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Persistence of Neointimal Growth 12 Months After Intervention and Occurrence of Delayed Restenosis in Patients With Left Main Coronary Artery Disease Treated With Drug-Eluting Stents

To the Editor: Although long-term follow-up after drug-eluting stent (DES) implantation shows a sustained clinical benefit in several registries and randomized trials (1), little is known about the pattern of neointimal growth beyond the first six to nine months. In particular, when exactly neointima growth after DES implantation begins to subside remains largely unknown.

The mechanism of action of DES on neointimal proliferation seems to be partially explained by a delay in vascular response, which has supported the concern that late restenosis (i.e., occurring beyond six months) might occur in humans (2).

This would be of clinical relevance especially for patients receiving DES implantation for the treatment of left main coronary artery (LMCA) disease, in whom restenosis is considered a major, and potentially fatal, complication after percutaneous intervention.

Up to March 6, 2004, a total of 110 consecutive patients were treated exclusively with one or more DES in the LMCA as part of an elective or non-elective revascularization procedure at our institution. Seventy-three patients received 6-month angiographic follow-up, of whom 15 underwent paired angiographic measures at 12 months, which was not preceded by target vessel reintervention, and constitute the patient population of the present report.

Quantitative angiographic analyses were performed with the use of edge-detection techniques (CAAS II, Pie Medical, Maastricht, the Netherlands). Binary restenosis was defined as stenosis of more than 50% of the luminal diameter in the target lesion. Late loss was defined as the minimal lumen diameter (MLD) immediately after the index procedure minus the MLD at angiographic follow-up.

Continuous variables are shown as median and interquartile range and were compared using Wilcoxon test or a general liner mixed model followed by post-hoc analysis after log transformation for normalization. Probability was significant at a level of <0.05.

The characteristics of the study population (Table 1) did not differ with respect to the patients receiving no or six-month angiographic follow-up only.

The reason for repeating a second coronary angiogram included risk-stratification before non-cardiac major surgery in three (Patients #1, #6, and #14), evidence of inducible ischemia at noninvasive stress test in two (Patients #4 and #15), a staged procedure for the treatment of the right coronary artery in one (Patient #13), and the willingness to repeat a second coronary angiogram in the remaining nine after counselling about the potential consequence of in-stent restenosis at the time of the index procedure. No major adverse cardiovascular event previously occurred in this cohort of patients, and all except one were asymptomatic at the time of repeated catheterization.

Quantitative coronary analysis on paired measurements in the main treated branch (i.e., LMCA or LMCA and the proximal tract of the left anterior descending artery) is shown in Table 1. When all intervened coronary segments were cumulatively considered ($n = 20$), including the stented proximal tract of the circumflex artery in five patients receiving bifurcation stenting, the MLD decreased from 2.78 (2.49 to 2.95) after the procedure to 2.44 mm (2.07 to 3.09) ($p = 0.37$) and 2.25 (1.85 to 2.70) ($p = 0.005$ vs. post-procedure and $p = 0.054$ vs. 6-month) at 6 and 12 months, respectively. The late loss (mm) increased from 0.29 (0.07 to 0.4) at 6 months to 0.63 (0.37 to 0.76) after 12 months ($p < 0.001$) (Fig. 1). Cumulatively, Patient #13, presenting with mild intimal hyperplasia at 6 months, received a target vessel revascularization at 12 months due to severe focal in-stent restenosis in the mid-shaft of the LMCA (Fig. 1C), while a focal restenosis in the ostium of the circumflex artery detected at 12-month follow-up in Patient #2 was left untreated due to normal coronary reserve at non-invasive nuclear stress imaging.

Previous serial angiographic analyses showed that intimal hyperplasia peaks after 12 to 16 weeks after intervention and that restenosis rarely occurs beyond 3 months after bare metal stent implantation (3). These observations justify current practice to perform angiographic follow-up six to eight months after percutaneous coronary revascularization, when the intimal growth has ceased and the net lumen gain is likely to be maintained over time. Indeed, a partial regression of the in-stent intimal hyperplasia at longer-term follow-up in patients receiving bare metal stents has been reported (3).

When exactly neointima growth after DES implantation begins to subside remains largely unknown, but based on experimental findings, a late *catch up* phenomenon has been hypothesized (2). Of some concern is the fact that similar argumentations have been previously raised after intravascular brachytherapy, based on findings on animals, which were subsequently confirmed in humans (4). In the longest available angiographic follow-up after DES implantation, neointimal growth has been shown to mildly non-significantly progress beyond one year (1). Whether this would result in delayed restenosis remained unclear.

In our small series of patients undergoing serial angiographic monitoring, a significant increase of late loss between 6 and 12 months was noted, and, more importantly, one patient developed late in-stent restenosis of the LMCA, which necessitated reintervention.

Our preliminary findings raise several unanswered questions. This study was not pre-specified, as it was urged by the one-year

Table 1. Baseline and Procedural Characteristics and Serial Quantitative Coronary Analysis of the Main Treated Branch

	Patient No.														
	1	**2**	**3**	**4**	**5**	**6**	**7**	**8**	**9**	**10**	**11**	**12**	**13**	**14**	**15**
Age, yrs	68	69	64	63	48	46	70	30	50	72	70	72	78	56	64
Gender	M	M	M	M	M	M	F	M	F	M	F	M	M	M	F
Diabetes	No	Yes	No	No	No	No	No	No	No	No	Yes	No	Yes	No	No
Creatinine (μmol/l)	79	69	85	90	94	98	53	68	68	73	61	70	92	187	254
Protected LMCA	No	No	No	No	Yes	No	No	No	No	No	Yes	No	No	No	No
Clinical presentation	STEMI	SA	SA	SA	SA	SA	STEMI	SA	UA III B	UA II B	SA	UA III A	SA	UA III B	UA II B
Parsonnet score	19.5	12	6.5	3.5	9	6.5	19.5	25.5	19	2.5	19	2.5	14	18	21
Lesion location	Mid	Distal	Distal	Ostial	Ostial	Mid	Distal	Distal	Mid	Mid	Distal	Mid	Distal	Ostial	Distal
Severe calcification	No	No	No	No	Yes	No	No	No	No	No	No	Yes	No	No	Yes
Stent type	SES	SES	SES	SES	SES	SES	SES	SES	SES	SES	PES	PES	PES	PES	PES
Stent no.	1	2	1	1	1	1	1	2	1	2	2	2	2	1	2
Total stent length, mm	18	51	18	8	18	33	18	26	33	16	36	16	40	32	28
Bifurcation stenting	No	Yes	No	No	No	No	No	Yes	No	No	Yes	No	Yes	No	Yes
Technique	—	T-stent	—	—	—	—	—	Crush	—	—	Culotte	—	Culotte	—	V-stent
Post-dilation	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	Yes	No	Yes	No	Yes
Final kissing	No	No	No	Yes	No	No	No	No	No	No	No	No	Yes	No	Yes
QCA post-PCI															
RVD (mm)	3.95	3.05	3.40	2.61	3.42	3.58	3.68	2.89	3.16	3.43	2.42	3.40	2.70	3.53	2.89
MLD (mm)	3.57	3.04	2.77	2.56	3.41	2.91	3.60	2.89	2.49	3.11	2.43	2.95	2.26	3.51	2.71
Vessel stenosis (%)	10	0	18	2	0	19	2	0	21	9	0	13	16	6	6
QCA at 6-month follow-up															
RVD (mm)	3.89	3.12	3.9	2.67	3.52	3.38	3.53	3.04	2.67	3.59	2.45	3.93	2.24	3.59	2.61
MLD (mm)	3.51	3.04	3.09	2.49	3.21	3.28	2.99	1.96	2.07	3.33	2.01	3.64	1.86	3.11	2.27
Vessel stenosis (%)	10	3	21	7	9	3	15	35	22	7	18	7	17	13	13
QCA at 12-month follow-up															
RVD (mm)	3.79	2.74	3.45	2.50	3.20	3.44	3.12	3.12	2.66	3.26	2.55	3.37	3.17	3.78	2.58
MLD (mm)	2.84	2.70	2.40	2.37	2.18	3.12	2.87	1.92	1.95	2.99	1.62	2.81	1.03	3.01	2.27
Vessel stenosis (%)	25	1	29	5	31	9	8	38	27	8	36	17	81	20	12

LMCA = left main coronary artery; MLD = minimal lumen diameter; PCI = percutaneous coronary intervention; PES = paclitaxel-eluting stent; QCA = quantitative coronary analysis; RVD = reference vessel diameter; SA = stable angina; SES = sirolimus-eluting stent; STEMI = ST-segment elevation myocardial infarction; UA = unstable angina followed by Braunwald classification.

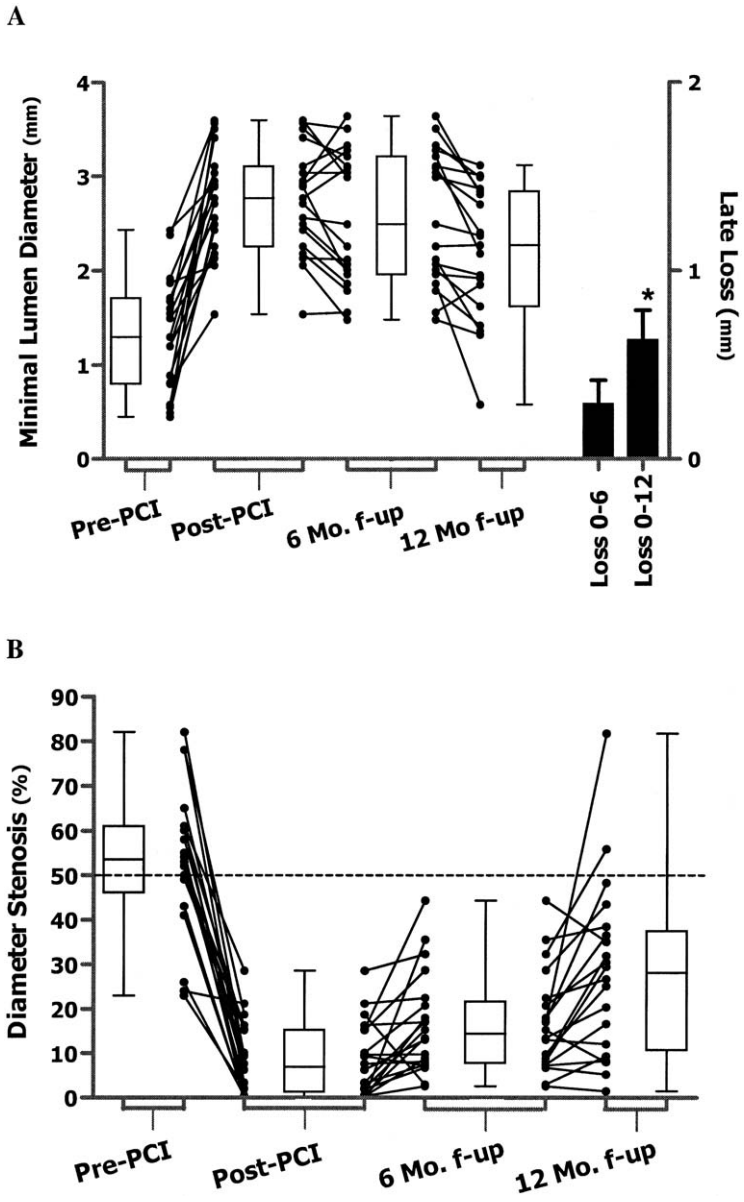

Figure 1. Change of minimal lumen diameter (MLD) **(A)** and lumen diameter stenosis **(B)** as a consequence of treatment in 20 intervened coronary segments, including the LMCA (and the proximal tract of the left anterior descending artery if stented) in 15 patients and the proximal segment of the circumflex artery in 5 patients who received bifurcation stenting. **(A)** At 12 months, the MLD (mm) reduced significantly compared to post-intervention ($p < 0.001$) and tended to be smaller than that noted at 6 months ($p = 0.054$). The late loss passed from 0.29 (0.07 to 0.4) at 6 months to 0.63 (0.37 to 0.76) after 12 months ($p < 0.001$). *$p < 0.001$ vs. late loss recorded at six months. **(B)** The vessel diameter stenosis (%) passed from 54 (50 to 60) before to 7 (2 to 10) after the procedure ($p < 0.001$), to 14 (9 to 18) at 6 months ($p = 0.3$ vs. post-procedure) and to 28 (17 to 35) at 12 months ($p = 0.066$ vs. 6 months). PCI = percutaneous coronary intervention.
Continued on next page.

findings on Patient #13. Importantly, the increase in late loss from 6 to 12 months turned out to be a consistent observation also in other LMCA-intervened patients, triggering the present report. It remains unclear based on our data whether intima hyperplasia peaks at 12 months or even later after DES LMCA stenting. Whether our results are applicable also to non-left main lesions is currently unknown.

Recently, Wessely et al. (5) reported on two patients treated with sirolimus-eluting stent in the left anterior descending artery and right coronary artery who presented at 13 and 19 months, respectively, with recurrence of symptoms and angiographically confirmed in-stent restenosis. Of note, both patients had undergone previous coronary angiogram at seven months, which showed no evidence of intima growth at that stage.

The finding that intima growth may persist well beyond the conventional six to eight months after intervention may cast a shadow of doubt on current attempts to employ power transformation of late loss at six to eight months to predict long-term stent performance.

The clinical implications of the delayed occurrence of in-stent restenosis after DES in patients undergoing intervention for LMCA disease remain unclear.

A prolonged clinical and angiographic surveillance in this subset of patients seems to be warranted.

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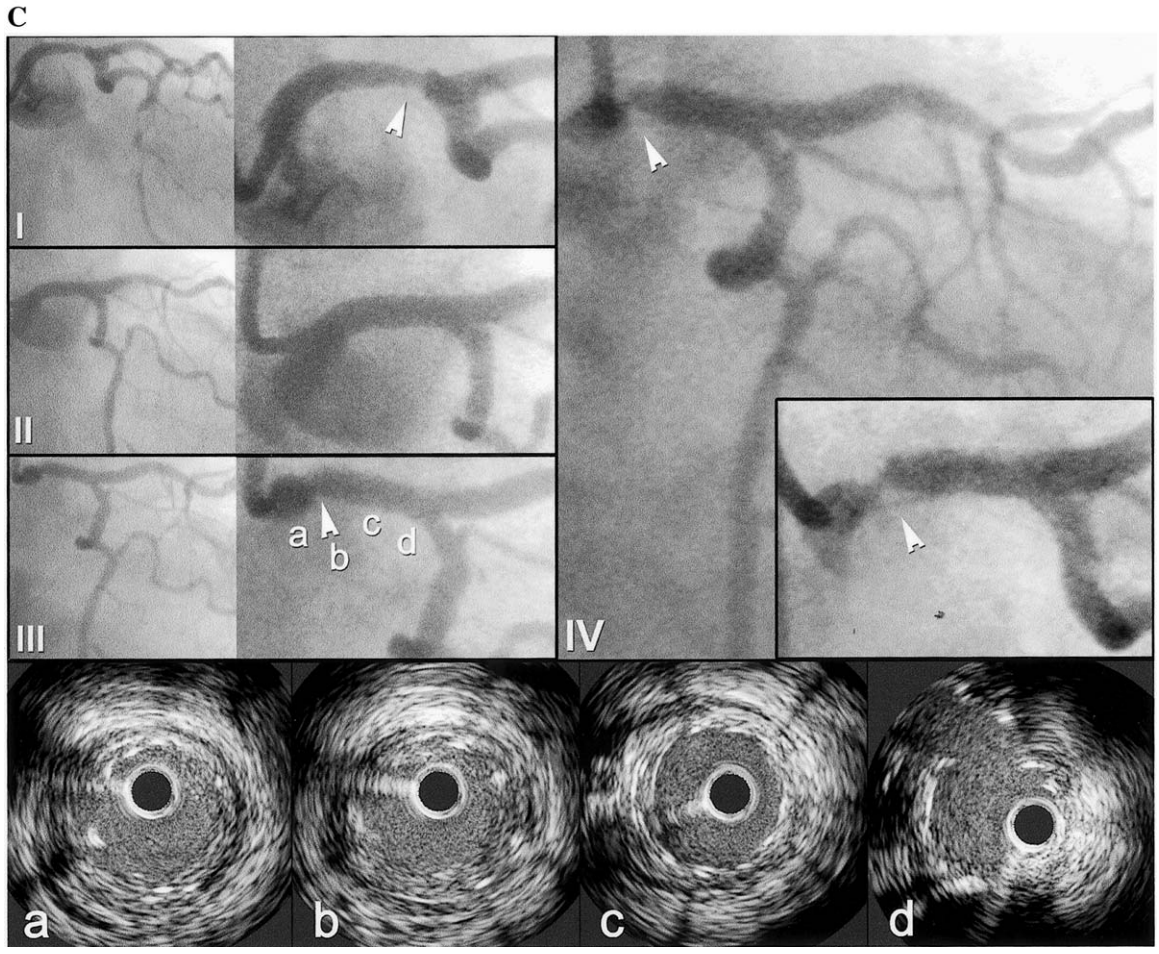

Figure 1 Continued. **(C)** Sequential coronary angiographies showing the left main coronary artery (magnified at the right) and the proximal and mid-tract of circumflex and anterior descending arteries of Patient #13. **Panel I:** A stenosed distal left main coronary artery with its magnification in the right quadrant and a suboccluded circumflex artery are visible before treatment. **Panel II:** Angiographic result immediately after treatment. At six months **(panel III)**, a moderate focal restenosis in the proximal tract of the left main coronary artery was present **(arrowhead)** that did not cause significant obstruction of the lumen at intravascular ultrasound (IVUS) investigation **(lower panel)** and did not result to be flow-limiting, with a fractional flow reserve of 0.85. At 12 months **(panel IV)**, control angiogram revealed a tight in-stent restenosis **(arrowhead)**, magnified in the insert, through which the IVUS probe could not be negotiated and required reintervention. **Lower panel** is showing four IVUS cross-sections (Atlantis 40 Mhz, Boston Scientific, Natick, Massachusetts) from the left main coronary artery at six months: **(a)** proximal edge of the stent in the left main coronary artery, with a malapposed strut visible at 7 o'clock; **(b)** in-stent concentric growth of intimal hyperplasia at the minimal lumen area; **(c)** minor degree of in-stent eccentric hyperplasia located in the mid-tract of the left main coronary artery at 9 o'clock; **(d)** left main coronary artery carina, showing no sign of intimal hyperplasia, with the stented circumflex artery originating at 11 o'clock.

Marco Valgimigli, MD
Patrizia Malagutti, MD
Carlos A. G. van Mieghem, MD
Sophia Vaina, MD
Jurgen M. Ligthart, BSc
George Sianos, MD, PhD
***Patrick W. Serruys, MD, PhD**

*Erasmus Medical Center
Thoraxcenter, Bd-406
Dr Molewaterplein 40
3015-GD Rotterdam
the Netherlands
E-mail: p.w.j.c.serruys@erasmusmc.nl

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