Comparison of Quantitative Angiographic Parameters With the Magnitude of Neointimal Hyperplasia Measured by Volumetric Intravascular Ultrasound in Patients Treated With Bare Metal and Nonpolymeric Paclitaxel-Coated Stents

Gary S. Mintz, MD, Myeong-Ki Hong, MD, Albert E. Raizner, MD, Cheol Whan Lee, MD, Jae-Joong Kim, MD, Esteban Escolar, MD, Neal E. Fearnot, PhD, Seong-Wook Park, MD, Seung-Jung Park, MD, and Neil J. Weissman, MD

We used data from the ASian Paclitaxel-Eluting Stent Clinical Trial (a 3-center, randomized, placebo-controlled trial of nonpolymeric paclitaxel-coated stents with a single-center intravascular ultrasound substudy) to compare angiographic indexes of drug-eluting stent efficacy with the magnitude of intimal hyperplasia (IH) assessed by intravascular ultrasound. Overall, percent IH (IH volume divided by stent volume) was larger in restenotic lesions than in nonrestenotic lesions (46 ± 19% vs 15 ± 13%, p <0.0001); angiographic late loss and follow-up diameter stenoses correlated strongly with percent IH. ©2005 by Excerpta Medica Inc.

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The major limitation of coronary stenting is in-stent restenosis secondary to intimal hyperplasia (IH).[1] Both quantitative coronary angiography (QCA; late loss and follow-up diameter stenosis) and intravascular ultrasound (IVUS; percent IH volume obstruction) end points have been used to assess in-stent restenosis. However, there has never been a systematic comparison of the different QCA and IVUS end points. The ASian Paclitaxel-Eluting Stent Clinical Trial (ASPECT) was a 3-center, triple-blind, randomized, placebo-controlled trial of nonpolymeric paclitaxel-coated stents to reduce in-stent restenosis in a single-center (Asan Medical Center) IVUS substudy.[2,3] There were 2 dose densities: −3.1 or 1.3 $\mu g/mm^2$, and a placebo arm. Late loss measured 1.06 ± 0.77 mm in patients who received placebo, 0.67 ± 0.66 mm in patients who received low doses, and 0.37 ± 0.57 mm in those who received high doses; percent IH volume obstruction measured 29.1 ± 19.2 in placebo patients, 18.7 ± 17.2 in low-dose patients, and 11.8 ± 13.0 in high-dose patients. The present study used data from ASPECT to compare QCA with IVUS indexes of efficacy. The 3 groups in the ASPECT allowed comparison across a wide range of neointimal responses.

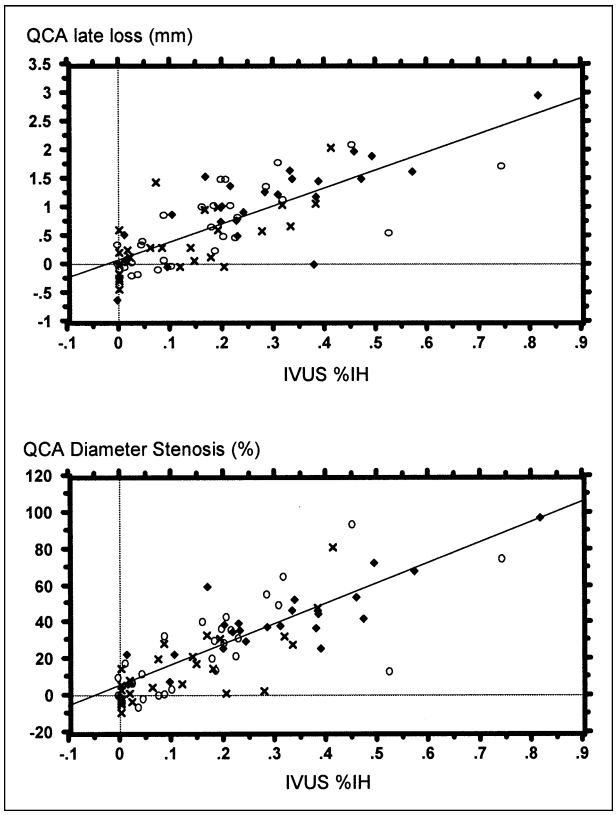

FIGURE 1. Correlation of QCA late lumen loss (millimeters) and diameter stenosis (percent) versus percent IH volume in ASPECT. *Solid diamonds,* patients who received placebo; *open circles,* patients receiving low doses; *crosses,* patients receiving high doses. The regression equation relating angiographic late loss to IVUS percent IH volume was: QCA late loss = 3.15 · (IH volume divided by stent volume) + 0.07. The regression equation relating follow-up angiographic diameter stenosis to IVUS percent IH volume was: diameter stenosis = 112 · (IH volume divided by stent volume) + 5.2.

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All patients gave written, informed consent. This study was approved by the Asan Medical Center Institutional Review Board. Ninety-eight patients were enrolled in the IVUS substudy. Complete serial (post-stent and 6-month follow-up) IVUS was available in 81 patients (25 controls, and 28 low- and 28 high-

From the Department of Medicine, University of Ulsan College of Medicine, Seoul, Korea; Cardiovascular Research Foundation, New York, New York; Washington Hospital Center, Washington, DC; MED Institute, Inc., West Lafayette, Indiana; and Cardiovascular Angiography Analysis Laboratory, Methodist DeBakey Heart Center, Houston, Texas. This study was supported by the Cardiovascular Research Foundation, Seoul, Korea, and Cook Incorporated, Bloomington, Indiana. Dr. Weissman's address is: Washington Hospital Center, 110 Irving Street, Suite 4B-1, Washington, DC 20010. E-mail: Neil.J.Weissman@medstar.net. Manuscript received August 6, 2004; revised manuscript received and accepted August 19, 2004.

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TABLE 1 Quantitative Coronary Angiography (QCA) Late Loss Versus Intravascular Ultrasound (IVUS) Correlations

	QCA (late loss)	IVUS (% IH)	r	p Value
Correlation				
Placebo	1.77 ± 0.77 mm	29.1 ± 19.2%	0.801	<0.0001
Low dose	0.67 ± 0.66 mm	18.7 ± 17.2%	0.709	<0.0001
High dose	0.37 ± 0.57 mm	11.8 ± 13.0%	0.703	<0.0001

TABLE 2 Quantitative Coronary Angiography (QCA) Diameter Stenosis Versus Intravascular Ultrasound (IVUS) Correlations

	QCA (% diameter, stenosis)	IVUS (% IH)	r	p Value
Correlation				
Placebo	31.4 ± 19.7%	29.1 ± 19.2	0.860	<0.0001
Low dose	14.5 ± 27.5%	18.7 ± 17.2	0.740	<0.0001
High dose	14.6 ± 24.2%	11.8 ± 13.0	0.787	<0.0001

dose patients). The details have previously been published.[2,3]

Procedural and follow-up angiograms were submitted to an independent angiographic core laboratory (Methodist DeBakey Heart Center, Houston, Texas). QCA (CAAS II, Pie Medical, Maastricht, The Netherlands) included standard measures of proximal and distal references and minimum lumen diameter before and after the procedure, and at follow-up.

IVUS imaging was performed after 0.2 mg of intracoronary nitroglycerin was administered using a motorized transducer pullback (0.5 mm/s) and a commercial scanner (SCIMED/BSC, Maple Grove, Minnesota), consisting of a 30-MHz transducer rotating at 1,800 rpm within a 3.2Fr imaging sheath.

Volumetric IVUS analysis was performed by an independent core laboratory (Washington Hospital Center, Washington, DC).[1,3,4] Using computerized planimetry, postintervention and follow-up stent, lumen, and IH (stent minus lumen) areas and thicknesses were measured every 1 mm within the stented segment. Volumes were calculated using Simpson's rule. Mean stent, lumen, and IH areas were calculated over the length of the stent. Percent IH volume obstruction was calculated as IH volume divided by stent volume.

Statistical analysis was performed with Statview 4.5 (SAS Institute, Cary, North Carolina). Data are presented as mean ± 1 SD and compared using regression analysis or analysis of variance.

QCA versus IVUS correlations are shown in Figure 1. Both QCA late lumen loss (postintervention minus follow-up minimum lumen diameter) and follow-up diameter stenoses correlated with IVUS percent IH volume ($r = 0.783$, $p < 0.0001$; $r = 0.821$, $p < 0.0001$, respectively). This was also true when the 3 groups (placebo, low dose, and high dose) were analyzed separately (Tables 1 and 2). Angiographic restenotic lesions (diameter stenosis >50%) had an IH volume obstruction of 46.2 ± 19.4%, whereas nonrestenotic lesions had an IH volume obstruction of 15.2 ± 13.3%.

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The present study demonstrated that angiographic variables often used to assess in-stent restenosis correlated closely with the magnitude of intrastent neointima as assessed by IVUS.

Angiography assesses lumen dimensions from what is essentially a "shadow-gram." Late loss is calculated as postintervention minimum lumen diameter minus follow-up minimum lumen diameter, regardless of the axial location of the minimum lumen diameter in either study. Conversely, IVUS provides tomographic images of the lumen, external elastic membrane, and plaque, and, in the case of stented lesions, images of stent and IH cross-sectional areas as well. Motorized transducer pullback allows calculation of volumetric IVUS parameters. Mehran et al[5] validated IVUS measurements of stent and IH volumes in a porcine coronary model in which in vivo IVUS measurements were compared with histomorphometry.

In the Randomized Study with the Sirolimus-Coated Bx Velocity Balloon-Expandable Stent in the Treatment of Patients with de Novo Native Coronary Artery Lesions (RAVEL), angiographic in-stent late loss measured 0.80 ± 0.53 mm in placebo stents versus −0.01 ± 0.33 in sirolimus-eluting stents; IH volume obstruction measured 29 ± 20% in placebo stents and 1 ± 3% in drug-eluting stents, respectively.[6] In the SIRolimus-coated Bx Velocity Balloon-Expandable stent in the treatment of patients with de novo coronary artery lesions (SIRIUS) trial, angiographic in-stent late loss measured 1.00 ± 0.70 mm in placebo stents versus 0.17 ± 0.45 mm in sirolimus-eluting stents, whereas IVUS IH volume obstruction measured 33.4% and 3.1%, respectively.[7] In Treatment of De Novo Coronary Disease Using a Single Paclitaxel-eluting stent (TAXUS-II), the slow-release paclitaxel stents had a late loss of 0.31 ± 0.38 mm (compared with 0.79 ± 0.45 mm in the slow-release controls) and an IH volume obstruction of 7.8 ± 9.9% (compared with a 23.2 ± 18.2% in controls).[8] The moderate-release paclitaxel stents had a late loss of 0.30 ± 0.39 mm (compared with 0.77 ± 0.50 mm in controls) and an IH volume obstruction of 7.8 ± 9.7% (compared with 20.5 ± 16.7% in controls).[8] In TAXUS-IV, the slow-release paclitaxel stents had an in-stent late loss of 0.39 ± 0.50 mm (compared with 0.92 ± 0.58 mm in controls), whereas IVUS at 9 months showed an IH volume obstruction of 12.2 ± 12.4% versus 29.4 ± 14.0%, respectively.[9] The regression line derived from the QCA and IVUS data of ASPECT was used to predict QCA late loss from IVUS-measured IH volume obstruction in these trials (Table 3). The predicted late loss was remarkably similar to the QCA measured late loss, although at

TABLE 3 Actual and Predicted Quantitative Coronary Angiography (QCA) Late Loss Using Reported Percent Intimal Hyperplasia (IH) Volume Obstruction

	IH Volume (IVUS)	Measured Late Loss (QCA) (mm)	Predicted Late Loss (QCA)* (mm)
RAVEL			
Sirolimus-eluting stent	1%	−0.01	0.10
Placebo	29%	0.80	0.98
SIRIUS			
Sirolimus-eluting stent	3.1%	0.17	0.17
Placebo	33.4%	1.00	1.12
TAXUS-II			
Slow-release paclitaxel	7.8%	0.31	0.32
Slow-release control	23.2%	0.79	0.80
Moderate-release paclitaxel	7.8%	0.30	0.32
Moderate-release control	20.5%	0.77	0.72
TAXUS-IV			
Slow-release paclitaxel	12.2%	0.39	0.45
Control	29.4%	0.92	1.00

*Using the regression line in Figure 1.

least 3 IVUS and 3 QCA core laboratories were involved in these studies.

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Intravascular Ultrasound Assessment of Neointima Distribution and the Length of Stent That Was Free of Intravascular Ultrasound-Detectable Intimal Hyperplasia in Paclitaxel-Eluting Stents

Gary S. Mintz, MD, Myeong-Ki Hong, MD, Albert E. Raizner, MD, Cheol Whan Lee, MD, Jae-Joong Kim, MD, Esteban Escolar, MD, Neal E. Fearnot, PhD, Seong-Wook Park, MD, Seung-Jung Park, MD, and Neil J. Weissman, MD

Using data from the ASian Paclitaxel-Eluting Stent Clinical Trial, a 3-center, randomized, placebo-controlled trial of nonpolymeric paclitaxel-coated stents with a single center, 81-patient intravascular ultrasound (IVUS) substudy, the length of a stent that was free of IVUS-detectable intimal hyperplasia measured 3.2 ± 4.8 mm in placebo stents, 6.1 ± 5.6 mm in low-dose stents, and 8.7 ± 6.1 mm in high-dose stents (p = 0.0029). IVUS percent neointima volume obstruction correlated with the length of this IVUS neointima-free segment (r = 0.785, p <0.0001); angiographic late lumen loss and follow-up diameter stenosis also correlated with the IVUS neointima-free length of the stents (r = 0.670, p <0.0001 and r = 0.679, p <0.0001, respectively.

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Drug-eluting stents reduce intimal hyperplasia (IH), the main cause of in-stent restenosis (ISR).[1] Intravascular ultrasound (IVUS) analyses in various drug-eluting stent trials have mainly focused on in-stent IH volume obstruction, stent edge effects, and late stent malapposition.[2–10] However, the length of a stent that is free of IVUS-apparent neointima has not

From the Department of Medicine, University of Ulsan College of Medicine, Seoul, Korea; Cardiovascular Research Foundation, New York, New York; Washington Hospital Center, Washington, DC; MED Institute, Inc., West Lafayette, Indiana; and Cardiovascular Angiography Analysis Laboratory, Methodist DeBakey Heart Center, Houston, Texas.

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Dr. Weissman's address is: Washington Hospital Center, 110 Irving Street, Suite 4B-1, Washington, DC 20010. E-mail: Neil.J.Weissman@medstar.net.

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