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New insights in mechanism, diagnosis and treatment of myocardial infarction

Bergheanu, S.C.

Citation

Bergheanu, S. C. (2011, April 21). *New insights in mechanism, diagnosis and treatment of myocardial infarction*. Retrieved from <https://hdl.handle.net/1887/17588>

Version: Corrected Publisher's Version

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CHAPTER

POST-INTERVENTION IVUS IS
NOT PREDICTIVE FOR VERY LATE
IN-STENT THROMBOSIS
IN DRUG-ELUTING STENTS



ABSTRACT

Objectives: Stent thrombosis is a life-threatening complication associated with sudden death and acute myocardial infarction. Histopathologic studies have linked the occurrence of very late stent thrombosis in drug-eluting stents (DES) with delayed endothelialization and stent malapposition.

Our aim was to investigate if late stent malapposition in DES could be predicted by immediate post-intervention intra-vascular ultrasonography (IVUS).

Methods and Results: From our MISSION! database of 184 consecutive patients with ST-elevation myocardial infarction (STEMI) who had immediate post-intervention and nine-month follow-up IVUS examinations we prospectively identified three patients with very late (>365 days) and definite (with angiographic evidence) in-stent thrombosis in DES. Patients had completed the twelve-month clopidogrel-aspirin dual treatment period, two of them were under aspirin therapy while the third patient had aspirin temporarily discontinued before planned surgery.

When assessed by serial documentary (immediate post-intervention and nine-month) IVUS, all three patients demonstrated stent malapposition at nine months: in two cases the malapposition was acquired (immediate post-intervention IVUS showed a well apposed stent) and one case presented persistent malapposition (the stent was found malapposed both at immediate post-intervention and nine-month follow-up IVUS).

Conclusions: Immediate post-intervention IVUS showing no malapposition does not guarantee an uneventful course after DES implantation.

Keywords: Drug-eluting stent, IVUS, stent malapposition, stent thrombosis

Sandrin C. Bergheanu * † ‡, Bas L. van der Hoeven *, Ayman K. M. Hassan *, Jouke Dijkstra §, Frits R. Rosendaal † ‡, Su-San Liem *, Martin J. Schalij *, Johanna G. van der Bom † ‡ and J. Wouter Jukema* ‡

Departments of *Cardiology, †Clinical Epidemiology, §Radiology and the ‡Eindhoven Laboratory for Experimental Vascular Medicine, Leiden University Medical Center, Leiden, The Netherlands

Acta Cardiol. 2009;64:611-616.

INTRODUCTION

Drug-eluting stents (DES) are preferred to bare-metal stents (BMS) by many cardiologists because of the decreased risk of restenosis and decreased need for repeat revascularization¹⁻³. Over the past years, in-stent thrombosis has emerged as a rare but serious side effect in stented patients and some studies suggest that stent malapposition (seen more frequently after DES rather than BMS implantation) seems to be of importance^{4,5}.

Stent malapposition represents a separation of the stent struts from the intimal surface of the arterial wall (in the absence of a side branch) with evidence of blood behind the struts⁶. Late stent malapposition may be persistent (present both immediately after implantation and at follow-up) or acquired (present only at follow-up). The precise role and indications of intra-vascular ultrasonography (IVUS) in assessing stent malapposition and the subsequent risk for in-stent thrombosis are not crystallized yet.

Three consecutive cases of very late (over one year) in-stent thrombosis were analyzed. Angiographies and IVUS examinations were performed both at stent implantation after the initial event and at nine-month follow-up as part of the treatment protocol. All three patients were treated with sirolimus-eluting stents and presented stent malapposition at the nine-month follow-up IVUS examination.

METHODS

Our MISSION!⁷ database contains 184 patients with acute ST-elevation acute myocardial infarction (STEMI) who had an IVUS examination both immediately post-stenting and at nine-month follow-up. We prospectively searched for patients with very late (> 365 days) and definite (angiographic evidence) in-stent thrombosis (definition of the Academic Research Consortium⁸). We used available MISSION! data⁷ to assess the risk of very late in-stent thrombosis in patients with late acquired stent malapposition. We further assessed the same risk in patients with non-late acquired stent malapposition and calculated a relative risk.

For each case of very very late in-stent thrombosis we first analyzed the nine-month follow-up IVUS and searched whether sites of stent malapposition could be identified. Stent, lumen, vessel and plaque areas in the most representative malapposition frames were analyzed for each case. Secondly, we identified the corresponding frames in the post-intervention IVUS examinations. Stent, lumen, vessel and plaque areas were measured within the identified post-intervention frames and then compared with the nine-month follow-up values.

All patients gave informed consent before the procedure. An additional informed consent was obtained for follow-up angiography and IVUS at nine months. IVUS imaging was performed with motorized pull-back (0.5mm/s) starting at least 10 mm distal to the stent and ending at the coronary ostium, using a 2.9F 20MHz catheter and a dedicated IVUS console (Eagle Eye, Volcano Corp. Rancho Cordova,

California, USA) ⁹. Each angiogram and ultrasound sequence was preceded by 200-300µg of intracoronary nitroglycerin. After the initial procedure aspirin (100 mg/day) was prescribed indefinitely and clopidogrel (75 mg/day) for twelve months. During follow-up, patients were treated with beta-blockers, statins and ACE-inhibitors or ATII-blockers, according to current guidelines ¹⁰. Follow-up angiography and IVUS imaging was performed at nine months. IVUS images were analyzed off-line, using quantitative IVUS analysis software (QCU-CMS 4.14, Medis, Leiden, The Netherlands) ¹¹.

RESULTS

6 Three cases of very-late in-stent thrombosis after DES implantation were identified in sirolimus-eluting (Cypher; Cordis, Johnson & Johnson) patients. Baseline characteristics are described in Table 1.

Table 1. Baseline characteristics at the time of the index event (myocardial infarction) for n=3 patients.

	Patient 1	Patient 2	Patient 3
Sex	Woman	Man	Woman
Age (Yrs.)	49	80	44
Smoker	Yes	No	Yes
Diabetes	No	No	No
Cardiac history	No	No	No
Site of occlusion	Proximal LAD	Proximal LAD	Mid LAD
Direct stenting	No	No	No
Maximum implant pressure (atm)	12	14	10
Post dilatation	No	No	No
Stent size	3.0 x 18 mm	3.5 x 28 mm	3.5 x 23 mm

LAD = left anterior descending coronary artery; SES = sirolimus-eluting stent. Stent size is presented in (diameter x length) mm.

Prior to the in-stent thrombosis all patients completed the twelve month dual anti-platelet treatment with aspirin 100 mg/day and clopidogrel 75 mg/day. For the first patient (Fig. 1), the stent thrombosis occurred at 25 months after the index event (at thirteen months after clopidogrel was discontinued but still under aspirin therapy), for the second patient (Fig.2) at 31 months after the index event (19 months after clopidogrel discontinuation and while aspirin being temporarily discontinued for elective surgery) and for the third patient (Fig. 3) at twelve months after the index event and two weeks after clopidogrel discontinuation. Other medication was prescribed according to guidelines ¹⁰.

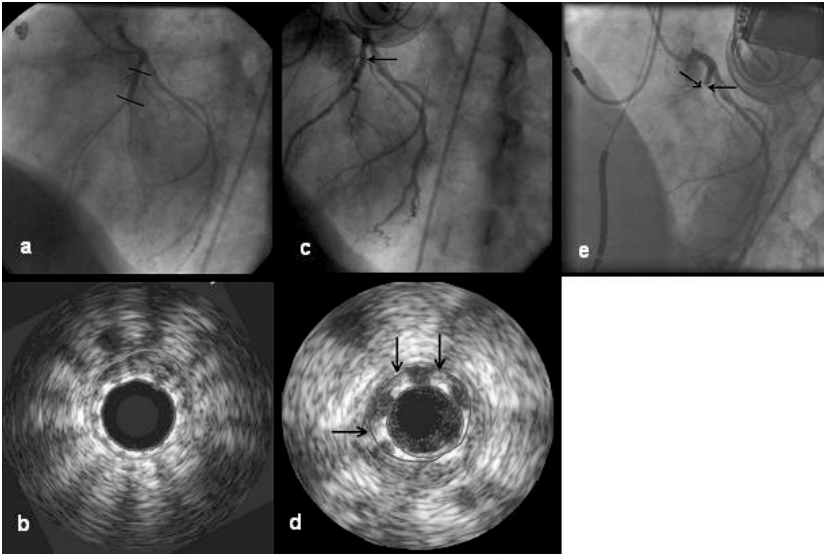


Figure 1. (a) Angiography after the index procedure. The DES is delimited by the two lines. (b) IVUS post-intervention demonstrates complete stent apposition. (c) Angiography at 9-month follow-up. Arrow indicates the site of stent malapposition. (d) IVUS at 9-month follow-up indicates severe stent malapposition (arrows). (e) Angiography reveals in-stent thrombosis (between arrows). Explanation of IVUS images: the outer borders show the vessel limits as delimited by the external elastic membrane (EEM); the middle borders delimitate the lumen; the inner borders delimitate the stent; stent struts appear in white.

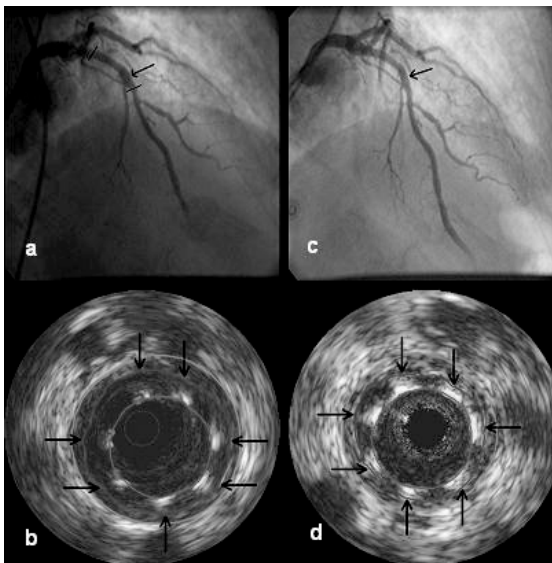


Figure 2. (a) Angiography after the index procedure. The two lines delimitate the DES. Arrow indicates the site of stent malapposition. (b) IVUS after the index event. Arrows indicate severe malapposition. (c) Angiography at 9-month follow-up. Arrow indicates the site of stent malapposition. (d) IVUS at 9 month follow-up revealing less severe (compared to immediate post-intervention IVUS) stent malapposition (arrows).

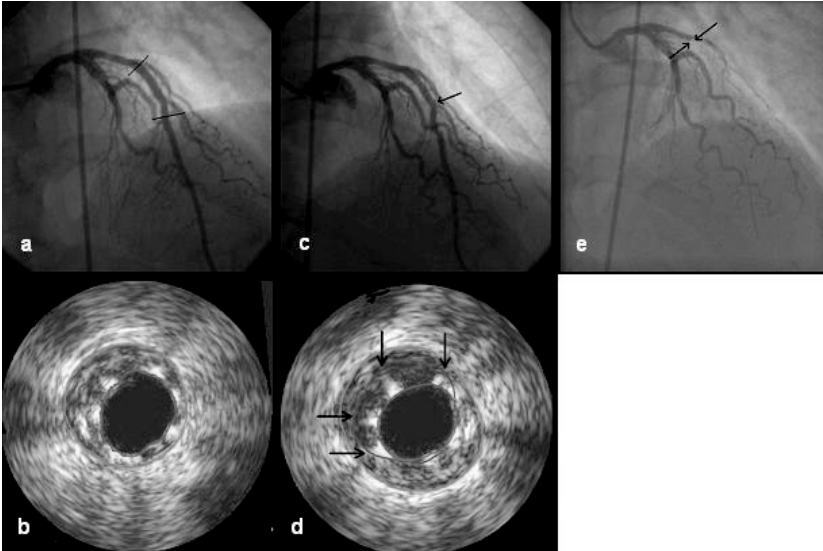


Figure 3. (a) Angiography after the index event. Two lines delimitate the DES. (b) IVUS after the index event. Complete stent apposition is observed. (c) Angiography at 9-month follow-up. Arrow indicates the site of stent malapposition. (d) IVUS at 9-month follow-up showing stent malapposition (arrows). (e) Angiography revealing in-stent thrombosis (arrows).

Table 2. IVUS findings post-intervention and at nine-month follow-up.

	Vessel (mm ²)	Stent (mm ²)	Lumen (mm ²)	Plaque burden (mm ²)
Patient 1				
Post-intervention	11.83	5.59	5.55	6.27
Follow-up	16.14	5.83	10.12	6.03
Δ	4.31	0.24	4.57	-0.24
Patient 2				
Post-intervention	29.20	10.40	21.52	7.68
Follow-up	24.58	10.21	16.88	7.71
Δ	-4.62	-0.19	-4.64	0.03
Patient 3				
Post-intervention	15.81	6.39	6.41	9.40
Follow-up	21.20	6.29	11.16	10.04
Δ	5.39	-0.1	4.75	0.64

Measurements were made in the representative locations for stent malapposition. The same locations were analyzed for post-intervention and the nine-month follow-up. All values are area (mm²). Δ=Post-intervention-Follow-up. Plaque burden is approximated as Vessel-Lumen areas.

Detailed results about the MISSION! intervention study are presented elsewhere ⁷. From a total of 184 patients, a number of 104 patients received a DES. At 9-month follow-up, 26/104 patients presented acquired stent malapposition. Among these 26 patients, two patients developed stent-thrombosis (patient 1 and patient 3). In the remaining 78 patients (including 65 with normal apposed stents and 13 with late persistent stent malapposition), one patient (patient 2) developed very late stent thrombosis.

In our study, patient 1 and patient 3 presented acquired stent malapposition (Δ Lumen = 4.57 and 4.75 mm² respectively) with positive remodeling (Δ Vessel = 4.31 and 5.39 mm² respectively). Interestingly, for the same type of drug eluting stent, patient 2 demonstrated a reduction of the initial stent malapposition (Δ Lumen = -4.64 mm²) with negative remodeling (Δ Vessel = -4.62 mm²). Plaque burden and stent areas were virtually unchanged in all three patients after nine months.

DISCUSSION

These three patients with very late in-stent thrombosis demonstrated late stent malapposition at nine months follow-up after stent implantation, either acquired (two cases) or persistent (one case). Our findings are in line with a recent study where stent malapposition was found highly prevalent in patients with very late stent thrombosis after DES implantation ⁵.

Stent expansion represents the minimum stent cross-sectional area compared with a predefined reference area, which can be the proximal, distal, largest, or average reference area ⁶ according to which variant best approximates the coronary lumen in the stented segment. Late persistent stent malapposition was mainly related to the failure of optimal stent expansion while late acquired stent malapposition was associated with: (1) decrease of the plaque volume (including clot lysis or plaque regression); (2) positive remodelling and (3) stent malapposition not recognized at implantation and detected at follow-up ^{5,12-14}. If late persistent stent malapposition incidence may be decreased by avoiding sub-optimal stent expansion, it is not clear whether a more aggressive implantation technique lowers or increases the incidence of late acquired stent malapposition ⁷.

All our patients benefited from primary intervention in acute myocardial infarction setting. Van der Hoeven et al. ⁷ shown a higher incidence of late-acquired stent malapposition in DES stents deployed in acute patients compared to the incidence already reported in elective patients studies. This is probably due in part to the stent deployment over thrombus that would later resorb and leave a gap between stent struts and vessel wall. The IVUS technique lacks the resolution to precisely identify thrombotic structures and thus stent struts deployed over thrombus may falsely seem well apposed immediately after implantation.

Hypersensitivity reaction to the polymer coating of sirolimus eluting stents¹⁵ and induction of apoptosis by sirolimus may also play a role in late-acquired stent malapposition, especially at sites of severe vessel damage during implantation^{16,17}.

The mechanism by which stent malapposition may contribute to stent thrombosis remains however unclear. In-stent thrombosis in DES during the first year after implantation¹⁸ was associated to the treatment of bifurcation lesions, the stent length or stent underexpansion as well as some clinical aspects (diabetes, low ejection fraction, renal failure or antiplatelet therapy discontinuation)¹⁹⁻²¹. Therefore, acute thrombotic events might benefit from IVUS examination in order to exclude incomplete stent expansion as an underlying and corrigible cause²². On the long term, stent malapposition may be the consequence of chronic inflammation and delayed healing, resulting in tissue necrosis and erosion around the stent²³. In addition, the positive remodeling may reduce the blood flow between the enlarged wall and the stent struts. Delayed re-endothelialization, impaired vasomotion, and chronic inflammation may be as well regarded as primary stent thrombosis mechanisms (stent malapposition being just the marker of the local on-going pathology) by allowing the platelet adhesion, initiation of the coagulation cascade, and subsequent thrombotic stent occlusion⁵.

Immediate post-intervention IVUS was not useful in predicting the long term risk for thrombosis in our three patients since two of them had normally apposed stents. Conversely, the nine-month follow-up offered perhaps more useful information, clearly demonstrating the malapposition. If stent malapposition is indeed a major player in late stent thrombosis, IVUS examination performed at nine months after stent deployment or before the completion of clopidogrel therapy may be a valuable predictor for this adverse outcome where immediate post-intervention IVUS showing no malapposition seems not to offer sufficient information. In the future, the use of more powerful tools such as optical coherence tomography (OCT), alone or in combination with IVUS, may decrease the incidence of unrecognized stent malappositions and prevent late stent thrombosis²⁴. For now, possible solutions to prevent late stent thrombosis in cases of IVUS documented late malapposition may include prolongation of dual antiplatelet therapy or percutaneous coronary angioplasty to resolve the stent malapposition. Both have, however, disadvantages: the risk of bleeding during extensive dual antiplatelet therapy and the risk of inducing restenosis and/or in-stent thrombosis after coronary re-intervention.

CONCLUSION

Immediate post-intervention IVUS showing no malapposition does not guarantee an uneventful course after DES implantation.

ACKNOWLEDGMENTS

Support was given by the Dutch Heart Foundation and The Netherlands Society of Cardiology.

SCB and BLvdH contributed equally to this work.

JWJ is an established clinical investigator of the Netherlands Heart Foundation (2001D032).

DISCLOSURE OF CONFLICT OF INTERESTS

The authors state that they have no conflict of interests.

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