JACC: CARDIOVASCULAR IMAGING VOL. 5, NO. 11, 2012

ISSN 1936-878X/$36.00
PUBLISHED BY ELSEVIER INC. http://dx.doi.org/10.1016/j.jcmg.2012.02.020

BRIEF REPORT

OCT-Verified Peri-Strut Low-Intensity Areas and the Extent of Neointimal Formation After 3 Years Following Stent Implantation

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Drug eluting stents (DES) have decreased substantially the neointimal formation after percutaneous coronary intervention (PCI). However, DES are not free from neointimal hyperplasia (NIH) and stent thrombosis, which are related to the delayed arterial healing following DES implantation. The recently introduced optical coherence tomography (OCT) enables a detailed investigation of vessel healing. The presence of peri-strut low intensity (PLI) has been described as a potential marker of abnormal neointimal healing (1,2). We investigated the late healing characteristics of stents implanted over 3 years, specifically the potential impact of PLI on NIH and restenosis.

OCT imaging (M2, Lightlab Imaging, Westford, Massachusetts) was performed in 99 patients who were treated with bare-metal stents (BMS), sirolimus-eluting stents (SES) (Cypher, Cordis, Bridgewater, New Jersey), or paclitaxel-eluting stents (PES) (Taxus, Boston Scientific, Natick, Massachusetts) from September 2007 to August 2009. The inclusion criteria were stent implanted in de novo lesion and time from index PCI >3 years. The exclusion criteria were left main, stent thrombosis, or target lesion revascularization.

Cross-sectional images of the stented segments were analyzed at 1-mm intervals. PLI was defined as homogenous low-intensity area around a stent strut without significant signal attenuation behind the area on a strut basis. The severity of PLI on a cross-sectional basis was evaluated semi-quantitatively by PLI score by the extent of PLI occupying the number of quadrants. Neointimal thickness and malapposition of each strut, neointimal lipid pool, calcification, microvessel, and OCT-derived thin cap neoatheroma (OCT-TCNA) were also defined (Fig. 1A) (3). A total of 3,365 OCT cross sections from 125 stents were assessed. After exclusion of overlapping stents (2,197 struts [6.7%]) and side branches ≥1.5 mm (277 struts [0.8%]), a total of 30,302 struts (92.5%) and 3,053 cross sections were included in the analysis.

By the OCT strut-level analysis, PLI was most common in BMS (19.4%), followed by PES (12.6%) and SES (6.0%; $p < 0.001$) (Table 1). NIH was higher in struts displaying PLI than struts without PLI in all stents ($p < 0.001$ for all). Interestingly, the NIH thickness was <0.3 mm even in the BMS strut without PLI, and it was >0.5 mm in SES struts with PLI (Fig. 1B). Significant correlation between the severity of PLI and the degree of NIH was found in both the cross-sectional and stent-level analyses ($r = 0.537$ to 0.846; $p < 0.05$) (Fig. 1B, Table 1). The frequency of OCT-TCNA per stent was 7.9% to

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Manuscript received January 6, 2012; revised manuscript received February 8, 2012, accepted February 9, 2012.

Figure 1. Representative Images of PLI and Impact of PLI on Strut-Level Neointimal Thickness and Stent-Level Angiographic Late Loss

(A) Representative optical coherence tomography (OCT) findings of neointima. Peri-strut low intensity (PLI) **(white arrows)** is seen as homogenous lower intensity adjacent to stent struts. PLI score is defined as the number of quadrants, 0 to 4, occupied by PLI. PLI may appear granular as shown by image in the rightmost middle row. OCT-derived thin cap neoatheroma (OCT-TCNA) was defined as the presence of TCNA having an angle of signal-poor lipid pool **(blue arrowhead)** in ≤2 quadrants and a fibrous cap thickness ≥65 μm **(pink arrows)** in 3 consecutive images. Microvessels are small vesicular tubular structures **(pink arrows)** visible in >1 cross-sectional image. Neointimal calcification is a well-delineated signal-poor mass with a sharp border **(blue arrowhead)**. *Continued on the next page.*

15.6% and not different between stent types (p = nonsignificant) (Table 1). The severity of PLI correlated with angiographic late loss in all groups (r = 0.407 to 0.583; $p < 0.05$) (Fig. 1B, Table 1). The presence of PLI in one quadrant of OCT image was related to a 6.6- to 130.0-fold increase of binary restenosis after adjustment for stent area ($p < 0.05$) (Table 1).

The vascular healing response of BMS implantation is known to be initial regression of neointima followed by a plateau at least up to 3 years, whereas that of DES is a mild but continuous growth. Little is known about the characteristics of late neointima. Our study showed that PLI is a common finding long after stent implantation and appears to be involved in neointimal proliferation.

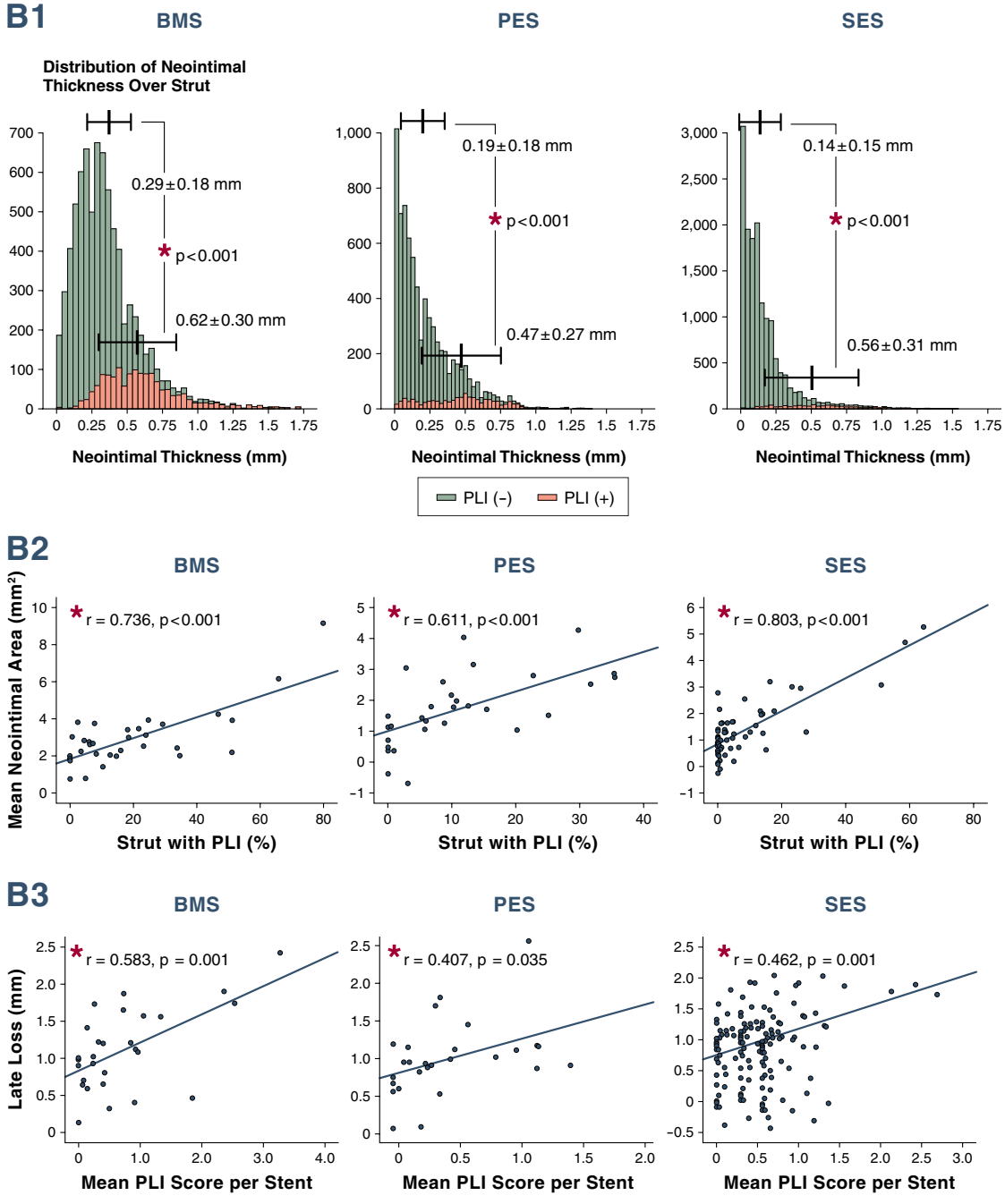

Figure 1. Continued

(B1) Distribution of neointimal thickness by PLI in strut level. The neointimal thickness over struts with PLI **(light blue bars)** was higher than neointimal thickness over struts without PLI **(red bars)** in all stent types (all $p < 0.001$). Even the neointimal thickness of sirolimus-eluting stents (SES) with PLI was higher than those of bare-metal stents (BMS) without PLI (0.56 ± 0.31 mm vs. 0.29 ± 0.18 mm; $p < 0.0001$). Correlation between severity of PLI and degree of neointimal hyperplasia or angiographic late loss is shown in **B2** and **B3**, respectively. PES = paclitaxel-eluting stents.

The histopathology of PLI is still not known well. PLI was correlated with the quality of the neointima with different stent types (2,4,5). In our study, the presence of PLI was the strongest factor related to neointimal proliferation. Considering contribution of continuous inflammation, fibrin deposition, extracellular matrix accumulation, or formation of neoatherosclerosis to

Table 1. Strut-Level, Cross-Sectional, and Stent-Level OCT Analysis

	BMS	PES	SES	p Value
Strut-level analysis				
N	7,740	7,551	15,011	
Neointimal thickness, mm	0.35 ± 0.24	0.22 ± 0.21	0.16 ± 0.19	<0.001
Uncovered strut	1.2 (90)	9.1 (686)	11.0 (1,644)	<0.001
Malapposed strut	0 (3)	1.7 (132)	2.0 (305)	<0.001
Strut with PLI	19.4 (1,501)	12.6 (955)	6.0 (907)	<0.001
Cross-sectional level analysis				
N	744	723	1586	
Stent area, mm^2	7.60 ± 2.67	7.89 ± 2.36	6.85 ± 2.00	<0.001
Luminal area, mm^2	4.45 ± 1.66	6.04 ± 2.37	5.59 ± 2.05	<0.001
Neointimal area, mm^2	3.15 ± 1.96	1.85 ± 1.61	1.26 ± 1.48	<0.001
Neointimal area, %	40.3 ± 15.2	23.7 ± 19.4	17.9 ± 18.8	<0.001
No. of PLI	1.98 ± 3.04	1.26 ± 2.57	0.57 ± 1.82	<0.001
PLI score	0.78 ± 1.19	0.50 ± 0.95	0.24 ± 0.77	<0.001
Lipid pool	8.5 (63)	4.1 (30)	3.0 (47)	<0.001
Microvessel	15.9 (118)	2.4 (17)	1.9 (30)	<0.001
Calcification	2.4 (32)	0.7 (5)	0.3 (4)	<0.001
Correlation between neointimal area and no. of PLI	r = 0.624	r = 0.425	r = 0.593	<0.001*
Stent-level analysis				
N	32	30	63	
Left anterior descending artery lesion	59.4 (19)	60.0 (18)	66.7 (42)	0.37
Imaged length, mm	17.5 ± 5.7	19.4 ± 6.0	21.4 ± 8.6	<0.001
Imaged length, %*	90.6 ± 17.5	89.3 ± 22.4	83.3 ± 26.1	0.048
Stent length, mm	20.0 ± 6.1	22.1 ± 6.0	25.8 ± 6.1	<0.001
Volumetric obstruction, %	38.0 ± 11.1	21.8 ± 13.7	18.5 ± 13.9	<0.001
Volumetric obstruction, mm^3	75.8 ± 62.9	48.2 ± 39.7	35.3 ± 29.3	<0.001
Any PLI within stent	87.5 (28)	80.0 (24)	66.7 (42)	0.07
Mean PLI score	0.76 ± 0.83	0.46 ± 0.44	0.30 ± 0.56	0.003
Lipid pool	59.3 (19)	33.3 (10)	15.9 (10)	<0.001
OCT-TCNA	15.6 (5)	13.3 (4)	7.9 (5)	0.49
Correlation between mean neointimal area and strut with PLI	r = 0.736	r = 0.611	r = 0.803	<0.001*
Angiographic binary restenosis and OCT imaging				
Mean PLI score per stent	6.612 (1.572–27.80)†	50.93 (1.945–1333)†	129.9 (9.168–1839)†	
Stent area, mm^2	0.922 (0.559–1.521)	0.460 (0.211–1.004)	0.988 (0.628–1.555)	

Values are mean ± SD, n (%), or odds ratio (95% confidence interval). The Kruskal-Wallis test was used for comparison among stent types. p Value among 3 stent types, except *Pearson's correlation coefficient ($p < 0.05$) and †odds ratio of multivariate logistic regression analysis ($p < 0.05$).
BMS = bare-metal stent(s); OCT = optical coherence tomography; OCT-TCNA = OCT-derived thin cap neoatheroma; PES = paclitaxel-eluting stent(s); PLI = peri-strut low intensity; SES = sirolimus-eluting stent(s).

the late neointimal growth, PLI may be the trace of burnt-out neointimal growth or sustained residual biological process occurring adjacent to the stent.

The limitations of this study are its cross-sectional nature and lack of neointimal histology. The histological validation and serial examination of our findings deserve further investigation because they may have clinical implications among patients undergoing stent implantation.

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JACC: CARDIOVASCULAR IMAGING, VOL. 5, NO. 11, 2012
NOVEMBER 2012:1156–60

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Key Words: optical coherence tomography ■ peri-strut low intensity ■ stent