In-Stent Neointimal Proliferation Correlates With the Amount of Residual Plaque Burden Outside the Stent
An Intravascular Ultrasound Study

Francesco Prati, MD; Carlo Di Mario, MD; Issam Moussa, MD; Bernhard Reimers, MD; Maria Teresa Mallus, MD; Antonio Parma, MD; Ernesto Lioy, MD; Antonio Colombo, MD

**Background**—The aim of this study was to evaluate the relationship between residual plaque burden after coronary stent implantation and the development of late in-stent neointimal proliferation.

**Methods and Results**—Between January 1996 and May 1997, 50 patients underwent intravascular ultrasound (IVUS) interrogation at 6±1.2 months after coronary stent implantation in native coronary arteries. IVUS images were acquired with a motorized pullback, and cross-sectional measurements were performed within the stents at 1-mm intervals. The following measurements were obtained: (1) lumen area (LA), (2) stent area (SA), (3) area delimited by the external elastic membrane (EEMA), (4) percent neointimal area calculated as (SA−LA)/SA×100, and (5) percent residual plaque area calculated as (EEMA−SA)/EEMA×100. Volume measurements within the stented segments were calculated by applying Simpson’s rule. In the pooled data analysis of 876 cross sections, linear regression showed a significant positive correlation between percent residual plaque area and percent neointimal area (r=0.50, y=45.03+0.29x, P<0.01). There was significant incremental increase in mean percent neointimal area for stepwise increase in percent residual plaque area. Mean percent neointimal area was 16.3±10.3% for lesions with a percent residual plaque area of <50% and 27.7±11% for lesions with a percent residual plaque area of ≥50% (P<0.001). The volumetric analysis showed that the percent residual plaque volume was significantly greater in restenotic lesions compared with nonrestenotic lesions (58.7±4.3% versus 51.4±5.7%, respectively; P<0.01).

**Conclusions**—Late in-stent neointimal proliferation has a direct correlation with the amount of residual plaque burden after coronary stent implantation, supporting the hypothesis that plaque removal before stent implantation may reduce restenosis. (Circulation. 1999;99:1011-1014.)

Key Words: ultrasonics ■ stents ■ restenosis

SeVERAL studies in animals have shown that the implantation of metal endoprosthesis in coronary arteries promotes late neointimal proliferation.1–4 This healing process was attributed to vessel trauma induced by stent implantation and by a “foreign body” reaction. These experiments, however, were performed in nonatherosclerotic coronary arteries; therefore, the contribution of the atherosclerotic plaque per se to the proliferative process has not been elucidated in these studies. Intravascular ultrasound (IVUS) observations in humans have confirmed that in-stent restenosis (Palmaz-Schatz stent) is primarily due to neointimal proliferation.5 In addition, it was observed that the late neointimal formation is greater in the midportion of the stented segment. Initially, it was thought that the presence of the central articulation in that particular stent was the reason for this finding, but similar results were confirmed with nonarticulated stent designs.6 These observations raise the possibility that the bulk of the intimal proliferation may be occurring at the original site of the lesion (where the plaque burden is largest). The aim of the present study was to evaluate the correlation between the residual plaque burden after stent implantation and the amount of neointimal proliferation at follow-up using IVUS.

**Methods**

**Study Population and Design**

Between January 1996 and May 1997, 72 patients who previously had coronary stent implantation (80 stents) returned for angiographic and IVUS follow-up studies. Twenty-two patients (with 30 stents) were excluded because of the inability to delineate the external elastic membrane (EEM) due to stent filament shadowing.

Thus, the study population consisted of 50 patients with 50 lesions who had a single stent implantation (34 Microstent, 7 Palmaz-Schatz, 3 BeStent, 2 Wiktor, and 4 Nir) and in whom it was possible to identify ≥80% of the EEM circumference in all slices of the stented segment at the follow-up study. The stent length was 8 to 30 mm.

Of this population, 15 patients originally had poststenotic IVUS assessment; therefore, it was possible to evaluate whether there were

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From the Catheterization Laboratory (F.P., M.T.M., A.P., E.L.), S. Camillo Hospital, Rome, Italy; and Centro Cuore Columbus (C.D.M., I.M., B.R., A.C.), Milan, Italy.

Correspondence to Antonio Colombo, MD, FACC, Centro Cuore Columbus, Via Buonarroti, 48, 20145 Milano, Italy.

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any variations in residual plaque burden and stent size between the time of stent implantation and the follow-up study.

Coronary Angiography
Coronary angiography was performed in a routine manner. Angiographic measurements were performed with digital electronic calipers (Brown and Sharp) from an optically magnified image in the view that shows the most severe narrowing. All angiograms were analyzed by an experienced angiographer who was not involved in the intervention and who was blinded to the IVUS measurements. Angiographic restenosis was defined as diameter stenosis of ≥50% at the treated site.

IVUS Assessment

Image Acquisition
Postintervention and follow-up IVUS images were obtained with a 3.2F short monorail imaging catheter (Cardiovascular Imaging Systems, Inc) after written informed consent had been obtained. The IVUS catheter incorporates a 30-MHz single-element bevelled transducer mounted at the distal end of the catheter and rotated at 1800 rpm. After coronary angiography, patients were administered heparin 5000 U IV in the arterial sheath and nitroglycerin 200 µg IC. The imaging probe was positioned distal to the stented segment and a mechanical pullback was performed at 0.5 mm/s. IVUS images were recorded onto high-resolution s-VHS videotape for offline analysis.

Quantitative IVUS Analysis
Cross-sectional vessel area, stent area, and lumen area measurements were performed every 2 seconds of videotape. Therefore, each stent was axially divided into several 1-mm segments. The following measurements were obtained: (1) lumen area (LA), (2) stent area (SA), and (3) area inside the external elastic membrane (EEMA). Two indexes were calculated: (1) percent neointimal area, defined as echogenic material within the stent and calculated as (SA−LA/SA) × 100; and (2) percent residual plaque area, calculated as (EEMA−SA)/EEMA×100. Volume measurements of the stented segments were calculated by applying Simpson’s rule.

The reproducibility of IVUS measurements of EEMA, SA, and plaque-plus-media area has already been reported. Because visualization of the EEM in stented segments can be hampered by stent filaments, the reproducibility of measurements of the EEM, stent, lumen, and plaque volumes was tested in a blind comparison performed by 2 independent operators in 10 stents (5 Palmaz-Schatz, 3 BeStent, and 2 NIR stents).

Statistical Analysis
Continuous variables were expressed as mean±SD values. Two-tailed t test was used for continuous variables. A χ² test was used to detect differences between categorical variables. Linear regression analyses were performed for pooled data and for each individual stented segment. A value of P<0.05 was considered statistically significant.

Results

Clinical and Angiographic Data

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Association Between Residual Plaque Burden After Stent Implantation and In-Stent Neointimal Proliferation
A pooled data analysis was performed on 876 intrastent ultrasound cross sections. Mean percent residual plaque area and mean percent neointimal area were 54.0±8.9% and 25.8±14.5%, respectively. A significant positive correlation between these 2 indices was found (r=0.50, y=45.03+0.29x, P<0.01) (Figure 1). A pooled data analysis was also obtained in the stent group with restenosis (210 intrastent cross sections) and confirmed the significant positive correlation.
The major finding of this study was that the amount of volume (from 170.3 to 400.1 mm$^3$ at postintervention to follow-up, respectively. Also, there was no correlation between percent neointimal area and percent residual plaque area was found in 37 of 50 lesions (74%).

In addition, as shown in Figure 2, an incremental increase of percent residual plaque area was associated with a stepwise increase in percent neointimal area. This association could be dichotomized using 50% residual plaque area as cut-off criterion. At this threshold, 2 lesion groups could be identified: group I with percent residual plaque area of <0.50 who had a mean percent neointimal area of 16.3±10.3%, and group II with percent residual plaque area of ≥0.50 who had a mean percent neointimal area of 27.7±11.0% (P<0.001). The same results were found in the patient group with restenosis. Mean percent neointimal area was significantly higher in group I (percent residual plaque area <0.50) than in group II (percent residual plaque area ≥0.50) (22.9±13.3% in group I versus 42.1±12.6% in group II, respectively; P<0.001).

Volumetric Analysis
Volume measurements of stent, EEM, and plaque measured by 2 independent observers were highly reproducible. Correlation of repeated measurements of stent EEM and plaque volume, obtained at either postintervention or follow-up, were 0.99, 0.98, and 0.98, respectively. Also, there was no volumetric variation in serial IVUS assessments of stent volume (from 170.3±98.0 mm$^3$ at postintervention to 167.1±84.2 mm$^3$ at follow-up, NS), EEM volume (from 404.4±202.2 to 400.1±178.4 mm$^3$, NS), and residual plaque volume (from 234.1±102.6 to 233±92.0 mm$^3$, NS).

In the pooled data analysis, percent residual plaque volume was 52±9.5% and percent neointimal volume was 25±8.8%. Percent residual plaque volume was significantly greater in the stent group with restenosis than in the group without restenosis (58.7±4.3% versus 51.4±5.7%, respectively) (P<0.01).

Discussion
The major finding of this study was that the amount of residual plaque burden present after stent implantation is related to the development of late in-stent neointimal proliferation. In this study, residual plaque area was determined at follow-up based on the assumption that these measurements did not change during the follow-up period. This assumption was confirmed in a subanalysis of 15 lesions in which a volumetric assessment was performed postintervention and at follow-up and demonstrated no significant variations in stent volume, EEM volume, and residual plaque volume. This is consistent with other studies that used serial IVUS assessment of Palmaz-Schatz stents to demonstrate the absence of late variations in stent volume.7,8

Our findings are consistent with previous observations that demonstrated that the residual plaque area after various coronary interventions influences late restenosis. In the GUIDE II trial,12 500 lesions were studied with IVUS after percutaneous transluminal coronary angioplasty or directional coronary atherectomy (DCA). The final MLD achieved and the residual percent plaque area were found to be predictors of late clinical recurrence or angiographic restenosis. These data were further supported by the results of 2 trials using IVUS-guided directional atherectomy (OARS and ABACAS).13,14 In the OARS trial, percent residual plaque area after directional atherectomy was 58%, which resulted in a restenosis rate of 29%. In the ABACAS trial, more aggressive IVUS-guided directional atherectomy was performed, achieving a 42% residual plaque area with a subsequent restenosis rate of 21%. Furthermore, Mintz et al15 reported an analysis of 343 lesions treated with percutaneous transluminal coronary angioplasty, laser, rotational, or directional atherectomy that showed the amount of residual plaque is a powerful predictor of restenosis.

In nonstent coronary interventions, restenosis is primarily due to late vessel constriction. Stent implantation eliminates this component of the restenotic process but may stimulate neointimal proliferation. Previous studies provided indirect evidence that the amount of plaque burden before stent implantation influences the development of in-stent neointimal proliferation: (1) few studies suggested that the percent plaque burden before stent implantation was significantly correlated with the development of angiographic late lumen loss and restenosis16-17; (2) other studies suggested that lesion-specific factors are related to in-stent restenosis, which is linearly related to the length of lesion and the angiographic vessel size, 2 conditions that are associated with the presence of diffuse atherosclerotic burden with IVUS8; and (3) serial IVUS assessment shows a larger neointimal formation in the midportion of the stented segments, where a large residual plaque should be expected. These findings were initially explained with the incomplete coverage at the site of the articularation in the Palmaz-Schatz stent, but they have been confirmed in nonarticulated stents.7,8,18 (4) In a large prospective series of lesions treated with directional coronary atherectomy before stent implantation, a low restenosis rate has been reported, significantly different from the restenosis observed in matched lesions treated with stent without previous debulking. This difference could not be explained only by the additional immediate gain allowed by the plaque removal because the most striking finding was a low late
lumen loss, suggesting that plaque removal diminishes the hyperplastic response after stent implantation.\(^1\)

**Study Limitations**

A limitation of the study was that the number of patients was relatively small and selection bias might have occurred because only patients with IVUS follow-up were studied. However, the majority of these patients returned for angiographic and IVUS studies as part of a routine follow-up, and only 28% of them were found to have angiographic restenosis. Despite these shortcomings, this study illustrates the quantitative relationship between plaque burden and in-stent neointimal proliferation, a finding that may have important clinical implications.

**Conclusions**

The amount of plaque burden that remains after stent implantation is strongly associated with the amount of late in-stent neointimal proliferation. This observation supports the use of plaque removal before stenting to reduce late neointimal proliferation. This study illustrates the clinical implications.

**References**


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