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Correlation of Angiographic Late Loss With Neointimal Proliferation in Stents Evaluated by OCT and Histology in Porcine Coronary Arteries

Jung-Sun Kim, MD, PHD,* David Wallace-Bradley, BS,* Carlos L. Alviar, MD,*†
Gerard Conditt, RCIS,* Krzysztof Milewski, MD, PHD,* Maxwell E. Afari, MD,*
Yanping Cheng, MD,* Catalina Gallego, MD,* Armando Tellez, MD,*
Gregg W. Stone, MD,* Greg L. Kaluza, MD, PHD,* Juan F. Granada, MD*
Orangeburg and New York, New York

OBJECTIVES We aimed to evaluate the correlation of angiographic late loss (LL) with the degree of in-stent neointimal proliferation assessed by optical coherence tomography (OCT) and histology.

BACKGROUND Angiographic LL is the most common endpoint used in clinical trials for the evaluation of the efficacy of drug-eluting stents (DES). However, there are few data in regards to the accuracy of angiographic LL in the evaluation of DES displaying lower degrees of neointimal proliferation.

METHODS A total of 49 stents (36 DES and 13 bare-metal stents) were deployed in coronary arteries of 23 domestic swine and followed up for 28 or 90 days, thus obtaining different degrees of neointimal proliferation. Each stent was divided into 8 to 9 segments along the longitudinal axis to match corresponding histological cross sections. Angiographic LL was calculated at each segment throughout the entire length of the stent and compared with in-stent neointimal thickness (NT) obtained by OCT and histology.

RESULTS A total of 382 angiographic segments were suitable for matched comparison with both OCT and histological findings. The mean LL at follow-up was 0.60 ± 0.57 mm (range: −0.46 to 2.3 mm) for all segments. Approximately 13.9% of stent segments had a LL between −0.5 and 0 mm, and 22.5% had a LL greater than 1.0 mm. The correlation between OCT and histology for the evaluation of NT was adequate regardless the level of angiographic LL. In addition, overall correlations between angiographic LL and NT by OCT or histology were adequate ($R = 0.77$ and 0.63, respectively). However, angiographic LL showed a poor correlation with NT by OCT or histology at a value <0.55 mm ($R = 0.38$ and 0.15, respectively).

CONCLUSIONS Angiographic LL below a threshold value of 0.55 mm correlates poorly with NT obtained by OCT and histology. These results suggest a cautious interpretation is needed to evaluate angiographic endpoints in DES trials in which LL values below this threshold are reported. (J Am Coll Cardiol Img 2011;4:1002–10) © 2011 by the American College of Cardiology Foundation

From the *Skirball Center for Cardiovascular Research, Cardiovascular Research Foundation, Orangeburg, New York; and the †St. Luke's-Roosevelt Hospital Center and Columbia University College of Physicians and Surgeons, New York, New York.
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Quantitative coronary angiography (QCA) is the most common diagnostic method used to assess the efficacy of drug-eluting stents (DES) (1,2). Angiographic late loss (LL) has been used as a surrogate endpoint in the evaluation of stent efficacy in clinical trials (3). By measuring the total amount of angiographic lumen loss at follow-up, an indirect assessment of the amount of neointimal proliferation formed within the stent can be made. It has been shown that angiographic LL seems to correlate with the occurrence of important clinical events, such as binary restenosis and target lesion revascularization (TLR), and its value as a surrogate endpoint for the assessment of restenosis propensity and stent performance has been suggested (2–4). Following the widespread use of DES, the degree of angiographic LL has consistently been reported to be usually less than 0.4 mm (1), a value close to the resolution threshold of angiography. To date, there are few data in regard to the accuracy of angiographic LL in the evaluation of DES displaying lower degrees of neointimal proliferation. In the present study, we aimed to determine the threshold at which angiographic LL correlates with neointimal thickness (NT) evaluated by in vivo optical coherence tomography (OCT) and histology.

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METHODS

Study design. The study protocol was approved by the local institutional animal care and use committee. All animals received humane care in compliance with the Animal Welfare Act and the "Guide for the Care and Use of Laboratory Animals." A total of 49 stents (13 Xience V [3.0 × 12 mm, Abbott Vascular, Santa Clara, California], 11 Endeavor Sprint [3.0 × 12 mm, Medtronic, Minneapolis, Minnesota], 12 Taxus Liberte [3.0 × 12 mm, Boston Scientific, Natick, Massachusetts], and 13 ML Vision [3.0 × 12 mm, Abbott Vascular]) were implanted in the coronary arteries of 23 domestic swine (25 to 40 kg). All animals were divided into 2 groups according to the length of follow-up: 28 days (n = 12; 23 stents) or 90 days (n = 11; 26 stents) in order to achieve different levels of neointimal formation. At the time of deployment, the location of each stent was systematically randomized to the coronary arteries of each animal.

Procedural description. Animals were pre-medicated with 325 mg of aspirin and 75 mg of clopidogrel at least 12 h before the procedure and pre-anesthetized with an appropriate mixture of glycopyrrolate, telazol, and xylazine based on animal weight. After an adequate anesthetic status, the animals were intubated and inhaled isoflurane (1% to 2%) delivered through a precision vaporizer and a circle absorption breathing system with periodic arterial blood gas monitoring. A vascular access sheath (7-F) was placed in the carotid artery by cut-down with sterile technique. Before catheterization, heparin (5,000 to 10,000 U) was injected to maintain an activated coagulation time of 250 to 300 s. Each stent deployment was with a stent-to-artery ratio of ≥1.1. After vessel allocation to an experimental group, the appropriate stent was delivered to the intended site over a guidewire using fluoroscopic guidance. Following stent implantation, hemostasis was obtained by arterial ligation using 2-0 silk suture and the incision site closed in 2 to 3 layers with appropriate suture material. All animals received aspirin (81 mg) and clopidogrel (75 mg) daily, and remained on a normal chow diet.

Angiographic analysis protocol. Quantitative coronary angiography (QCA) was performed at baseline, following stent implantation, and at the terminal procedure using the QAngio XA 7.1 Medis System (Medis Medical Imaging Systems, Leiden, the Netherlands). All angiograms were analyzed by an operator blinded to both stent type and termination time point. Each stent was divided into 9 segments along the longitudinal axis to match corresponding histological segments (Fig. 1). Each individual segment underwent QCA analysis for the assessment of minimal lumen diameter (MLD) immediately post-implantation and at follow-up. Angiographic LL was determined at each individual segment by subtracting the MLD at follow-up from the MLD assessed immediately post-stenting as previously described (5). The MLD was considered the smallest lumen diameter in each segment within the stent automatically identified by the software and confirmed by the QCA operator. Percent diameter stenosis was calculated according to the following formula: percent diameter stenosis = [1 − (lumen diameter/mean reference vessel diameter)] × 100.

OCT imaging protocol and analysis. OCT images were obtained using the M2 OCT imaging system

ABBREVIATIONS AND ACRONYMS

AS = area stenosis
CS = cross section(s)
DES = drug-eluting stent(s)
LL = late loss
MLD = minimal lumen diameter
NT = neointimal thickness
OCT = optical coherence tomography
QCA = quantitative coronary angiography
TLR = target lesion revascularization

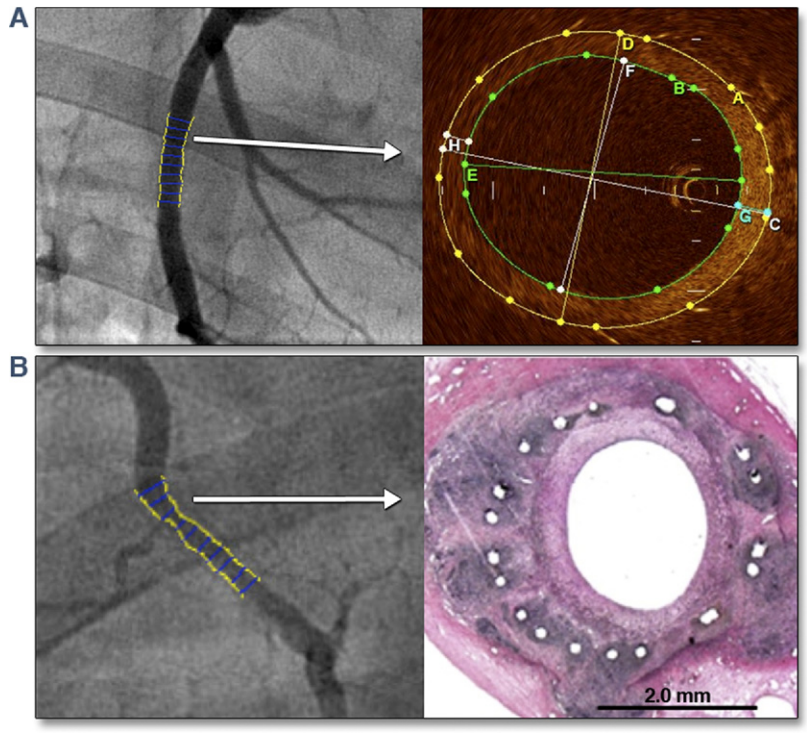

Figure 1. Representative Images for Matching Segment Between Angiographic LL and OCT, or Histology CS

Each stent at angiography was divided into 8 to 9 segments along the longitudinal axis, and each individual angiographic segment underwent a quantitative coronary analysis (QCA). Each stent segment at angiography was matched to the corresponding optical coherence tomography (OCT) **(A)** and histological **(B)** section. CS = cross section; LL = late loss.

(LightLab Imaging, Inc., Westford, Massachusetts) at 28 or 90 days after stent implantation. Motorized OCT pullbacks were performed at a rate of 1.0 mm/s. If the initial pullback was not of adequate quality, sequential pullbacks were performed until an optimal sequence was achieved. All images were stored on the system hard drive for offline analysis.

Every subsequent millimeter was specified by the OCT frame-rate, allowing for precise histological–OCT frame matching. Stent area (SA) was defined as the circumferential area limited by the contours of the struts. Lumen area (LA) was defined by the evaluator as the leading edge of the circumferential hyper-reflective zone covering the stent struts. Neointimal area was calculated by subtracting the LA from the SA. To analyze NT, the distance between the center of each strut and the luminal border was measured in the direction of the stent center of gravity. The percentage area stenosis (AS) was calculated according to the following formula: percent AS = $[1 - (LA/SA)] \times 100$. A stent strut was considered covered if NT was ≥ 20 μm. Complete strut coverage was defined as 100% of struts covered with neointima thicker than 20 μm in each cross section (CS). The neointimal unevenness score was calculated in each individual CS by dividing the maximal NT by the average NT within the same CS (6).

Tissue harvesting and histology protocol. All animals were euthanized immediately following follow-up imaging under general anesthesia. Hearts were excised and pressure-perfused with 0.9% saline followed by pressure-perfusion fixation in 10% neutral-buffered formalin until hardening of the heart muscle was clearly perceptible as previously described (7,8). Prior to histological processing, intact hearts with stented vessels were imaged by capturing high-contrast film-based radiographs (Faxitron X-ray Corp, Model 43855A, National X-Ray, Lawrenceville, Georgia) to locate and assess stent location. The stented arterial segments were then carefully dissected. After polymerization, 8 to 9 sections, each measuring approximately 1.3 mm, were sawed from each stent, beginning at the distal stent edge. Individual slides were cut on a rotary microtome at 4 to 6 μm, mounted, and stained with hematoxylin and eosin, and elastic Van Gieson stains. All sections were examined by light micros-

copy for the presence of inflammation, thrombus, neointimal formation, and vessel wall injury. The cross-sectional areas (external elastic lamina [EEL], internal elastic lamina [IEL] and LA) of each section were measured using ImagePro Plus 4.5 (Media Cybernetics, Bethesda, Maryland). NT was measured as the distance from the center of each stent strut to the luminal border in the direction of the stent center of gravity. Area measurements were used to calculate vessel layer areas: media (EEL area − IEL area), neointima (IEL area − LA), and %AS (1 − [LA/IEL area] × 100). Complete strut coverage was defined as 100% of struts covered with neointima in each CS. Endothelial coverage was semiquantified and expressed as the percentage of the lumen circumference covered by endothelium. Complete endothelial coverage was defined as 100% of strut covered with endothelial cell at each CS.

Imaging coregistration protocol. Each harvested stent was divided into 8 or 9 segments ranging between 1.19 mm and 1.59 mm in thickness. In order to accurately match the histological CS with both imaging modalities, each OCT frame and QCA measurement site was assessed at the exact site of histological cutting. The locations of the OCT frames were selected using the pullback speed and frame numbers to precisely determine the position of the in vivo image within the stent. QCA measurements were precisely matched using the built-in distance function within the analytical software utilized (Fig. 1).

Statistical analysis. Continuous variables were expressed as a mean ± SD. Student *t* test was performed to compare continuous variables; a Mann-Whitney *U* test was used for skewed distributions. The categorical variables were expressed as both number and percentage, and were compared using the chi-square test or Fisher exact-test. All OCT measurements were performed by 2 experienced operators, and their results were compared to gauge the interobserver variability of the study. Repeated measurements were obtained by the primary observer after 2 weeks in order to assess intraobserver variability. Linear regression analysis was performed on all corresponding datasets, and the resulting correlation coefficient (R value) was reported. To identify the optimal level of LL, which was adequately correlated with NT by OCT or histology, intervals were divided according to LL value with the same standard deviation of 0.1 mm because the Pearson correlation coefficient is dependent on the standard deviation of the variables used. We therefore tried to eliminate differences in correlation coefficients between intervals that would be due simply to between-interval differences in the standard deviation of the LL. To minimize an effect for this, we specified mutually exclusive and exhaustive intervals of LL that had the same standard deviation of 0.10. Using this method, we found a cutoff value (0.55 mm of LL) to diverge the correlation coefficient (Fig. 2). The correlation analysis between angiographic LL and OCT or

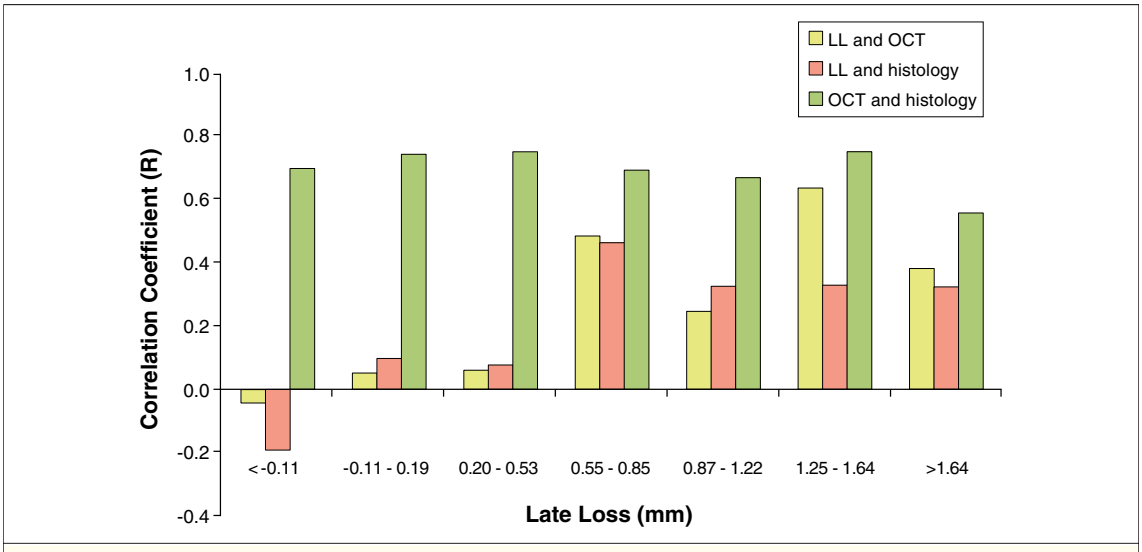

Figure 2. Correlation Coefficient Between Angiographic LL, NT by OCT, and NT by histology

Each interval was divided with the value of LL within 0.1 mm of standard deviation. NT = neointimal thickness; other abbreviations as in Figure 1.

histology in all and each interval (<0.55 mm of LL and ≥0.55 mm of LL) was analyzed using the Spearman correlation test due to the fact that the distribution of the data was skewed. In addition, a nonlinear model with 95% prediction interval was utilized to evaluate the error of fit across ranges. Data were analyzed with the SPSS 16.0 software for Windows (SPSS, Chicago, Illinois). A p value <0.05 was considered statistically significant.

RESULTS

Angiographic LL analysis. A total of 49 stents were included in the analysis, yielding a total sample of 382 angiographic stent segments that were matched with corresponding OCT and histological imaging frames. The average number of segments analyzed per stent was 7.9 ± 0.5 (range: 6 to 9 segments). By angiography, the mean MLD immediately after stent implantation was 2.90 ± 0.23 mm (range: 1.95 to 3.48 mm). At follow up, the mean MLD was 2.31 ± 0.53 mm (range: 0.87 to 3.44 mm). The mean LL at follow-up was 0.60 ± 0.57 mm (range: −0.46 to 2.30 mm) for all examined segments (Table 1). Approximately 13.9% of stent segments had a LL between −0.5 and 0 mm, and 22.5% had a LL >1 mm. Most angiographic stent segments (63.6%) had a LL between 0 and 1.0 mm at follow-up.

Angiographic LL and OCT correlation. The mean neointimal area was 2.10 ± 1.65 mm^2 (range: 0 to 6.60 mm^2), and the mean NT was 0.28 ± 0.22 mm (range: 0 to 1.01 mm). Approximately 82.2% of stent segments had a NT less than 500 μm. Intraobserver variability was very low for the measurement of NT and area by OCT (R = 0.99 and R = 0.99, respectively), as was interobserver variability (R = 0.98 and R = 0.98, respectively). Overall angiographic LL correlated well with NT, neointimal area, and percent AS obtained by OCT analysis (R = 0.77, R = 0.76, and R = 0.76, respectively). However, correlation between angiographic LL and NT assessed by OCT appeared to be affected by the level of neointima proliferation.

Table 1. Morphological Parameters Assessed In Vivo by QCA and OCT, and Ex Vivo by Histology in a Total of 382 Matched CS

	All (n = 382)	Group 1 (LL <0.55 mm) (n = 206)	Group 2 (LL ≥0.55 mm) (n = 176)	p Value
QCA				
MLD at post-stent, mm	2.90 ± 0.23	2.86 ± 0.25	2.95 ± 0.21	<0.001
MLD at follow-up, mm	2.31 ± 0.53	2.69 ± 0.30	1.86 ± 0.38	<0.001
Diameter stenosis, %	22.7 ± 16.6	12.5 ± 11.8	34.9 ± 12.9	<0.001
LL, mm	0.60 ± 0.57	0.18 ± 0.25	1.09 ± 0.42	<0.001
OCT				
Neointimal thickness, mm	0.28 ± 0.22	0.15 ± 0.11	0.43 ± 0.22	<0.001
Lumen area at follow-up, mm^2	4.94 ± 1.76	5.89 ± 1.20	3.71 ± 1.49	<0.001
Neointimal area, mm^2	2.10 ± 1.65	1.13 ± 0.84	3.24 ± 1.64	<0.001
Percent area stenosis, %	30.0 ± 22.7	16.2 ± 13.0	46.0 ± 21.0	<0.001
*Percentage of strut coverage, %	93.7 ± 13.7	88.0 ± 16.6	98.3 ± 6.6	<0.001
†Complete strut coverage	273/382 (71.5%)	113/206 (54.9%)	160/176 (90.9%)	<0.001
‡Neointimal unevenness score	1.82 ± 0.56	1.99 ± 0.61	1.64 ± 0.45	<0.001
Histology				
Neointimal thickness, mm	0.29 ± 0.22	0.18 ± 0.15	0.42 ± 0.22	<0.001
Lumen area at follow-up, mm^2	4.18 ± 1.61	4.98 ± 1.33	3.23 ± 1.37	<0.001
Neointimal area, mm^2	2.47 ± 1.37	1.77 ± 0.84	3.30 ± 1.40	<0.001
Percent area stenosis, %	37.9 ± 20.4	27.1 ± 14.6	50.6 ± 18.9	<0.001
*Percentage of strut coverage, %	99.4 ± 2.9	99.0 ± 3.7	99.8 ± 1.6	0.003
†Complete strut coverage	362/382 (94.8%)	189/206 (91.7%)	173/176 (98.3%)	0.004
§Percentage of endothelial coverage, %	98.6 ± 4.1	98.3 ± 4.8	99.1 ± 3.2	0.23
‖Complete endothelial coverage	291/382 (76.2%)	153/206 (74.3%)	138/176 (78.4%)	0.34
Neointimal unevenness score	1.82 ± 0.60	1.96 ± 0.66	1.66 ± 0.47	<0.001

Values are n (%) or mean ± SD. *Percentage of strut coverage was defined as % of strut covered with neointima (≥20 μm thickness) in OCT CS or any neointima in histological CS. †Complete strut coverage was defined as 100 % of strut covered with neointima (≥20 μm thickness) in OCT CS or any neointima in histological CS. ‡Neointimal unevenness score was calculated for each segment as maximal neointimal thickness in one CS divided by the average neointimal thickness of the same CS (6). §Percentage of endothelial coverage was defined as % of strut covered with endothelial cell in histological CS. ‖Complete endothelial coverage was defined as 100 % strut covered with endothelial cell in histological CS.

CS = cross section; LL = late loss; MLD = minimal lumen diameter; OCT = optical coherence tomography; QCA = quantitative coronary angiography.

The correlation coefficient was poor below 0.55 mm of LL and significantly increased once LL reached a threshold of 0.55 mm or higher when compared with the NT values obtained by OCT (Figs. 2 and 3). The neointimal unevenness score of OCT was significantly higher in the group with <0.55 mm of LL than that with ≥0.55 mm of LL.

Angiographic LL and histology correlation. A summary of the histological morphometric analysis is shown in Table 1. The mean histological in-stent percent diameter stenosis was 37.9 ± 20.4% (range: 7.6% to 88.6%). The mean NT obtained by histology was 0.29 ± 0.22 mm (range: 0.01 to 0.93 mm). Similarly, overall angiographic LL correlated reasonably well with NT, neointimal area, and percent AS obtained by histology (R = 0.63, R = 0.59, and R = 0.60, respectively). However, the correlation coefficient was poor below 0.55 mm of LL and significantly increased from 0.55 mm of angiographic LL compared with NT by histology (Figs. 2 and 4). The neointimal unevenness score of histology was also significantly higher in the group with <0.55 mm of LL than that with ≥0.55 mm of LL.

OCT-histology correlation. Paired OCT and histological findings were examined to assess their correlation. Neointimal thickness (R = 0.84), neointimal area (R = 0.80), and percent AS (R= 0.86) displayed a high degree of correlation. The correlation coefficient between both techniques was constant irrespective of the level of angiographic LL (Fig. 2).

Stent strut coverage. Overall strut coverage at each CS observed by OCT and histology were 93.7 ± 13.7% and 99.4 ± 2.9%, respectively. The percentage of struts covered by neointima at each CS found by OCT analysis was significantly greater in the group with LL ≥0.55 mm compared with those with LL <0.55 (98.3 ± 6.6% vs. 88.0 ± 16.6%, p < 0.001). In addition, the frequency of complete strut coverage at each CS was also higher in the group with LL ≥0.55 mm (90.9% vs. 54.9%, p < 0.001 in OCT and 99.8% vs. 99.0%, p = 0.003 in histology, Table 1).

DISCUSSION

Angiographic LL has been widely used in most DES studies as a surrogate endpoint of device efficacy. Its simple methodology allows the measurement of the absolute level of neointimal proliferation, and it has been widely adopted as a surrogate marker for the evaluation of in-stent restenosis (9). In addition, several publications suggest that this angiographic variable may accurately predict important clinical outcomes such as TLR, thus

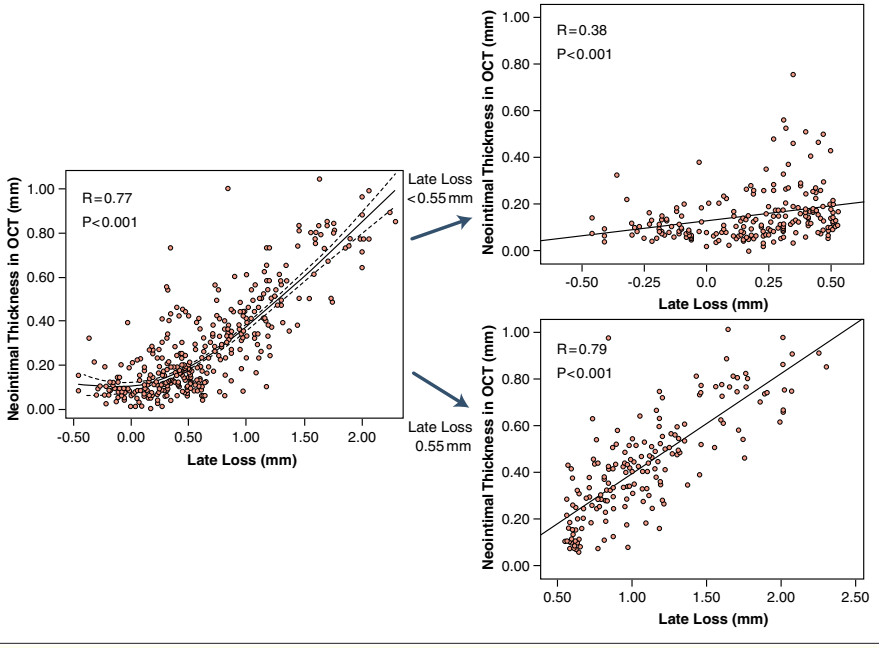

Figure 3. Correlation Between Angiographic LL and NT by OCT

A nonlinear model with 95% prediction interval bands was shown in overall range of LL. All correlation coefficients and p values were derived from Spearman correlation analysis. Abbreviations as in Figures 1 and 2.

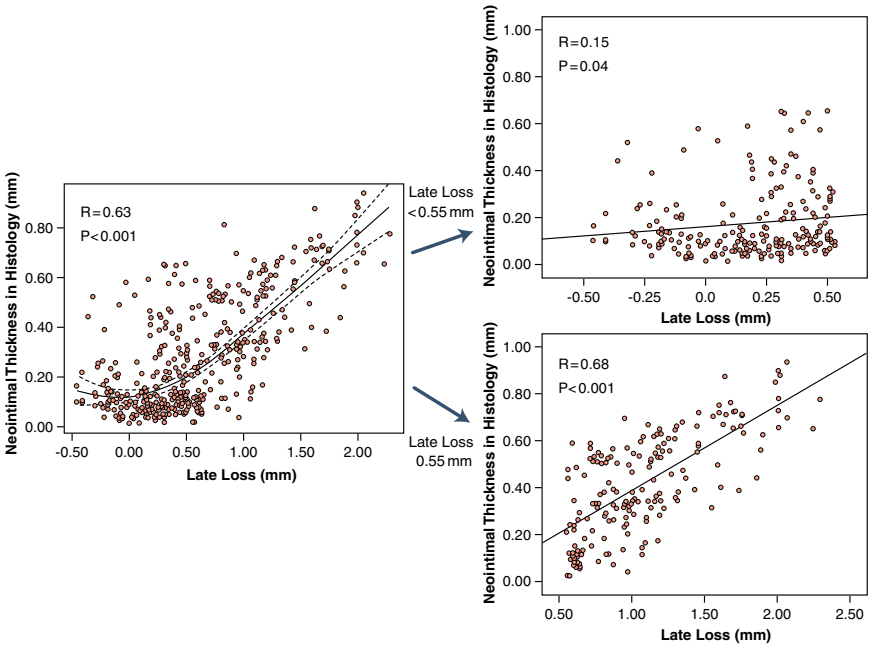

Figure 4. Correlation Between Angiographic LL and NT by Histology

A nonlinear model with 95% prediction interval bands was shown in overall range of LL. All correlation coefficients and p values were derived from Spearman correlation analysis. Abbreviations as in Figures 1 and 2.

supporting its potential value in the determination of restenosis propensity and stent efficacy (2,10). However, despite its widespread utilization in clinical trials, the real correlation of angiographic LL with the degree of in-stent neointimal proliferation is still unknown. This question remains particularly important because most of the DES used today display a level of angiographic LL that is below the threshold of detection of coronary angiography (11).

The aim of the present study was to evaluate the ability of angiographic LL to accurately assess the degree of neointimal proliferation within implanted coronary stents displaying different levels of neointimal proliferation. In the study, resulting angiographic LL of the stented segments was compared with corresponding areas analyzed with OCT and histology. Our group has previously validated the use of OCT as a tool for the evaluation of neointimal formation by comparing the resulting morphological parameters with histology (8). As a result, OCT imaging was utilized as a way to acquire in vivo in-stent morphometric data and thus serving as an internal control for the histology results.

Utilizing successive correlation analysis pairing QCA and OCT or histology at each interval of LL, we were able to identify the level at which angiographic LL appropriately correlated with neointimal proliferation as assessed by histology and OCT. For the entire group, the correlation between angiographic LL and NT determined by OCT or histology was adequate (R = 0.77 and R = 0.63). However, at lower levels of neointimal proliferation (<0.55 mm), angiographic LL had a poor correlation when compared with the degree of NT acquired with either OCT or histology. Our findings suggest that differences in angiographic LL below this threshold are difficult to interpret, particularly when the differences described between stents technologies are minimal (range: −0.01 to 0.39 mm). Our findings support some of the clinical data that describe the limitations of this angiographic variable. Agostoni et al. (11) reported that the use of LL may lead to an overestimation of the risk of restenosis when comparing different types of DES. It was postulated that stronger evidence was needed to confirm the reliability and reproducibility of this method as a valid endpoint. In addition, there have been significant discrepancies between the level of angiographic LL and clinical outcomes in large clinical studies (12,13). In some of these studies, different levels of LL did not necessarily correlate with a higher frequency of adverse clinical events (14,15). Therefore, it has been suggested that the utilization of LL as a surrogate endpoint may be of limited use in clinical practice when the calculated

values range between 0 and 0.5 mm. The data from the TAXUS-IV study suggested a marked increase of TLR when the LL reached a threshold of 0.5 mm or higher (15). Another study showed that the relationship between LL and TLR is exponential, and does not become linear until LL is <0.5 mm (4). As a consequence, several publications suggest the need for revascularization only when the angiographic LL threshold reaches this value because it seems to more accurately correlate with future TLR events and to a higher homogeneity within the LL effect (a low variance of values) (15). We believe that our findings appear to confirm this hypothesis because a similar threshold of angiographic LL correlated well with the degree of neointimal growth assessed by 2 independent analytical modalities.

In addition, the OCT-histology correlation demonstrated good intermodality concordance irrespective of level of late loss, although some variation occurred at a higher level of late loss. The differences encountered between histology and OCT at a higher level of neointimal formation may be related to the variability commonly encountered in histological analysis due to tissue shrinking and histological processing. However, regardless of these differences, this study confirms again that the degree of neointimal proliferation measured by OCT appropriately correlated with the values determined by histology and seems to provide more accurate information than the standard QCA analysis, particularly in the settings of low levels of neointimal proliferation.

Another interesting finding of this study was the correlation of angiographic LL with strut coverage in OCT or histology. At lower levels of LL (<0.55 mm), OCT underestimated the degree of strut coverage (54.9%) compared with histology (99.0%). There are several reasons that can explain these findings. First, the imaging resolution is different between both analytical techniques. Also, there are important differences in regard to the definitions of strut coverage between both techniques. Although in histology, uncovered struts are clearly identifiable, by OCT, the presence of uncovered struts are defined if the neointima is <20 μm (8). This definition aims to overcome the challenge of measuring a thin neointima in the presence of the strut-derived blooming artifact (typically ~37 μm in thickness bidirectionally). In any case, based on current definitions, OCT appears to underestimate the degree of strut coverage compared with histology at these levels of angiographic LL. Interestingly, at higher levels of LL (≥0.55 mm), complete strut coverage by OCT (90.9%) was comparable to the value encountered in histology (98.3%). Therefore, at this level of LL, OCT appears to be a reasonable indicator of the level of strut coverage as compared with histology.

Study limitations. The main limitation of the study was the experimental nature of the procedure and the fact that stents were implanted in normal porcine arteries. Although widely used for the validation of stents, this model does not provide a baseline angiographic luminal obstruction and complex atherosclerotic lesion as is seen in humans. Therefore, the results of this study need to be interpreted with caution and within the context of an experimental setting. However, the utilization of this model and methodology permitted the controlled analysis of all angiographic variables because all stents started with a similar baseline angiographic luminal stenosis. Another limitation relies on the challenges of in vivo imaging, coregistration, and histological tissue processing potentially causing some variability to the data. In addition, QCA analysis is limited in detecting the development patterns of neointimal growth throughout the stent. However, in order to solve this issue, we selected the optimal view at each stented segment, avoiding foreshortening at the time of analysis. Identical imaging projections were used at different time points for QCA analysis. However, we believe that the methodology used in our study properly addressed potential confounding variables, allowing the proper testing of the proposed hypothesis. In addition, the study included a large sample size, including stents displaying a wide variety of degrees of neointimal proliferation, allowing an accurate statistical analysis.

CONCLUSIONS

In summary, the results of the present study suggest that the accuracy of angiographic LL appears compromised in segments in which NT falls below 500 μm, a finding consistent with the visual resolution previously described for QCA (16). In stents displaying low degrees of neointimal proliferation, the applicability of LL calculation for restenosis evaluation becomes limited due to drawbacks in image resolution inherent to the QCA technique. Our data suggest cautious interpretation of the results in contemporary DES trials and support ongoing efforts to identify intravascular image modalities with resolution high enough for the detection of any

level of in vivo neointimal growth following coronary stent implantation. Further study is warranted to evaluate these findings in more detail and their applicability in human coronary arteries.

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Reprint requests and correspondence: Dr. Juan F. Granada, Skirball Center for Cardiovascular Research, Cardiovascular Research Foundation, 8 Corporate Drive, Orangeburg, New York, 10962. *E-mail: jgranada@crf.org.*

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