these findings, some methodological issues should be discussed. First, OCT imaging was performed in the acute setting of ST. Previous studies with deferred imaging strategies had been criticized, as a delay between PCI and intravascular imaging may affect the results (7,11). Nevertheless, a substantial number of patients presenting with ST are in instable clinical condition, additionally it is often impossible to restore blood flow without balloon inflation or even stent implantation, before acquisition of OCT images. In line with these considerations, the proportion of images with residual thrombus burden in this study was high, occurring in more than 95% of cases. Although, only 6% of cases had image quality that precluded further analysis, the high thrombus burden may impact the assessment of the underlying mechanisms of ST, especially in the detection of malapposed and uncovered stent struts.

Second, as the inclusion of patients presenting with hemodynamic instability was not recommended, this subgroup is most likely un-/under-represented in the current analysis.

Finally, the present study did not address the interaction between patient and lesion related factors. Although data on platelet function testing were available in 37% of patients, of which almost three quarters showed high platelet reactivity, data on antiplatelet treatment are only provided for the entire cohort. Therefore, the current study does not provide insights in the specific interaction of platelet reactivity and antiplatelet regime and the association with the etiology of ST in the individual patient.

Uncovered struts, underexpansion, malapposition and neoatherosclerosis

Vascular healing plays a central role in the risk for ST after coronary stent implantation. Autopsy series of patients with ST within BMS identified incomplete or uncovered stent struts as the underlying mechanism in the vast majority of cases (12). In line, endothelial coverage was the strongest histological predictor of late or very late ST within DES in a study by Finn *et al.* (13). In the PESTO registry (Morphological Parameters Explaining Stent Thrombosis assessed by OCT) uncovered struts (>20%) were frequently observed and accounting for almost 75% of cases of ST with no cause identified (7). Uncovered stent struts were a frequent finding in the PRESTIGE registry, with 33% in patients with late ST and 20% in patients with very late ST. In accordance with previous findings, the proportion of patients with uncovered stent struts was lowest in patients presenting with BMS-ST (7,10). Interestingly, there was no difference in the proportion of uncovered stent struts between patients presenting with ST in first versus second generation DES. This finding is in contradiction to OCT studies supporting a more favorable vascular response and improved neointimal coverage in second—as compared with first-generation DES (14,15).

Stent underexpansion is a well-recognized independent predictor of early ST in both, patients treated with BMS and DES (16,17). Retrospective registries with intravascular ultrasound (IVUS) imaging in patients with BMS-ST, report of stent underexpansion as the cause of early ST in more than every second case (18). Indeed, severe stent underexpansion is more common in subjects with early ST, suggesting that early and late ST have different underlying mechanisms (4,7,19). Underexpansion and acute malapposition occurs as a result of inadequate stent expansion during index PCI. Previous studies report malapposition as the main mechanism in the group of patients presenting with early ST (7,9). In this vein, an autopsy study has shown an association between suboptimal stent implantation in unstable lesions and ST (20), suggesting that improvements of implantation techniques and the reduction of malapposition may lead

to a reduction of early ST. Late-acquired malapposition, on the other hand, appears subsequent, as consequence of different mechanisms, including recoil, plaque regression and vessel remodeling mostly observed within DES. In the PRESTIGE registry malapposed struts were reported in 25% of patients presenting with early ST and in 14% of patients presenting with very late ST. These results might reflect the different mechanisms causing malapposition, depending on the timing of diagnosis by OCT.

Thrombotic events related to atherosclerosis and plaque rupture in native coronary arteries is accepted as cause of acute myocardial infarction and sudden death. Consequently, newly formed atherosclerotic changes, within the neointima above a stent, may contribute to thrombosis associated with stents. Although, neoatherosclerosis is observed in both DES and BMS, though there is an ongoing debate on differences in timing and frequency between BMS and DES. Overall, neoatherosclerosis seems to be observed more frequently and earlier in DES as compared with BMS (21). Neoatherosclerosis is associated with ST. Several OCT studies have confirmed that a majority of cases of very late ST in BMS and DES are attributable to neoatherosclerosis (22,23). This is in accordance with the findings of current OCT ST-registries, reporting neoatherosclerosis in up to every third patient presenting with very late ST (7,10). Overall, there is a growing body of evidence implicating that neoatherosclerosis is associated with ST especially in events that occur years after stent implantation. This underlines the importance of new considerations on therapies which target progression of atherosclerosis rather than solely the suppression of neointimal growth after coronary stent implantation. Given the growing number of patients presenting years or even decades after PCI, these concerns, will gain importance.

Clinical perspective

In 1991, one of the first studies reporting outcomes of patients undergoing PCI with placement of a self-expandable BMS reported ST rates as high as 25% (24). Although ST rates declined dramatically over the last decades, when ST occurs it still remains a dramatic iatrogenic event with high mortality (1-3). Nevertheless, there are no current international guidelines to guide treatment (25). This lack of consensus reflects the paucity of evidence in this field. The results of the PRESTIGE Consortium, reported by Adriaenssens *et al.* (10), further improves our understanding of morphological findings in ST; however, the mechanisms by which morphologic findings interact with patient related factors to cause ST remain open to question. The future diagnostic challenge in ST is to provide accurate assessment of the underlying cause in order to implement appropriate strategies in prevention and therapy in the individual patient. In this vein, intravascular imaging by OCT will play a key role to guide optimal stent implantation in the first instance and to provide further diagnostic insights when ST occurs in the course of time.

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Footnote

Conflicts of Interest: The authors have no conflicts of interest to declare.

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