Journal of the American College of Cardiology
© 2007 by the American College of Cardiology Foundation
Published by Elsevier Inc.

Vol. 50, No. 15, 2007
ISSN 0735-1097/07/$32.00

CORRESPONDENCE

Research Correspondence: Expedited Publication

Impact of Late Drug-Eluting Stent Malapposition on 3-Year Clinical Events

To the Editor: There are questions regarding long-term safety of drug-eluting stents (DES), especially concern about an increased rate of late DES thrombosis compared with bare-metal stents. Numerous intravascular ultrasound (IVUS) studies have reported an increased frequency of late stent malapposition (LSM) in patients with DES (1–3), speculating that there may be a relationship between LSM and late stent thrombosis. The present study reports the long-term (>2 years) follow-up after the diagnosis of LSM was made using serial IVUS examination after DES implantation.

We previously reported 82 patients (85 lesions) with LSM from an overall cohort of 557 patients (705 native lesions) who underwent DES implantation (mean interval between baseline and follow-up IVUS of 6.1 ± 2.1 months). No intervention was performed in 542 patients (683 lesions) at 6-month follow-up (3). At least 2-year follow-up was available for all but 10 patients (12 lesions). Therefore, the present study reports 532 patients (98% follow-up rate) with 671 lesions; 80 patients (83 lesions) had LSM, and 452 patients (588 lesions) did not.

Long-term (i.e., beyond 6 months) clinical follow-up data were obtained from outpatient records or telephone interviews. Major adverse cardiac events (MACE) were defined as cardiac death, acute myocardial infarction (AMI), or target lesion revascularization (TLR). Death, AMI, TLR, and stent thrombosis were defined according to Academic Research Consortium criteria (4). All patients were followed for a minimum of 24.0 months (range 24.0 to 41.6 months) after the 6-month follow-up angiogram and IVUS, except for the patients who were lost to follow-up or who had MACE events during the 2-year follow-up period.

Serial IVUS imaging and analysis were performed as previously described (3). Late stent malapposition was defined as a separation of at least 1 stent strut from the intimal surface of the arterial wall that was not present immediately after stent implantation.

Data were compared with chi-square statistics or Fisher exact test and unpaired Student *t* test or Mann-Whitney *U* test. Event-free survival was analyzed with the Kaplan-Meier method and log-rank test. Multiple stepwise logistic regression analysis was performed to assess independent predictors for MACE.

Late stent malapposition (mean area of 3.0 mm^2) was documented in 80 patients with 83 lesions (12.4%). The duration of clinical follow-up was 31 ± 6 months after the 6-month angiogram: 32 ± 6 months in LSM patients and 31 ± 6 months in non-LSM patients ($p = 0.3$). The duration of follow-up after cessation of dual antiplatelet therapy was 27 ± 9 months and 27 ± 8 months, respectively ($p = 1.0$).

There was 1 cardiac death (1.3%) and 1 AMI (1.3%) in the LSM group, whereas in the non-LSM group there were 2 cardiac deaths (0.4%) and 2 AMIs (0.4%) ($p = 0.2$). The cause of all 3 AMIs was very late definite stent thrombosis 21, 24, and 27 months after the 6-month angiogram and 18 to 24 months after stopping clopidogrel (Table 1). Target lesion revascularization was necessary in 1 LSM patient (1.3%) and in 8 non-LSM patients (1.8%; $p = 0.7$). Clinical profiles of the 15 patients who developed MACE events during follow-up are shown in Table 1. There was no significant difference in 3-year MACE-free survival rate between the 2 groups (log rank $p = 0.7$). Postprocedural incomplete stent apposition, which was observed in 51 lesions, was not related with any MACE for the 3-year follow-up.

Multiple stepwise logistic regression analysis was performed to determine predictors of MACE. The following variables were tested (all variables with $p < 0.2$ in univariate analysis): age, preintervention minimal lumen diameter, and total stent length. Late stent malapposition and LSM area were forced into the model. There were no significant independent predictors for MACE.

Numerous studies have speculated that LSM is a cause of late stent thrombosis after DES implantation. A recent study reported that incomplete stent apposition was related to very late stent thrombosis. However, lack of post-stent IVUS was a significant limitation (5). Our study and other studies have reported no negative clinical events associated with LSM treated with DES implantation (1–3). Degertekin et al. (6) reported 13 patients from the RAVEL (Randomized Comparison of a Sirolimus-Eluting Stent With a Standard Stent for Coronary Revascularization) study, who received sirolimus-eluting stents, showed stent malapposition at angiographic follow-up, and remained asymptomatic during the subsequent 12-month period. However: 1) these previous studies were multicenter randomized studies with specific indications excluding complex lesions; 2) with the exception of the TAXUS-II (Paclitaxel-Eluting Stents in the Treatment of Longer Lesions) study, the number of patients in each IVUS substudy was small, often representing <25% of the DES cohort; 3) added together, these IVUS substudies did not include the number of LSM patients in the present report; 4) the size of the stent-vessel wall gaps were modest; and 5) follow-up was limited to 12 months beyond the 6- or 9-month angiogram and IVUS, similar to our previous report (3). The present analysis was designed to overcome some of these previous limitations, especially the duration of follow-up. The mean follow-up beyond the 6-month angiogram and IVUS in the current report was 31 months, 27 months without dual antiplatelet therapy, and thus was much longer than these multicenter studies.

Table 1 Clinical Profiles of the 15 Patients Who Developed MACE During Follow-Up

Patient #	Age (yrs)	Gender	Clinical/ Angiographic Diagnosis	Risk Factors	Site	LSM CSA/MSA (mm^2)	Type, Number (Length, mm) of DES	Clopidogrel Treatment (Months) After 6-Month Angiogram	MACE and Their Onset After 6-Month Angiogram
LSM patients									
1	61	F	UAP/2VD	D, H	LCX	3.2/6.6	SES, 1 (18)	2	Death, 25 months
2	40	M	AMI/1VD	D, H, S	LAD	4.9/3.4	SES, 3 (18,33,33)	3	AMI, 21 months
3	33	M	UAP/2VD	S	LAD	2.4/8.9	SES, 2 (33/33)	0	TLR, 16 months
Non-LSM patients									
4	48	M	AMI/2VD	S	LCX	—/6.2	SES, 1 (23)	3	AMI, 27 months
5	66	M	UAP/2VD	H	LAD	—/9.3	SES, 2 (23,23)	5	Death, 31 months
6	54	M	AMI/2VD	H	LAD	—/5.1	PES, 1 (24)	2	AMI, 24 months
7	60	M	SAP/3VD		RCA	—/9.8	SES, 1 (33)	2.6	Death, 2.6 months
8	50	M	UAP/1VD	H	LAD	—/6.3	SES, 2 (18,23)	4	TLR, 14 months
9	38	M	UAP/1VD	D, H, S, C	LAD	—/6.5	PES, 2 (24,28)	8	TLR, 8 months
10	63	F	SAP/3VD	D	LAD	—/4.8	SES, 1 (33)	11	TLR, 20 months
11	66	M	SAP/3VD	S	LAD	—/9.4	SES, 1 (28)	2	TLR, 25 months
12	58	F	SAP/3VD		RCA	—/6.8	SES, 2 (23,23)	0	TLR, 20 months
13	63	F	UAP/2VD	H	RCA	—/5.2	SES, 1 (23)	8	TLR, 8 months
14	67	M	SAP/3VD	C	LAD	—/6.1	SES, 2 (23,33)	13	TLR, 15 months
15	52	M	SAP/2VD	D, H	LAD	—/3.0	SES, 3 (18,33,33)	0	TLR, 13 months

AMI = acute myocardial infarction; C = hypercholesterolemia; CSA = cross-sectional area; D = diabetes mellitus; DES = drug-eluting stent; H = hypertension; LAD = left anterior descending artery; LCX = left circumflex artery; LSM = late stent malapposition; MACE = major adverse cardiac events; MSA = minimum stent area; PES = paclitaxel-eluting stent; RCA = right coronary artery; S = smoking; SAP = stable angina pectoris; SES = sirolimus-eluting stent; TLR = target lesion revascularization; UAP = unstable angina pectoris; VD = vessel disease.

This was a retrospective observational analysis without additional angiographic or IVUS data (IVUS study at the time of late stent thrombosis or longitudinal IVUS). This study is underpowered to show a significant difference in MACE rates between LSM versus non-LSM patients during a mean 31 months of clinical follow-up after the 6-month angiogram. The relationship between LSM, LSM area, or duration of antiplatelet treatment and MACE requires further analysis with a larger number of patients.

In conclusion: 1) MACE and stent thrombosis were not more frequent in LSM patients compared with non-LSM patients; and 2) LSM after DES implantation was not a predictor of MACE during a mean follow-up of 31 months after the 6-month IVUS in a cohort of this size.

Myeong-Ki Hong, MD
Gary S. Mintz, MD, FACC
Cheol Whan Lee, MD
Duk-Woo Park, MD
Seung-Whan Lee, MD
Young-Hak Kim, MD
Duk-Hyun Kang, MD
Sang-Sig Cheong, MD
Jae-Kwan Song, MD, FACC
Jae-Joong Kim, MD
Seong-Wook Park, MD, FACC
***Seung-Jung Park, MD, FACC**

*Department of Medicine
University of Ulsan College of Medicine
Cardiac Center
Asan Medical Center
388-1 Poongnap-dong
Songpa-gu, Seoul, 138-736
Korea
E-mail: sjpark@amc.seoul.kr

doi:10.1016/j.jacc.2007.07.038

REFERENCES

1. Tanabe K, Serruys PW, Degertekin M, et al. Incomplete stent apposition after implantation of paclitaxel-eluting stents or bare metal stents: insights from the randomized TAXUS II trial. Circulation 2005;111:900–5.
2. Ako J, Morino Y, Honda Y, et al. Late incomplete stent apposition after sirolimus-eluting stent implantation: a serial intravascular ultrasound analysis. J Am Coll Cardiol 2005;46:1002–5.
3. Hong MK, Mintz GS, Lee CW, et al. Late stent malapposition after drug-eluting stent implantation; an intravascular ultrasound analysis with long-term follow-up. Circulation 2006;113:414–9.
4. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials; a case for standardized definitions. Circulation 2007;115:2344–51.
5. Cook S, Wenaweser P, Togno M, et al. Incomplete stent apposition and very late stent thrombosis after drug-eluting stent implantation. Circulation 2007;115:2426–34.
6. Degertekin M, Serruys PW, Tanabe K, et al. Long-term follow-up of incomplete stent apposition in patients who received sirolimus-eluting stent for de novo coronary lesions: an intravascular ultrasound analysis. Circulation 2003;108:2747–50.