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The course of late stent malapposition assessed by long-term serial intravascular ultrasound studies after primary percutaneous coronary intervention for ST-segment elevation myocardial infarction

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ABSTRACT

Aims

To evaluate the course of late stent malapposition (LSMA) with intravascular ultrasound (IVUS) during long-term follow-up in ST-segment elevation myocardial infarction (STEMI) patients treated with primary percutaneous coronary intervention (PCI).

Methods

IVUS results three years after primary PCI were compared with 9-month results in 20 patients with 32 LSMA sites.

Results

Of all LSMA sites, 56% was shown to persist. Although non-significant, external elastic membrane (EEM) (p=0.10) and lumen-behind-stent area (p=0.08) tended to be larger at nine months in those sites that proved persistent during follow-up. Negative vessel wall remodelling was observed equally frequent in resolved (86%) and persistent sites (83%) after three years with similar degree of remodelling. Plaque burden expanded in resolved LSMA sites (0.41mm^2) while a decline was observed in persistent sites (-0.98 mm^2, p=0.015). Both the degree of change in EEM area (i.e. remodelling) and change in plaque burden were associated with the persistence of LSMA (OR2.29, p=0.04 and OR0.25, p=0.009, respectively).

Conclusions

Of all LSMA sites at nine months, 56% persisted three years after primary PCI in STEMI patients. Both change in plaque burden and degree of remodelling were associated with persistence of LSMA, however the role of plaque burden appeared more prominent.

ABBREVIATIONS

PCI	percutaneous coronary intervention
STEMI	ST-segment elevation myocardial infarction
SMA	stent malapposition
LSMA	late stent malapposition
DES	drug-eluting stent
IVUS	intravascular ultrasound
EEM	external elastic membrane
CSA	cross-sectional area
LBS	lumen behind stent
P&M	plaque plus media

INTRODUCTION

Primary percutaneous coronary intervention (PCI) is the preferred treatment of ST-segment elevation myocardial infarction (STEMI) . However, with the introduction of coronary artery stenting , stent thrombosis has been a relatively infrequent but alarming complication with poor prognosis[1]. The mechanism behind stent thrombosis appears to be multifactorial. However, several patient-, lesion-, procedure- and stent-related factors have been associated with stent thrombosis, including stent malapposition (SMA)[2-4]. The role of SMA has been studied more extensively in the era of drug-eluting stents (DES) since its frequency increased with implantation of DES compared to bare-metal stents[5]. Previous studies described the development of late stent malapposition (LSMA) up to one year post stent implantation[6-10]. However, few data exist about the progression of LSMA thereafter[11;12]. The purpose of the present study was therefore to evaluate the course of LSMA with serial intravascular ultrasound (IVUS) examination during long-term follow-up in patients with STEMI treated with primary PCI.

METHODS

Design

The present study is a substudy of the MISSION! Intervention Study; a single-center, single blind, prospective randomized controlled trial (ISRCTN62825862), which has been described previously in more detail[13;14]. The MISSION! Intervention Study was designed to evaluate the angiographic and IVUS outcomes at nine months and clinical outcomes at 12 months after primary PCI with implantation of sirolimus-eluting stents (Cypher, Cordis Corp., Miami Lakes, FL, USA) versus bare-metal stents (Vision, Guidant Corp., Indianapolis, IN, USA) in patients with STEMI. The study protocol was approved by the institutional ethical committee and written informed consent was obtained from all patients before enrollment and separately for 9-month and 3-year follow-up angiography. Patients and operators performing the follow-up angiography were blinded for the assigned treatment. Patients were enrolled from February 2004 to October 2006. The present substudy evaluated the course of LSMA on IVUS examination during long-term follow-up after primary PCI for STEMI. Therefore only patients with LSMA present on 9-month IVUS imaging were selected from the MISSION! Intervention Study population. Detailed information on study design, in- and exclusion criteria, endpoint definitions and main outcomes of this randomized trial were published previously[13].

Study procedures

All patients underwent primary PCI with implantation of either of the study stents, randomized in a 1:1 ratio. Peri-procedural antithrombotic therapy included upfront abciximab (bolus of 25 μg/kg in-ambulance followed by 10 μg/kg/min for 12 hours), loading doses of aspirin (300 mg) and clopidogrel (600 mg), and heparin (5,000 IU) at the start of the procedure. Lesions were treated according to current interventional practice, with direct stenting allowed. Number of stents, stent size and length were selected at the discretion of the operator by visual estimation. IVUS imaging was performed with motorized pullback (0.5 mm/s) starting at least 10 mm distal to the stent and ending at the coronary ostium, using a 2.9-F 20-MHz catheter and a dedicated IVUS console (Eagle Eye, Volcano Corp., Rancho Cordova, CA, USA) and was preceded by 200 to 300 μg of intracoronary nitroglycerin. During follow-up, patients were treated with dual antiplatelet therapy, betablocking agents, angiotensin-converting enzyme inhibitors and statins, and were examined at the outpatient clinic at 30 days, 3, 6 and 12 months according to protocol. After the first year of follow-up, patients were monitored with outpatient clinic visits and/or telephone inquiry. Follow-up angiography and IVUS imaging were performed at nine months and three years after the index procedure.

Quantitative coronary angiography analyses

Coronary angiograms were digitally recorded and analyzed offline using automated edge-detection software (Medis QCA-CMS version 6.0, Medis Medical Imaging Systems, Leiden, The Netherlands). Angiograms were analyzed by two experienced analysts blinded for the assigned treatment. The segments of interest were evaluated, including the stented zone and the proximal and distal 5 mm stent edges. The reference diameter was determined by interpolation. The minimal lumen diameter and percentage diameter stenosis were determined within the stented segment. Late luminal loss was defined as the decline in minimal luminal diameter pertaining to the post-procedural angiography.

Intravascular ultrasound analyses

IVUS images were analyzed offline, using quantitative IVUS analysis software (QCU-CMS 4.14, Medis, Leiden, the Netherlands)[15]. Analyses were performed by two experienced analysts. SMA was defined as separation of at least one stent strut from the intimal surface without involvement of a side branch, and IVUS evidence of blood speckles behind the stent strut[16]. LSMA refers to SMA detected during follow-up as a result of either persistence of acute SMA – i.e. immediately after implantation – or acquired during follow-up. In the current study LSMA, present in all participants, was defined as SMA present at 9-month IVUS. Persistent LSMA was defined as LSMA present at both 9-month and 3-year IVUS imaging. In order to evaluate the 9-month LSMA sites on 3-year IVUS images and determine whether SMA persisted or resolved, 9-month and 3-year image

loops were compared side by side. The corresponding 9-month and 3-year frames with the maximum lumen area behind the stent were selected for comparison of contours and measurements. In these frames, the external elastic membrane (EEM) cross-sectional area (CSA), stent CSA, total lumen CSA, lumen-in-stent CSA, maximum depth of lumen-behind-stent (LBS) and the maximum arc of LBS were measured (**Figure 1**). The LBS CSA was calculated by subtracting the stent CSA from the total lumen CSA. In case there was evidence of neointima, LBS CSA was alternatively determined by tracing contours. Neointimal CSA was calculated by subtracting the lumen-in-stent CSA from the stent CSA. Plaque burden was defined as plaque plus media (P&M) CSA and calculated by subtracting the total lumen CSA from the EEM CSA. The percentage of plaque burden was calculated relative to the EEM CSA. Positive vessel wall remodelling was defined as an increase in EEM CSA during follow-up; negative remodelling as a decrease in EEM CSA.

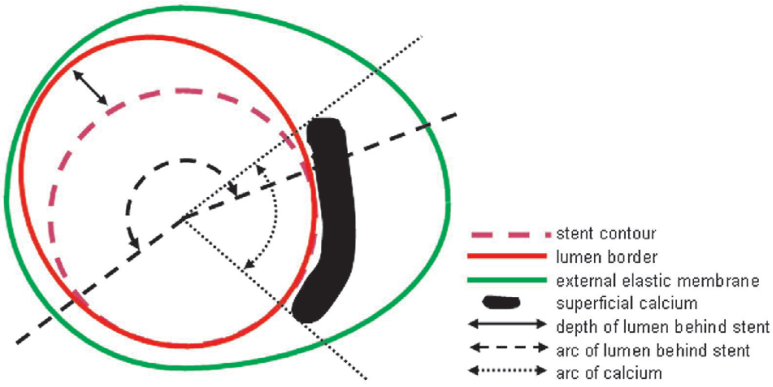

Figure 1. Schematic diagram illustrating intravascular ultrasound contours and measurements.
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Statistical analysis

Continuous variables are presented as mean ± standard deviation or median (interquartile range) and compared between treatment groups with a Student's t test or, in case of a non-Gaussian distribution, with a nonparametric test. Categorical variables are presented as number (%) and compared with the Pearson's Chi-square test or Fisher's exact test, as appropriate. Logistic regression analysis was performed to investigate the independent associations of vessel wall remodelling and change in plaque burden with the persistence of LSMA. All p-values were 2-sided, and a p-value <0.05 was considered to be statistically significant. All analyses were conducted with IBM SPSS Statistics 20 (SPSS Inc., Chicago, Illinois).

RESULTS

Out of 310 patients enrolled in the randomized MISSION! Intervention Study, 254 patients (84%) underwent follow-up angiography nine months after the index event, based on the presence of informed consent. In 49 (27%) out of the 184 patients with 9-month IVUS image loops eligible for analysis and evaluation of stent apposition, LSMA was present at 9-month follow-up angiography. Three-year IVUS images eligible for analysis and stent apposition evaluation were available in 20 out of 49 LSMA patients and were therefore enrolled in the current substudy (**Figure 2**).

Patient and procedural baseline characteristics are listed in **Table 1**. Results of the quantitative coronary angiography analyses are shown in **Table 2**. In-stent late luminal loss increased during long-term follow-up but the increase between nine months and three years did not reach statistical significance (p=0.059). Late luminal loss at the proximal stent edge had remained stable during follow-up. At the distal stent edge, there was even a larger minimal luminal diameter nine months after stent implantation compared with the post-procedural measurement, resulting in a negative value for late luminal loss at nine months. However, late luminal loss increased significantly thereafter (p=0.019).

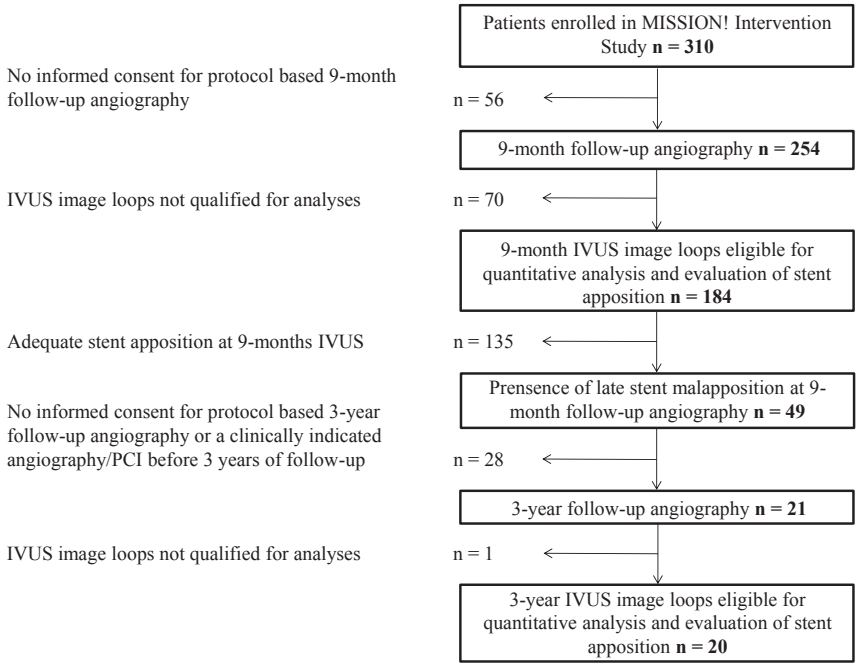

Figure 2. Flowchart of patient inclusion.
IVUS = intravascular ultrasound; PCI = percutaneous coronary intervention

Table 1. Clinical and procedural baseline characteristics

Variable		All patients (N=20)
Age (years)		64 ± 8
Male gender		17 (85%)
Hypertension *		8 (40%)
Hyperlipidemia †		3 (15%)
Diabetes mellitus		-
Current smoker		9 (45%)
Positive family history		8 (40%)
Previous acute myocardial infarction		1 (5%)
Previous PCI or CABG		-
Symptoms-balloon time (min)		168 (124-275)
Out-of-hospital cardiac arrest		1 (5%)
Culprit vessel	*LAD*	9 (45%)
	LCx	7 (35%)
	RCA	4 (20%)
Multivessel coronary artery disease		9 (45%)
Initial TIMI flow ≥2		5 (25%)
Pre-procedural vessel reference diameter (mm)		2.97 ± 0.60
Pre-procedural minimal lumen diameter (mm)		0.31 ± 0.50
Pre-procedural diameter stenosis (%)		90.3 ± 14.9
Direct stenting		6 (30%)
Stent type	*drug-eluting stent*	16 (80%)
	bare metal stent	4 (20%)
No. of stents implanted		1.3 ± 0.5
Implanted stent length		26.6 ± 9.5
Post dilatation		8 (40%)
Maximum balloon diameter (mm)		3.40 ± 0.21
Maximum balloon pressure (atm)		12.5 ± 2.1
Maximum balloon:artery ratio		1.10 ± 0.16
Post-procedural vessel reference diameter (mm)		3.26 ± 0.45
Post-procedural minimal lumen diameter (mm)		2.90 ± 0.40
Post-procedural diameter stenosis (%)		10.8 ± 6.2
Final TIMI flow 3		18 (90%)
Peak CK (U/L)		2167 (1613-3959)
LV ejection fraction (%) ‡		53 (47-61)

Data are expressed as number (%) or mean ± standard deviation (SD) or median (interquartile range).
* Blood pressure ≥ 140/90 mmHg or previous pharmacological treatment; † Total cholesterol ≥ 190 mg/dl or previous pharmacological treatment; ‡ Residual left ventricular ejection fraction determined at 3 months after STEMI.
CABG = coronary artery bypass graft surgery; CK = creatine kinase; LAD = left anterior descending artery; LCx = left circumflex artery; LV = left ventricle; PCI = percutaneous coronary intervention; RCA = right coronary artery; TIMI = thrombolysis in myocardial infarction.

Table 2. Late luminal loss since stent implantation measured at quantitative coronary angiography at 9 months and 3 years

Variable	9-month follow-up	3-year follow-up	P value
Late luminal loss in-stent (mm)	0.32 ± 0.47	0.53 ± 0.41	0.059
Late luminal loss proximal edge (mm)	0.27 ± 0.25	0.29 ± 0.27	0.82
Late luminal loss distal edge (mm)	-0.10 ± 0.38	0.26 ± 0.46	0.019

Data are expressed as number (%) or mean ± standard deviation (SD) or median (interquartile range).

In this study population, 32 LSMA sites were identified at nine months after stent implantation, predominantly located along the body of the stent (59%). Of all LSMA sites at nine months, 18 (56%) persisted during three years of follow-up. Examples of resolved and persistent LSMA are shown in **Figure 3**. Evaluation of all 32 sites (**Table 3**) revealed a significant decrease in both EEM CSA (p<0.001) and total lumen CSA (p<0.001) at 3-year compared with 9-month IVUS. Negative remodelling was observed at 27 sites (84%). In-stent lumen CSA, neointimal CSA and P&M CSA, i.e. plaque burden, remained unchanged during long-term follow-up. Consequently, the percentage of plaque burden

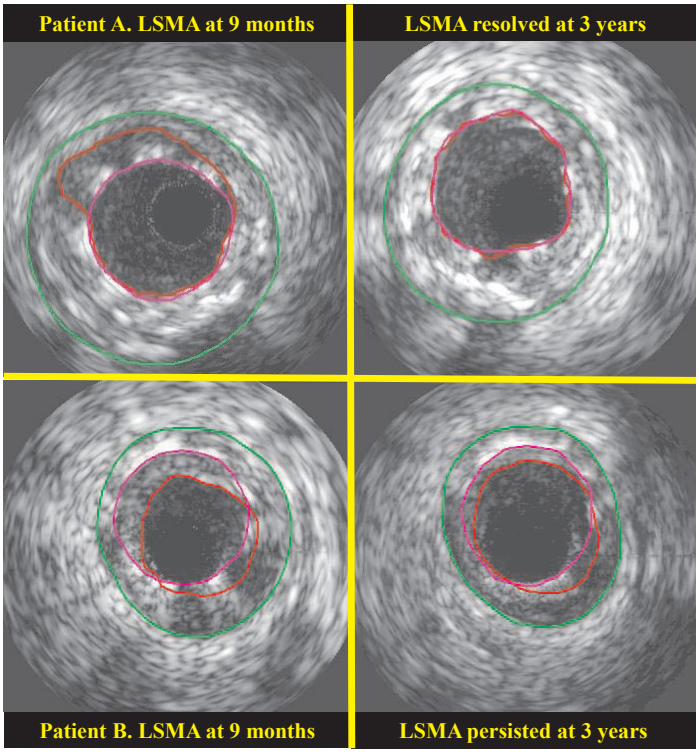

Figure 3. Example of A. resolved late stent malapposition and B. persistent late stent malapposition.
LSMA = late stent malapposition

Table 3. Intravascular ultrasound results at 9-month and 3-year follow-up angiography

Variable	9-month IVUS	3-year IVUS	P value
External elastic membrane CSA (mm^2)	23.8 ± 6.1	21.9 ± 5.3	<0.001
Stent CSA (mm^2)	8.5 ± 1.5	8.5 ± 1.5	0.94
Total lumen CSA (mm^2)	11.5 ± 3.0	10.1 ± 2.6	<0.001
In-stent lumen CSA (mm^2)	8.4 ± 1.5	8.4 ± 1.6	0.73
Neointimal CSA (mm^2)	0.14 ± 0.60	0.13 ± 0.36	0.96
Plaque & media CSA (mm^2)	12.1 ± 4.4	11.8 ± 4.0	0.32
Plaque burden (%)	50 ± 8.6	53 ± 8.4	0.007
No. of LSMA sites	32	18	-
Lumen behind stent CSA (mm^2) †	3.7 ± 2.4	3.0 ± 2.0	0.12
Lumen behind stent depth (mm) †	0.90 ± 0.39	0.87 ± 0.39	0.71
Maximum arc of lumen behind stent (º) †	211 ± 89	164 ± 62	0.04

Data are expressed as number (%) or mean ± standard deviation (SD). † Only compared between patients with persistent late stent malapposition (n=18).
CSA = cross-sectional area; IVUS = intravascular ultrasound; LSMA = late stent malapposition.

relative to the EEM CSA significantly increased at 3-year compared with 9-month IVUS (p=0.007). In patients with persistent LSMA, the LBS CSA was comparable between 9-month and 3-year IVUS (p=0.12). However, the maximum arc of LBS significantly decreased during follow-up (p=0.04).

The evolution of LSMA site characteristics during long-term follow-up was compared between resolved and persistent LSMA sites (**Table 4**). In persistent LSMA sites, negative vessel wall remodelling was observed as frequently as in resolved LSMA sites and the size of reduction in EEM CSA was similar in both groups. However, EEM CSA at nine months tended to be larger in sites that turned out to persist compared with sites that resolved during 3-year follow-up (25.3 ± 6.7 mm^2 vs. 21.8 ± 4.7mm^2, respectively, p=0.10). Likewise, a non-significant difference was observed in LBS CSA at nine months between persistent

Table 4. Development of intravascular ultrasound characteristics between 9 months and 3 years in patients with persistent versus resolved late stent malapposition

Variable	Resolved LSMA (n=14)	Persistent LSMA (n=18)	P value
External elastic membrane CSA (mm^2) Δ	-1.99 ± 2.09	-1.76 ± 2.01	0.75
Negative remodelling (%)	12 (86%)	15 (83%)	1.00
Total lumen CSA (mm^2) Δ	-2.48 ± 1.14	-0.69 ± 1.76	0.002
In-stent lumen CSA (mm^2) Δ	0.07 ± 0.30	-0.12 ± 0.82	0.43
Neointimal CSA (mm^2) Δ	0.01 ± 0.27	-0.06 ± 0.42	0.60
Plaque & media CSA (mm^2) Δ	0.41 ± 1.56	-0.98 ± 1.50	0.015
Plaque burden (%) Δ	6.8 ± 3.8	0.3 ± 5.4	0.001

Data are expressed as number (%) or mean ± standard deviation (SD) or median (interquartile range).
CSA = cross-sectional area; LSMA = late stent malapposition

and resolved LSMA sites (3.7 ± 2.4 mm^2 vs. 2.5 ± 1.2 mm^2, respectively, p=0.08). In-stent lumen CSA and neointimal CSA remained more or less constant in both groups. The development of P&M CSA however, was significantly different between groups with expansion of plaque burden in resolved LSMA sites whilst a decline was observed in persistent LSMA sites at three years post stent implantation (p=0.015). Although the percentage of plaque burden relative to the EEM CSA increased in both groups, the increase in resolved LSMA sites was significantly higher compared with persistent LSMA sites (p=0.001). The persistence of LSMA during long-term follow-up was independently associated with both the degree of change in EEM CSA and change in P&M CSA. A LSMA site showing a 1 mm^2 increase in EEM CSA during follow-up was more than twice as likely to persist (OR 2.29, 95% CI 1.04-5.06, p=0.04). In contrast, a site showing a 1 mm^2 increase in P&M CSA during follow-up was four times less likely to persist (OR 0.25, 95% CI 0.09-0.71, p=0.009).

DISCUSSION

Main findings of the present study investigating the 3-year course of LSMA in patients who underwent primary PCI for STEMI were: 1) 56% of LSMA sites as observed at 9-month IVUS imaging persisted during long-term follow-up. 2) Evaluation of all LSMA sites revealed negative vessel wall remodelling in the vast majority and occurred equally frequent among resolved and persistent LSMA. 3) Plaque burden expanded in resolved LSMA sites, whilst in persistent LSMA sites regression was observed. 4) The degree of remodelling and change in plaque burden were both significantly associated with the persistence of LSMA. However, the role of change in plaque burden appeared more prominent.

LSMA is a well-known phenomenon after coronary stent implantation. Although the exact role of LSMA in the development of (very) late stent thrombosis remains a topic of debate[17;18], several studies demonstrated that at least in some patients LSMA is likely to be involved[2-5] and is therefore of clinical importance. The underlying mechanism behind this relationship is supposed to be the absence of neointimal coverage of inadequately apposed stent struts[9;19]. LSMA is common, in particular after primary stenting for acute myocardial infarction[5] and after the implantation of DES[7;20], albeit in varying degrees depending on type of DES[21;22]. Whereas acute SMA is most likely the result of undersizing or underexpansion of the stent during the index procedure, the most frequently observed pathophysiological mechanism associated with LSMA is focal positive vessel wall remodelling[6]. Other, less frequently reported mechanisms include plaque regression or thrombus dissolution[8;23;24], a hypersensitive response to one of the stent components[25] and genetic susceptibility[26]. Plaque composition might also have a role in the course of stent

apposition[27;28]. Chronic stent recoil is an often postulated mechanism, however no data supported this hypothesis to date. Although sufficient data on the development of LSMA are available up to one year follow-up, few data actually describe its course thereafter[11;12]. No long term data are available in patients after primary PCI.

In the present analysis, 56% of the 9-month LSMA sites were found to persist up to three years of follow-up, although the maximum arc of malapposition declined.

The resolved sites in this study could be partly attributed to negative remodelling at sites that already had a smaller vessel size at nine months. Moreover, the initial extent of malapposition (LBS CSA) in the resolved sites tended to be smaller at nine months as well. These findings are in line with those of Aoki et al.[12] who demonstrated a decreased incidence of malapposition between six months and two years follow-up in relation to focal negative vascular remodelling. In contrast are the results of Kang et al.[11] showing ongoing positive remodelling during 2-year follow-up with dynamic progression of LSMA and newly detected LSMA sites. Type of stent, in the latter also predominantly sirolimus-eluting, did not seem to be the explanation for these conflicting results. Expansive vascular remodelling is presumed to be a result from the chronic inflammatory response to the stent polymer or drug and is therefore a plausible finding at short- (or mid-) term follow-up[29]. However, it is at least remarkable that this process of vascular expansion would continue long after the completed release of the antiproliferative agent. Reverse (negative) remodelling at long-term follow-up, as demonstrated in the present study, would be more likely in this perspective.

In addition to remodelling, change in plaque burden was even more closely involved in the 3-year course of LSMA sites. In contrast to the expansion of plaque burden in resolved LSMA sites, plaque burden declined substantially in persistent LSMA sites. Thrombus dissolution is a potential cause of plaque regression in the development of LSMA[8;23]. However, this seems rather unlikely in pre-existing LSMA and the time elapsed since the index procedure. Plaque regression as a result of intensive statin therapy has also been suggested, but does not apply to the present study population, certainly not the high-intensity as described by Nissen et al[30]. Moreover, this does not explain why in one LSMA site plaque expands while in the other regression occurs under a similar statin regimen.

After adjustment for the other, both vessel wall remodelling and change in plaque burden were independently associated with the persistence of LSMA. It is noteworthy however, that the present data underlined the substantial contribution of change in plaque burden to the course of LSMA during long-term follow-up. Previous literature considered plaque regression as a potential but minor contributor to stent malapposition, or predominantly restricted to bare-metal stents[14;23;31]. Further research is needed to determine what the underlying mechanism is for plaque regression.

Limitations

Some limitations of the present study should be mentioned for correct interpretation of the results. First of all, study procedures were designed for the original purpose only with angiographic late luminal loss at nine months follow-up as primary endpoint. Long-term outcomes as described in the present study were not prespecified and therefore results should be interpreted with caution. Secondly, because of the selection of merely LSMA patients, the quality of IVUS image loops required for proper analysis and the limited number of patients with informed consent for follow-up angiography, sample size was substantially reduced. For this reason, no differentiation was made between initially acute but persisting 9-month LSMA and acquired 9-month LSMA in the selected study population, although the evolution possibly might differ. However, even though the sample size is limited, long-term IVUS data in this patient subset are scarce and do provide more insight in the pathophysiology.

Conclusions

Of al LSMA sites as demonstrated at IVUS examination at nine months after primary PCI for STEMI, 56% was shown to persist during 3-year follow-up. Both the degree of remodelling and change in plaque burden were associated with the persistence of LSMA, however the role of plaque burden appeared more prominent. Given the persistence of the majority of malapposition sites during long-term follow-up, it is important to gain more insight regarding the pathophysiology of this phenomenon and its potential relationship with late adverse events.

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