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Journal of the American College of Cardiology Vol. 48, No. 6, 2006
© 2006 by the American College of Cardiology Foundation
Published by Elsevier Inc.
ISSN 0735-1097/06/$32.00
doi:10.1016/j.jacc.2006.05.050

Characterization of Plaque Prolapse After Drug-Eluting Stent Implantation in Diabetic Patients

A Three-Dimensional Volumetric Intravascular Ultrasound Outcome Study

Hideki Futamatsu, MD, PHD,* Manel Sabaté, MD, PHD,† Dominick J. Angiolillo, MD, PHD, FACC,* Pilar Jimenez-Quevedo, MD,† Cecilia Corros, MD,† Kino Morikawa-Futamatsu, MD,* Fernando Alfonso, MD, PHD,† Julie Jiang,* Pavel Cervinka, MD, PHD,* Rosana Hernandez-Antolin, MD, PHD,† Carlos Macaya, MD, PHD,† Theodore A. Bass, MD, FACC,* Marco A. Costa, MD, PHD, FACC*

Jacksonville, Florida; and Madrid, Spain

OBJECTIVES The aim of this research was to evaluate the plaque prolapse (PP) phenomenon after bare-metal (BMS) and drug-eluting stent (DES) implantation in patients with diabetes mellitus using 3-dimensional volumetric intravascular ultrasound (IVUS).

BACKGROUND Plaque prolapse has been observed in up to 22% of patients treated with BMS. Diabetic patients have a larger atherothrombotic burden and may be more prone to have PP. However, the incidence of PP and its clinical impact after DES implantation is unknown.

METHODS Three-dimensional IVUS was performed after intervention and at 9-month follow-up in 168 patients with diabetes (205 lesions) treated with bare BX Velocity stents ((BX Velocity/Sonic, Cordis, Johnson & Johnson) (BMS, n = 65), sirolimus-eluting stents (Cypher, Cordis) (SES, n = 69), and paclitaxel-eluting stents (Taxus, Boston Scientific, Natick, Massachusetts) (PES, n = 71). Intravascular ultrasound data at the sites of PP were compared with stented segments without PP in each lesion. Outcomes were evaluated at 9- and 12-month follow-up.

RESULTS There were 42 sites of PP (BMS = 11, SES = 11, PES = 20, p = NS) in 34 stented segments of 205 (16.6%) lesions. Plaque prolapse was more frequent in the right coronary artery and in chronic total occlusion lesions. Post-procedure PP volume was 1.95 mm^3 in BMS, 2.96 mm^3 in SES, and 4.53 mm^3 in PES. At follow-up, tissue volume increased at PP sites in both BMS and PES, but not after SES. Neointimal proliferation was similar between PP and non-PP sites. Stent thrombosis and restenosis rates were similar between PP and non-PP lesions.

CONCLUSIONS The incidence of PP after implantation of new generation tubular stents in patients with diabetes remains high. Drug-eluting stent implantation was not associated with increased risk of PP. Plaque prolapse was not associated with stent thrombosis or increased neointimal proliferation. (J Am Coll Cardiol 2006;48:1139–45) © 2006 by the American College of Cardiology Foundation

Angiography is limited to detect prolapse or herniation of atheromatous plaque material into the coronary lumen through the stent struts (1). However, plaque prolapse (PP) is not a rare phenomenon and has been detected frequently by intravascular ultrasound (IVUS). Up to 22% of patients treated with bare-metal stents (BMS) may develop PP (2). When PP occurs, cardiologists usually face the dilemma of further balloon dilation or additional stent deployment to improve lumen dimensions or prevent complications such as thrombosis and restenosis. Plaque prolapse may generate further clinical uncertainty after deployment of drug-eluting stents (DES), because of their cost and potential risk of thrombosis (3). However, detailed outcome analysis of PP using serial IVUS imaging has not been reported yet. Furthermore, the incidence and clinical impact of PP after DES implantation has yet to be investigated.

Drug-eluting stents have been demonstrated to be efficacious in the treatment of coronary artery disease (4–9). The efficacy of DES for the treatment of coronary artery diseases in diabetic patients has been reported as well (10). Diabetic patients have more extensive, diffuse, and large atherothrombotic burden (11). However, data on the incidence, IVUS characteristics, and clinical impact of PP in diabetic patients are also lacking.

The aim of the present study was to evaluate the incidence and characteristics of PP as well as its clinical impact in diabetic patients treated with BMS and DES using 3-dimensional (3D) volumetric IVUS imaging.

From the *Division of Cardiology and Cardiovascular Imaging Core Laboratories, University of Florida, Jacksonville, Florida; and the †Cardiovascular Institute, San Carlos University Hospital, Madrid, Spain. Dr. Hideki Futamatsu was supported by grants from the Japan Heart Foundation/Bayer Yakuhin Research Grant Abroad. Dr. Costa has received speaker fees from Cordis, Johnson & Johnson.

Manuscript received February 6, 2006; revised manuscript received April 4, 2006, accepted May 15, 2006.

JACC Vol. 48, No. 6, 2006
September 19, 2006:1139–45

Abbreviations and Acronyms

BMS	= bare-metal stents
CSA	= cross-sectional area
DES	= drug-eluting stents
DIABETES	= Diabetes and Sirolimus-Eluting Stent trial
DS	= diameter stenosis
EEM	= external elastic membrane
IVUS	= intravascular ultrasound
MLD	= minimal lumen diameter
PP	= plaque prolapse
3D	= 3-dimensional

METHODS

Population. Two-hundred forty diabetic patients were enrolled in the DIABETES (Diabetes and Sirolimus-Eluting Stent) I and II multicenter, prospective trials. Patients were randomly assigned to receive BMS (BX Velocity/Sonic, Cordis, Johnson & Johnson) or sirolimus-eluting stents (SES) (Cypher, Cordis) in the DIABETES I trial (10). All patients in the DIABETES II trial, which had the same inclusion and exclusion criteria of DIABETES I study, received paclitaxel-eluting stents (PES) (Taxus, Boston Scientific, Natick, Massachusetts) (12). Protocols were approved by the ethics medical committee of participating institutions. All patients gave written informed consent. All patients presented de novo coronary stenoses in ≥1 native vessel with symptoms or objective evidence of ischemia. Patients with <72 h of myocardial infarction, impaired left ventricular function (left ventricular ejection fraction <25%), stenoses located in saphenous bypass, arterial bypass grafting, unprotected left main, or severe hepatic or renal disease were not included in the study. Intravascular ultrasound was performed after intervention and/or at 9-month follow-up in 168 diabetic patients with 205 lesions (patients/lesions: BMS: n = 56/65; SES: n = 57/69; PES: n = 55/71, respectively). The cohort of patients assessed by IVUS represented 70% of the enrolled population, and 76% of patients with follow-up assessments. Intravascular ultrasound analysis could not be performed in 9 cases with complete serial IVUS data because of poor image quality or inadequate pullback speed. Intravascular ultrasound imaging for serial comparison was not available either at baseline or follow-up in the remaining patients. Nevertheless, patients with serial IVUS analysis had similar baseline characteristics and clinical outcomes to those not evaluated by IVUS, not included in the present study. Angiographic restenosis and stent thrombosis rates were evaluated at 9- and 12-month follow-up, respectively. Stent thrombosis was defined as an acute coronary syndrome with angiographic documentation of either vessel occlusion or thrombus within or adjacent to a previously successfully stented vessel. In the absence of angiographic confirmation, either acute myocardial infarction in the distribution of the treated vessel or sudden death was considered as stent thrombosis. "Binary" restenosis was defined as stenosis of more than 50% of the luminal diameter in the target lesion at follow-up.

Coronary stent procedure. Coronary angioplasty was performed according to standard practice. Predilation with the use of a conventional balloon before stent implantation was optional. When multisegment or multivessel treatment was performed, all implanted stents had to be of the same type. All patients were treated with oral aspirin indefinitely (100 to 300 mg/daily) and clopidogrel (300 mg loading dose and 75 mg/daily maintenance dose for 1 year).

Quantitative coronary angiographic analysis. The angiographic analysis was blinded to treatment assignment by an independent core laboratory (University of Florida Cardiovascular Imaging Core Laboratories, Jacksonville, Florida). Coronary angiograms obtained at 270 days of follow-up were analyzed with the use of a computer-based system (13). The in-stent analysis encompassed only the segment covered by each stent. The diameter stenosis (DS) and minimal lumen diameter (MLD) were measured before intervention and at follow-up. Balloon–artery ratio was measured by stent size divided by reference vessel diameter.

IVUS imaging protocol. Intravascular ultrasound images were acquired using a motorized pullback at a constant speed of 0.5 mm/s, and volumetric quantification was performed. Images were recorded on high-resolution s-VHS tape for off-line analysis.

Qualitative and quantitative volumetric IVUS analyses were performed by an independent core laboratory (University of Florida Cardiovascular Imaging Core Laboratories, Jacksonville, Florida). Quantitative 3D IVUS analysis was performed using a dedicated quantitative IVUS analysis system (Pie Medical Imaging, Maastricht, the Netherlands) (14). The quantitative IVUS analysis system enables semiautomatic contour detection of the lumen, vessel, and stent as well as quantitative analysis of their dimensions in longitudinal and cross-sectional views. Longitudinal reconstructed views at 5° increments are displayed. The resulting cross-sectional Bezier contours can be visualized immediately superimposed on a running video loop and may be edited manually. The mathematical description consists of a connected series of Bezier curves. Lumen, stent, and external elastic membrane (EEM) areas were measured along the entire target segment. This system has been validated and used in previous clinical studies (15). Volumes were determined from a summation of measured cross-sectional area (CSA) in all frames of pullback region based on Simpson's rule; between 200 and 1,000 CSA were measured per segment. Mean areas were calculated as volumes divided by segment length.

Plaque prolapse was defined as tissue extrusion through the stent strut post-procedure, and the volume of PP was automatically calculated by subtracting lumen volume from stent volume. Neointimal hyperplasia was defined as subtracting lumen volume from stent volume at follow-up. Delta volumes and mean areas were calculated as follow-up minus post-values for EEM, lumen, and plaque.

Serial IVUS analysis was performed for the stent segment encompassing PP (PP site). At follow-up, the stented segment that matched the location of the site of PP post-procedure was selected for comparison. The remaining stented segments without PP were also quantified by serial IVUS (non-PP sites).

Statistical analysis. Quantitative variables are presented as mean ± SD and categorical variables as percentages. Student *t* test and one-way analysis of variance (ANOVA) were used to compare continuous variables. The paired-samples Student *t* test was used for within-group comparisons. The pair-wise comparison between groups was performed when statistical difference was detected by means of ANOVA. Categoric variables were compared by means of the chi-square or Fisher exact test for comparisons between groups (Stat View, SAS Institute, Inc., Cary, North Carolina). No adjustments for multiple comparisons were made. Differences were considered statistically significant at $p < 0.05$.

RESULTS

The baseline characteristics of the present study population (BMS: n = 56; SES: n = 57; PES: n = 55) were similar to those of the overall DIABETES I and II study populations (Table 1) (10,12). There were 42 sites of PP (BMS = 11, SES = 11, PES = 20) in 34 stented segments (33 patients) of 205 (16.6%; 95% confidence interval: 0.115 to 0.217) lesions. Baseline demographics between patients with and without PP were similar, except for a higher prevalence of men in the population with PP (Table 1). Plaque prolapse was visible by angiography in 18 of the 34 lesions with PP (52.9%), and did not produce severe residual stenosis or significant impairment in coronary flow. Angiographic and clinical outcomes of patients with angiographically visible versus non-visible PP were similar (data not shown). Further, there was no association between volume of PP and outcomes (data not shown). There was no significant difference in the incidence of PP among the 3 stent types. There was no significant difference in the volume of PP among the different stent groups (Fig. 1A). Plaque prolapse was detected more frequently in the right coronary artery or chronic total occlusion lesions. Conversely, PP was detected less frequently in the left anterior descending and left circumflex arteries ($p < 0.05$) (Table 2).

There were no differences in mean stent length and size between lesions with versus without PP. Balloon–artery ratio was not significantly different between PP and non-PP lesions. Further, pre-procedure percent DS in PP lesions was significantly higher, and MLD was significantly smaller than in non-PP lesions. At follow-up, the incidence of stent thrombosis and angiographic restenosis rate was not significantly different between PP and non-PP lesions (Table 2).

PP versus non-PP sites. In lesions with PP, mean stent, lumen, and in-stent plaque (PP or neointimal hyperplasia) areas at follow-up were not significantly different between the sites of PP versus non-PP sites in each group (Table 3).

Table 1. Clinical Characteristics

	All (n = 168)			BMS (n = 56)			SES (n = 57)			PES (n = 55)		
	PP	Non-PP	p	PP	Non-PP	p	PP	Non-PP	p	PP	Non-PP	p
No. of patients	33	135		9	47		9	48		15	40	
Age (yrs)	65.3 ± 9.7	66.2 ± 9.2		64.2 ± 10.8	68.9 ± 8.8		64.3 ± 9.8	65.9 ± 8.2		66.6 ± 9.4	63.5 ± 10.0	
Men (%)	84.8	69.6*		77.8	57.4		77.8	66.7		93.3	57.5*	
Previous myocardial infarction (%)	48.5	41.5		66.7	40.4		22.2	27.1		53.3	60.0	
Previous angioplasty or cardiac surgery (%)	21.2	20.7		33.3	19.1		22.2	27.1		13.3	22.5	
Clinical presentation (%)												
Acute coronary syndrome	45.5	43.7		66.7	48.9		55.6	62.5		26.7	15.0	
Systemic hypertension (%)	57.6	65.9		66.7	66		44.4	60.4		60.0	75.0	
Diabetes (%)												
Insulin-dependent	27.3	29.6		44.4	27.7		33.3	22.9		13.3	40.0	
Non–insulin-dependent	72.7	70.4		55.6	72.3		66.7	77.1		86.7	60.0	
Hypercholesterolemia (%)	66.7	71.7		55.6	66.0		88.9	64.6		60.0	85.0	
Smoking (%)	57.6	53.3		55.6	51.7		66.7	50.0		53.3	60.0	
Multivessel disease (%)	72.7	65.9		88.9	72.3		88.9	58.3		53.3	67.5	
Ejection fraction (%)	62.1 ± 11.9	66.8 ± 13.2		56.7 ± 14.0	66.2 ± 14.4		68.1 ± 9.3	67.0 ± 13.5		61.7 ± 10.9	67.4 ± 11.3	
Adjunct antithrombotic therapy (%)												
Glycoprotein IIb/IIIa inhibitors	69.7	62.2		88.9	53.2		88.9	58.3		46.7	77.5	
Clopidogrel	100.0	100.0		100.0	100.0		100.0	100.0		100.0	100.0	

Data are mean ± SD. *$p < 0.05$; PP vs. non-PP.
BMS = bare-metal stent; SES = sirolimus-eluting stent; PES = paclitaxel-eluting stent; PP = plaque prolapse.

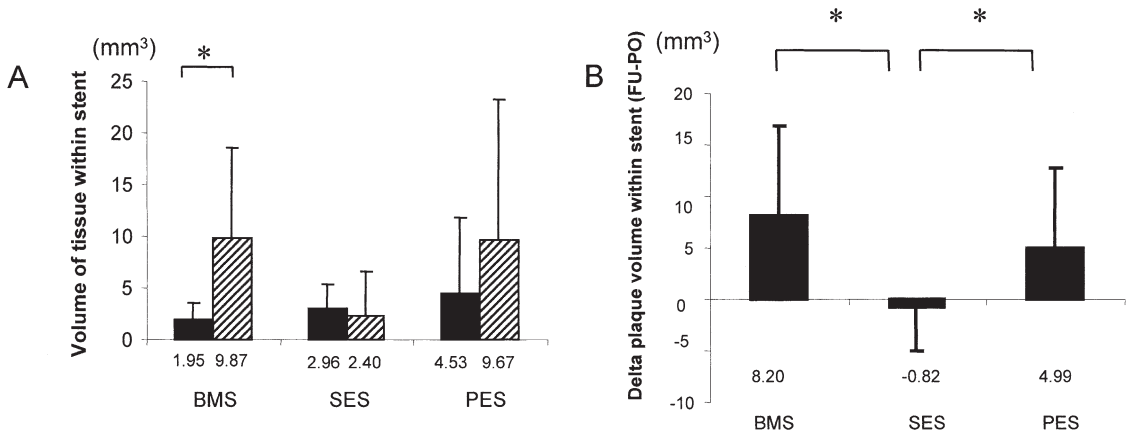

Figure 1. Change of tissue volume in the plaque prolapse sites within various stent types. The volume of tissue within stent at follow-up (FU) increased as compared with that at post-intervention (PO) in both bare-metal stents (BMS) and paclitaxel-eluting stents (PES), but there was tendency to decrease in sirolimus-eluting stents (SES) **(A)**. The delta volume of tissue within the stent in BMS or PES was significantly larger than that in SES **(B)**. *$p < 0.05$. **Black bars** = PO; **hatched bars** = FU.

Post-procedure plaque volume behind the stent struts was also measured. Plaque behind the stent may represent a surrogate of pre-procedure plaque burden, because debulking was not performed in this study. There were no differences in plaque burden behind the stent between PP sites and non-PP sites.

The volume of in-stent tissue within the PP site increased significantly after 9 months in the BMS group, but remained unchanged after SES. A trend in tissue volume increase in-stent was observed in the PES group ($p = 0.074$). There was a different pattern in plaque volume changes within the PP site in the BMS and PES versus SES (Fig. 1).

In both BMS and PES, the mean plaque/tissue area within the stent increased in both PP and non-PP sites at follow-up. However, delta plaque was similar between PP and non-PP sites in these groups. Indeed, there was plaque/tissue growth only in the non-PP sites in the SES group, although this was not statistically significant (Fig. 2). At the site of segments with PP, the minimum lumen CSA at follow-up was located within the PP site in 31.0% (BMS: 36.4%; SES: 27.3%; PES: 30.0%) (Table 3).

DISCUSSION

Plaque prolapse has been reported as an intraluminal tissue (atheroma or thrombus) protruding through the stent struts (1,16). Plaque prolapse within BMS has been found frequently during IVUS-guided stenting. A single study evaluated the overall outcomes of patients with PP after BMS (2). However, detailed assessment of the vessel wall reaction at the site of PP and the relative contribution of PP on neointimal formation remained unknown. The present study focused on diabetic patients who are known to have large atherothrombotic burden and may be more prone to develop PP after stenting. These patients have marked proliferative response after stenting (17), which may amplify the impact of PP. Our data suggest that PP is frequent in this patient population treated with new generation tubular stents (DES and BMS), but the incidence of PP was not higher than that previously reported. Whether the difference in stent design may account for these findings needs to be further evaluated (2). In particular, the BX Velocity stent is the platform in both SES and BMS groups.

We examined various factors to evaluate the conditions that predispose the occurrence of PP. Plaque prolapse was detected more frequently in men, but other baseline characteristics and stent dimensions were not associated with PP. There was a higher chance of PP after stenting severe stenoses, chronic total occlusions, and right coronary artery lesions. The use of specific stent designs with larger surface coverage or debulking techniques to prevent PP in these clinical scenarios remains speculative and would require proper evaluation in future studies. In addition, whether total occlusion in non-diabetic patients would also be associated with a higher incidence of PP after stenting remains to be investigated.

The apprehension that PP represents a milieu for enhanced thrombus formation or intimal proliferation has plagued cardiologists performing complex percutaneous interventions for years. This is emphasized if one considers the prothrombotic status that already characterizes diabetic patients even when treated with antiplatelet agents (18). In a recent IVUS evaluation on the causes of BMS thrombosis, investigators listed PP as a potential contributor to thrombosis, although only 1 of 23 patients investigated showed PP post-stenting (19). Finally, increased neointimal hyperplasia has been associated with the accumulation of circulating bone marrow–derived smooth muscle cells (20). Whether PP sites would provide a medium for attachment and proliferation of such circulating cells remains unclear.

Particularly in the era of DES, PP may represent a source of treatment failure as it may alter drug-elution profiles. Plaque prolapse may also represent a source for thrombus accumulation in a potential highly thrombogenic environment. Indeed, impaired neointimal healing and stent

Table 2. Background and Outcome of PP

	All (n = 205)			BMS (n = 65)			SES (n = 69)			PES (n = 71)		
	PP Lesion	Non-PP Lesion	p	PP Lesion	Non-PP Lesion	p	PP Lesion	Non-PP Lesion	p	PP Lesion	Non-PP Lesion	p
No. of lesions	34	171		9	56		9	60		16	55	
Treated artery												
LAD (n = 89)	9 (10.1%)	80 (89.9%)		3 (33.3%)	28 (50%)		1 (11.1%)	27 (45%)		5 (31.2%)	25 (45.5%)	
LCx (n = 30)	3 (10.0%)	27 (90.0%)		0 (0%)	9 (16.1%)		1 (11.1%)	10 (16.7%)		2 (12.5%)	8 (14.5%)	
RCA (n = 86)	22 (25.6%)	64 (74.4%)		6 (66.7%)	19 (33.9%)		7 (77.8%)	23 (38.3%)*		9 (56.3%)	22 (40%)	
Mean stent length (mm)	21.4 ± 6.4	19.9 ± 8.0		21.9 ± 7.4	19.7 ± 7.0		20.8 ± 6.7	19.6 ± 7.2		21.6 ± 5.7	20.5 ± 9.7	
Mean stent size (mm)	3.1 ± 0.4	3.0 ± 0.4		3.2 ± 0.5	3.0 ± 0.5		2.9 ± 0.5	2.9 ± 0.3		3.2 ± 0.4	3.0 ± 0.4	
Pre												
%DS	74.2 ± 20.0	61.7 ± 13.5*		69.8 ± 24.4	58.9 ± 10.4		71.0 ± 22.3	58.4 ± 15.4		79.0 ± 15.0	68.0 ± 12.2	
MLD (mm)	0.7 ± 0.5	1.0 ± 0.4*		0.7 ± 0.6	1.0 ± 0.4		0.8 ± 0.7	1.0 ± 0.4		0.5 ± 0.4	0.9 ± 0.4	
CTO (n = 18)	8 (44.4%)	10 (55.6%)		3 (33.3%)	4 (7.1%)*		2 (22.2%)	3 (5.0%)		3 (18.8%)	3 (5.5%)	
Non-CTO (n = 187)	26 (13.9%)	161 (86.1%)		6 (66.7%)	52 (92.9%)		7 (77.8%)	57 (95.0%)		13 (81.2%)	52 (94.5%)	
Lesion length	15.6 ± 4.5	15.1 ± 7.9		14.6 ± 4.8	15.9 ± 8.0		15.5 ± 5.0	13.7 ± 6.7		16.3 ± 4.5	15.6 ± 8.9	
Reference diameter (mm)	2.6 ± 0.6	2.5 ± 0.5		2.2 ± 0.4	2.4 ± 0.6		3.0 ± 0.8	2.4 ± 0.4		2.6 ± 0.4	2.6 ± 0.4	
Overlaping (%)	14.7	8.2		33.3	12.5		22.2	5		0	7.3	
Balloon–artery ratio	1.1 ± 0.1	1.1 ± 0.2		1.1 ± 0.1	1.2 ± 0.2		1.1 ± 0.2	1.2 ± 0.2		1.1 ± 0.1	1.1 ± 0.1	
Post												
%DS	14.5 ± 6.7	16.6 ± 9.7		21.1 ± 12.5	14.8 ± 6.7		14.5 ± 16.2	15.1 ± 7.6		12.7 ± 9.9	13.6 ± 6.1	
MLD (in-stent) (mm)	2.3 ± 0.4	2.3 ± 0.4		2.0 ± 0.5	2.2 ± 0.4		2.4 ± 0.4	2.2 ± 0.4		2.4 ± 0.3	2.4 ± 0.4	
MLD (in-lesion) (mm)	1.9 ± 0.5	1.9 ± 0.4		1.6 ± 0.5	1.8 ± 0.4		2.1 ± 0.5	1.8 ± 0.4		2.1 ± 0.4	2.1 ± 0.4	
Angiographic evidence (%)	52.9	—		55.5	—		66.7	—		43.8	—	
Follow-up												
%DS	23.4 ± 13.1	25.9 ± 16.7		33.6 ± 14.0	37.4 ± 19.1		15.4 ± 0.6	18.0 ± 13.1		22.3 ± 9.3	23.1 ± 10.8	
MLD (in-stent) (mm)	1.9 ± 0.6	1.9 ± 0.6		1.4 ± 0.6	1.5 ± 0.7		2.4 ± 0.5	2.2 ± 0.5		2.0 ± 0.3	2.0 ± 0.5	
MLD (in-lesion) (mm)	1.7 ± 0.6	1.7 ± 0.6		1.3 ± 0.6	1.4 ± 0.6		2.1 ± 0.4	1.8 ± 0.5		1.8 ± 0.4	1.7 ± 0.5	
Late loss (in-stent)	0.3 ± 0.4	0.4 ± 0.5		0.6 ± 0.4	0.7 ± 0.5		−0.02 ± 0.2	0.04 ± 0.3		0.4 ± 0.2	0.4 ± 0.4	
Late loss (in-lesion)	0.2 ± 0.3	0.3 ± 0.4		0.4 ± 0.3	0.4 ± 0.5		0.03 ± 0.2	−0.02 ± 0.3		0.3 ± 0.2	0.4 ± 0.3	
Restenosis (%)	14.7	11.7		44.4	25		0	3.3		6.3	7.3	
Thrombosis (%)	0	0		0	0		0	0		0	0	

Data are presented as mean ± SD and frequency. *$p < 0.05$; PP lesion vs. non-PP lesion.

BMS = bare-metal stent; CTO = chronic total occlusion; DS = diameter stenosis; LAD = left anterior descending; LCx = left circumflex; MLD = minimal lumen diameter; PES = paclitaxel-eluting stent; PP = plaque prolapse; RCA = right coronary artery; SES = sirolimus-eluting stent.

Table 3. Characterization of PP Site

	BMS (n = 11)		SES (n = 11)		PES (n = 20)	
	PP Site	Non-PP Site	PP Site	Non-PP Site	PP Site	Non-PP Site
Post						
Mean stent CSA (mm^2)	10.6 ± 3.1	10.2 ± 3.6	8.8 ± 3.5	9.2 ± 3.1	9.7 ± 2.6	10.1 ± 3.2
Mean lumen CSA (mm^2)	10.0 ± 2.9	10.2 ± 3.6	8.1 ± 3.2	9.2 ± 3.1	9.3 ± 2.6	10.1 ± 3.2
EEM CSA (mm^2)	23.3 ± 5.8	21.5 ± 6.5	18.4 ± 6.5	17.4 ± 4.6	21.2 ± 6.4	20.2 ± 8.2
Plaque behind the stent (mm^2)	12.6 ± 3.4	12.1 ± 4.4	10.0 ± 3.6	10.6 ± 3.4	11.5 ± 4.9	11.9 ± 3.9
Follow-up						
Mean stent CSA (mm^2)	10.5 ± 2.7	10.0 ± 3.0	9.5 ± 2.9	9.1 ± 2.1	10.4 ± 2.9	11.1 ± 3.2
Mean lumen CSA (mm^2)	7.2 ± 3.3	6.8 ± 3.2	9.0 ± 2.9	8.4 ± 1.5	8.9 ± 2.7	9.9 ± 3.0
EEM CSA (mm^2)	21.0 ± 6.0	19.4 ± 5.8	17.9 ± 3.8	18.4 ± 4.4	22.9 ± 4.5	22.7 ± 6.1
Delta EEM CSA (mm^2)	−1.3 ± 4.4	−0.68 ± 3.3	0.80 ± 5.8	1.3 ± 3.5	0.25 ± 3.4	2.0 ± 5.5
Location of mimimum lumen CSA (%)	36.4	63.6	27.3	72.7	30.0	70.0

Data are mean ± SD. p value: no significance; PP site vs. non-PP site.
CSA = cross-sectional area; EEM = external elastic membrane; other abbreviations as in Table 1.

thrombosis has been associated with prolapse of necrotic core between stent struts (21).

In the present study, serial IVUS evaluation of 42 sites of PP did not demonstrate increased neointimal proliferation compared with sites without PP in new generation tubular stents (Fig. 2). Restenosis or thrombosis rates were similar between prolapsed lesions and non-PP lesions in each stent group. Further, angiographic in-stent late loss was similar between PP and non-PP sites in the BMS group. These findings corroborate a previous report on the lack of association between PP and restenosis in BMS (2). In the present study, a more detailed evaluation of vessel wall response at the site of PP revealed a different pattern of tissue growth between SES and BMS or PES. Unlike BMS and PES, tissue volume in the PP sites of SES decreased. Delta plaque volume was significantly lower in the SES than in BMS and PES ($p < 0.05$) (Fig. 1).

Previous reports have suggested that SES could suppress not only accumulation of medial smooth muscle cells originated from the adjacent media but also accumulation of circulating bone marrow–derived cells (22). Whether these findings may explain the different pattern in plaque volume changes at the PP site between SES and PES and BMS (Fig. 1) remains to be evaluated. It is nevertheless important to notice that similar patterns of plaque growth were observed in non-PP sites among the stent groups.

The benign outcomes observed in the present study for patients with diabetes mellitus who developed PP after DES implantation is comforting, because the incidence of this phenomenon will likely increase as more complex interventions are performed worldwide. Importantly, in our study population, no therapeutic measures were taken in the presence of PP. The study findings may provide a reference for cardiologists when facing this disturbing phenomenon, and suggest that non–flow-limiting PP detected by either IVUS or angiography does not warrant further interventional maneuvers or unnecessary use of additional devices.

Study limitations. The present study involved a large cohort of patients with scheduled serial IVUS examination. However, our findings may not be applied to the general population, particularly patients with bypass graft disease and acute ST-segment elevation myocardial infarction. In these clinical scenarios, careful differentiation between PP and new thrombus formation should be made, and the association between PP and clinical outcomes remains to be investigated. Drop-outs and exclusions may have affected the study findings, which mainly reflect outcomes of patients who were alive and without complications at the time of follow-up examination.

Lack of pre-procedure IVUS data represents another limitation of the present study. Thus, correlation between plaque characteristics and PP was not performed. However, plaque behind the stent provided an indirect assessment of plaque burden, and allowed the evaluation of the relationship between local plaque burden and sites of PP.

Finally, this mechanistic and descriptive study may have limited statistical power to detect small differences in clinical outcomes between patients with and without PP. Thus, our results should be interpreted with caution because of potential type I error. However, the benign outcomes observed in our study population with PP, composed exclusively of diabetic subjects who are known to have a more enhanced thrombotic milieu (18), are encouraging, and it is unlikely that different outcomes will be observed in non-diabetic patients.

Conclusions. The present study demonstrated a high incidence of PP in diabetic patients treated with BMS and DES. The incidence of PP was similar between BMS and DES, although there was a trend toward a higher incidence of PP in patients treated with PES. Plaque prolapse was not associated with exaggerated neointimal proliferation in either BMS or DES groups. Indeed, no neointimal proliferation was observed in the PP sites of patients treated with SES. Plaque prolapse was not associated with increased risk of stent thrombosis or restenosis.

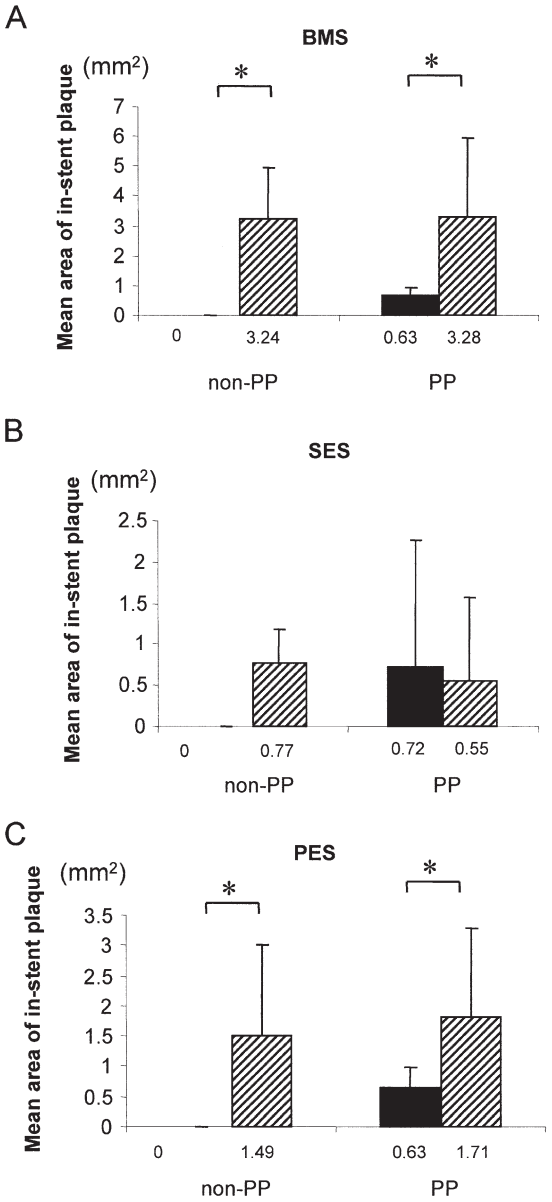

Figure 2. Change of the mean area of tissue between plaque prolapse (PP) sites and non-PP sites. In both BMS and PES, the mean area of tissue through the stent struts in both non-PP and PP sites significantly increased at follow-up **(A and C)**. In SES, the mean area of tissue through the stent struts increased in non-PP sites, but decreased in PP sites **(B)**. *$p < 0.05$. **Black bars** = PO; **hatched bars** = FU. Abbreviations as in Figure 1.

Reprint requests and correspondence: Dr. Marco A. Costa, Division of Cardiology and Cardiovascular Imaging Core Laboratories, University of Florida, 655 West 8th Street, Jacksonville, Florida 32209. E-mail: marco.costa@jax.ufl.edu.

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