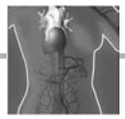
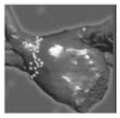


Drug-eluting stent malapposition and its relationship to drug-eluting stent thrombosis

Stent malapposition (whether acute and persistent, or late and acquired) is common, occurring in 10–20% of drug-eluting stent implantations in stable patients and 30–40% of ST-elevated myocardial infarction patients. Acute stent malapposition is not a predictor of early stent thrombosis. Conversely, late stent malapposition, especially the large late stent malapposition area, might be a cause of late stent thrombosis and very late stent thrombosis in some patients. Other causes such as vessel wall inflammation, positive vessel wall remodeling, in-stent neoatherosclerosis with plaque rupture, stent fracture and delayed re-endothelialization with uncovered stent struts may also contribute to late and very late stent thrombosis.

KEYWORDS: drug-eluting stent ■ intravascular ultrasound ■ optical coherence tomography ■ stent malapposition ■ stent thrombosis

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Stent thrombosis is a safety concern associated with use of drug-eluting stents (DES) [1–3]. According to the definition of the Academic Research Consortium, stent thrombosis can be classified as early (0–30 days post-stent implantation), late stent thrombosis (LST; >30 days) and very late stent thrombosis (VLST; >12 months) based on the elapsed time since stent implantation. The mechanisms leading to stent thrombosis are complex and incompletely understood. In particular, the correlation of DES malapposition with stent thrombosis has been a matter of concern and debate.

What is malapposition? How often does it occur? What is its mechanism?

Stent malapposition, synonymous with incomplete stent apposition, is the lack of stent–vessel wall contact and is identified using intravascular ultrasound (IVUS) as blood speckle behind stent struts not overlying a side branch, and by optical coherence tomography (OCT) as a distance between the leading edge of the strut artifact and the intimal surface that is greater than the structural thickness of the stent strut. Stent malapposition can be acute (ASM, occurring at the time of stent implantation) or late (LSM, detected at follow-up). LSM is classified as late acquired if it is not present immediately after the procedure, but occurs during follow-up, or persistent if it is present at both baseline and follow-up [4,5].

In the STRUT, CRUISE and AVID studies, the incidence of ASM was 4–22% [6]. In a study by Hong *et al.*, it was 7.2%, similar to the TAXUS-II IVUS substudy (7.5%) [7,8]. However, serial IVUS study in ST-elevation myocardial infarction (STEMI) patients found ASM in 30–40% of both DES- and bare-metal stent (BMS)-treated lesions [5,9]. One OCT study suggested the incidence of malapposition at postintervention was 29.7% [101]. ASM was mostly technique dependent and occurred after implantation of any stent type [4].

ASM can either resolve or persist. The TAXUS-II IVUS substudy showed that >50% of ASM resolved at follow-up because of an increase of peri-stent plaque without any change in external elastic membrane dimensions [8]. Conversely, an IVUS substudy of HORIZONS-AMI showed that approximately 40% of ASM resolved at follow-up because of negative remodeling without peri-stent plaque progression, no matter whether it was DES-associated or BMS-associated ASM [5]. Persistent ASM was associated with less neointimal hyperplasia compared with ASM that resolved [5,7,10]. In addition, persistent ASM was associated with a larger immediate post-stent ASM area [5,9].

As noted, LSM, typically detected beyond 6 months, can be late-acquired stent malapposition (LASM) or persistent ASM. A higher frequency of LSM (combining LASM and persistent ASM) was detected in lesions treated with DES mainly due to more LASM compared with BMS-treated lesions [5,9,11]. Primary stenting in acute myocardial infarction (AMI) was an independent predictor of LASM after DES implantation: the incidence of LASM after stenting in STEMI patients was 25–30% compared with approximately 12% overall in

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stable patients [5,7,9,12]. Numerous IVUS studies showed that LASM was attributable to:

- Positive remodeling without an equal amount of peri-stent plaque growth or abluminal intimal hyperplasia so that the vessel pulls away from the stent, particularly in DES;
- Plaque/thrombus resolution so that a gap forms between the stent and the vessel wall after primary stenting in AMI patients [5,7–9,12].

Furthermore, Kang *et al.* identified that LASM after DES implantation at 6 months continuously progressed; and new areas of malapposition developed, all related to ongoing positive remodeling [12].

Does ASM cause early stent thrombosis?

The distinction between patients with early stent thrombosis versus VLST is important, especially after DES implantation, because their fundamental mechanisms seem to be different [13]. Clinically, many physicians believe that ASM is an important cause of early stent thrombosis. However, an integrated IVUS analysis of TAXUS IV, V and VI and TAXUS ATLAS Workhorse, Long Lesion and Direct Stent studies showed that routinely detected ASM in BMS or TAXUS patients was not associated with early- and long-term adverse clinical events, in particular any early stent thrombosis, LST or VLST [14]. Similarly, several studies identified that there was no difference in major adverse cardiac events between patients with versus without ASM after primary stenting of STEMI patients in both DES and BMS cohorts [5,9].

■ What are the predictors of early stent thrombosis?

A qualitative and quantitative coronary angiographic analysis of ACUITY trial showed early stent thrombosis was relatively common in acute coronary syndromes and was predicted by diffuse atherosclerosis, suboptimal angiographic results and inadequate pharmacotherapy [15]. The IVUS-identified causes or predictors of early stent thrombosis are mechanical and procedure related. Liu *et al.* showed that DES-treated lesions, which developed thrombosis or restenosis were often underexpanded, but underexpansion associated with thrombosis was more severe, diffuse and proximal in location [16]. In several studies including stable angina, patients and STEMI patients treated with DES, stent underexpansion and residual reference segment problems (a larger plaque burden, a small lumen area and/or a large dissection at either stent edge) were associated with stent thrombosis after successful DES implantation [17–19]. Notably, none of these studies showed ASM to be one of the predictors of early stent thrombosis.

Is LSM associated with LST or VLST?

There are concerns regarding long-term safety (especially an increased rate of LST and VLST) of DES compared with BMS. Numerous IVUS studies reported an increased frequency of LSM in patients with DES, speculating that there may be a relationship between LSM and stent thrombosis. However, Hong *et al.* reported 3-year clinical events of late DES malapposition [20]. In this single-center study, 532 patients with 671 lesions were included; of these, 80 patients (83 lesions) had LSM and 452 patients (588 lesions) did not. There was one cardiac death (1.3%) and one AMI (1.3%) in the LSM group, whereas in the non-LSM group there were two cardiac deaths (0.4%) and two AMIs (0.4%); all AMIs were caused by VLST. Multiple stepwise logistic regression analysis showed that neither LSM nor its area was related with any major adverse cardiac events at 3-year follow-up.

Cook *et al.* were the first to document the association of LSM and VLST [21]. In this study, VLST was encountered in 13 patients at a mean of 630 days after DES implantation. LSM was present in ten VLST patients (77%) compared with 21 DES controls (12%), and maximal LSM area in VLST patients was twice the size of the average LSM area of the control patients. Subsequently, Cook *et al.* investigated the impact of incidentally discovered LSM as assessed by IVUS 8 months after DES implantation on the long-term clinical outcome and found that LSM was more prevalent among segments treated with sirolimus-eluting than paclitaxel-eluting stents (27 vs 9%; $p = 0.001$) [22]. VLST was more common among patients with LSM than without LSM (Academic Research Consortium-definite stent thrombosis: 13.5 vs 0.6%, hazard ratio = 23.2, 95% CI: 2.65–203; $p < 0.001$). Similarly, one meta-analysis of five studies suggested that there was an increased frequency of VLST with LSM compared with those with no LSM (odds ratio = 6.51, 95% CI: 1.34–34.91) [11].

Recently, Imai *et al.* demonstrated that peri-stent contrast staining (PSS) within 12 months after sirolimus-eluting stent implantation appeared to be associated with subsequent VLST. PSS was defined as contrast staining outside the stent contour extending to ≥20% of the stent diameter. Overall, 3081 lesions (1998 patients) were enrolled in this single-center study. At follow-up,

late-acquired PSS was observed in 58 lesions (1.9%) in 49 patients (2.5%). Definite VLST at 3 years in the PSS group was higher than that in the non-PSS group (8.2 vs 0.2%) [23]. However, Yakushiji *et al.* using HORIZONS-AMI data found no relationship between PSS at 13 months and subsequent VLST. In this study, PSS was present in 23 patients (2.0%) at angiographic follow-up, was not more common with paclitaxel-eluting stents than BMS, but correlated with IVUS LSM. During 3-year follow-up, stent thrombosis developed in zero out of 23 patients with PSS, compared with eight out of 1092 PSS-negative patients (0 vs 0.8%; p = 0.68). The rates of revascularization and major adverse cardiac events were also not increased with PSS [24].

The mechanisms by which LSM may contribute to LST or VLST remain unclear. It has been speculated that LSM may serve as a local nidus for thrombus formation by allowing fibrin and platelet deposition [25]. LSM may be the consequence of chronic inflammation and delayed healing, resulting in tissue necrosis and erosion around the stent [26]. In addition, LSM may only be a marker for other mechanisms primarily causing stent thrombosis such as delayed re-endothelialization, impaired vasomotion and chronic inflammation, which allow for platelet adhesion, initiation of the coagulation cascade and subsequent thrombotic stent occlusion [21].

What are the other causes of LST or VLST?

Lee *et al.* investigated 30 consecutive VLST patients with AMI (DES, n = 23; BMS, n = 7). Although stent malapposition was observed in 73.9% of DES patients (vs 0% of BMS patients; p < 0.001), disease progression with neointimal rupture within the stent was observed in ten DES patients (43.5%) and seven BMS patients (100%; p < 0.010) [27]. Kang *et al.* performed OCT in patients with DES restenosis, including patients presenting with an acute coronary syndrome, and found that 52% of lesions had at least one OCT-defined in-stent thin-cap fibroatheroma-containing neointima and 58% had at least one in-stent neointimal rupture [28]. A pathology study speculated that the development of neoatherosclerosis may be yet another contributing factor to late thrombotic events following DES implantation [29]. In the Nordic IVUS study, stent fracture was seen in approximately 20% of VLST cases [102]. In a second study, Cook *et al.* reported 28 patients with very late DES thrombosis and 26 controls (including patients with spontaneous AMI, early BMS thrombosis, early DES thrombosis and late BMS thrombosis). Histopathological analysis showed that the mean number of eosinophils per high-power field was higher in specimens from very late DES thrombosis than in those from controls. Eosinophil count correlated with the area of LSM. This study implicated vessel wall inflammation as an important mechanism of VLST in DES-treated patients [30]. Guagliumi *et al.* used both IVUS and OCT to access the mechanisms of DES VLST [31]. By OCT, patients with LST, compared with control subjects, had a higher percentage of uncovered and malapposed struts. By multivariable analysis, the length of segment with uncovered stent struts by OCT and the remodeling index by IVUS were independent predictors of LST. Finally, Nakazawa *et al.* identified that the underlying mechanism(s) of LST was strikingly different between different DES platforms; localized strut hypersensitivity was exclusive to sirolimus-eluting stent, whereas malapposition secondary to excessive fibrin deposition was the underlying cause in paditaxel-eluting stent [32]. Finally, a paper by Ko *et al.* indicated that more than one mechanism may be present [33]. Therefore, VLST is a syndrome with many potential underlying mechanisms beyond LSM including neoatherosclerosis with plaque rupture, strut fracture, vessel wall inflammation and lack of stent strut tissue coverage.

Future perspective

Almost all of the above studied stent thrombosis in first-generation DES, including sirolimus-eluting stents and paclitaxel-eluting stents. However, the rate of stent thrombosis in second-generation DES is significantly less than the first-generation devices. Is stent malapposition, especially LSM, still an issue to be concerned for the second-generation stents? Are the mechanisms of LST/VLST of second-generation stents similar or different compared with first-generation DES? More IVUS and OCT studies need to be carried out in the future to determine the answers to these questions.

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Executive summary

What is malapposition? How often does it occur?

- Stent malapposition, synonymous with incomplete stent apposition, is the lack of stent–vessel wall content and is identified using intravascular ultrasound as blood speckle behind stent struts not overlying a side-branch and by optical coherence tomography as a distance between the leading edge of the strut artifact and the intimal surface that is greater than the structural thickness of the stent strut.
- Stent malapposition (whether acute and persistent, or late and acquired) is common, occurring in 10–20% intravascular ultrasound to 30% optical coherence tomography of drug-eluting stent implantation in stable patients and 30–40% intravascular ultrasound of ST-elevated myocardial infarction patients.

Does acute stent malapposition cause early stent thrombosis

- There is no evidence supporting that acute stent malapposition is an important cause of early stent thrombosis.

Is late stent malapposition associated with late or very late stent thrombosis? What are the other causes of late or very late stent thrombosis?

- Late stent malapposition, especially large late stent malapposition area, might be a cause of, or contribute to, late stent thrombosis and very late stent thrombosis in some patients.
- Histopathologic and intravascular imaging studies have shown that there may be many other causes such as vessel wall inflammation and/or localized strut hypersensitivity, positive vessel wall remodeling, in-stent neoatherosclerosis with plaque rupture, stent fracture and delayed re-endothelialization with uncovered stent struts.

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