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

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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. ©2005 by Excerpta Medica Inc.

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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

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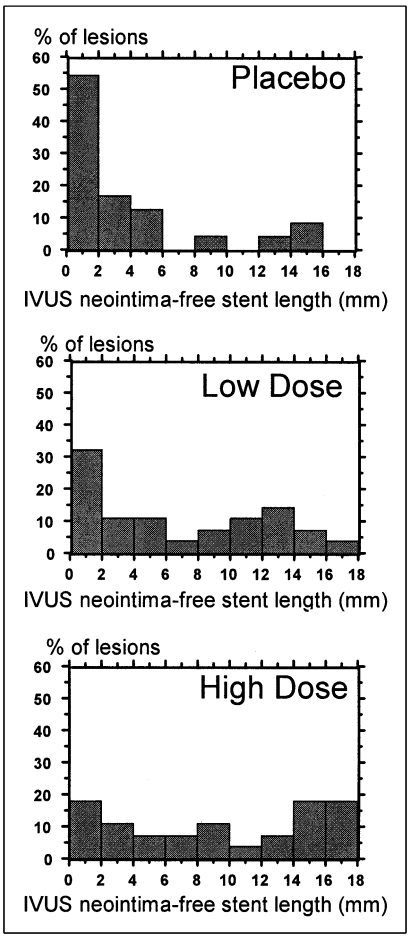

FIGURE 1. Frequency distribution of length of stent that was free of IVUS-evident neointima in the placebo, low-dose, and high-dose groups of ASPECT.

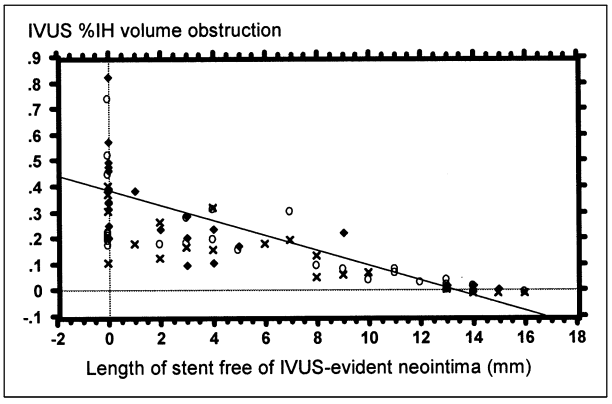

FIGURE 2. Percent IH volume obstruction correlated with the length of stent (millimeter) that was free of IVUS-evident neointima. *Solid diamonds,* placebo patients; *open circles,* low-dose patients; *crosses,* high-dose patients. The regression line was: IVUS percent IH volume obstruction = 0.44 to 0.02 · (length of stent without IVUS-evident neointima).

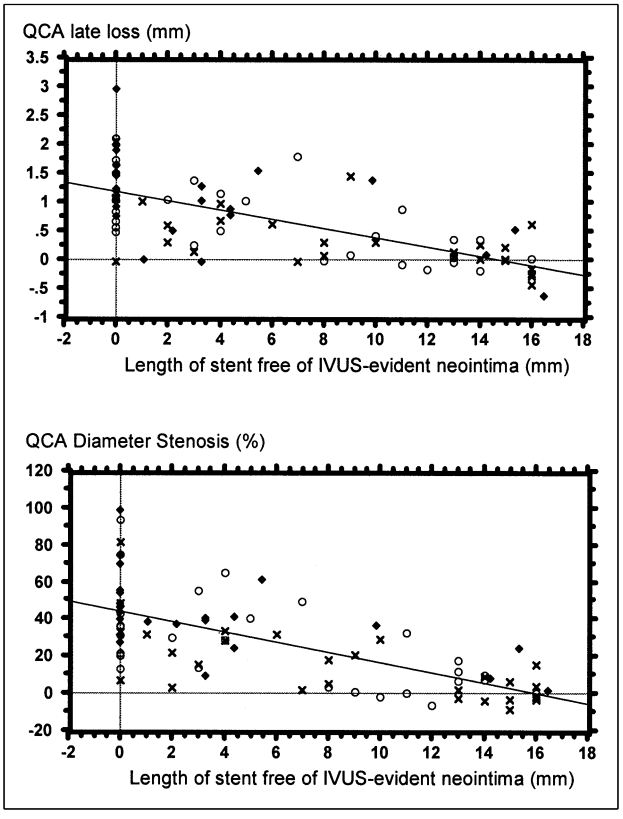

FIGURE 3. Correlation of QCA late lumen loss (millimeters) and diameter stenosis (percent) versus the length of stent (millimeters) that was free of IVUS-evident neointima. The regression lines are: QCA late loss = 1.175 to 0.08 · (length of stent without IVUS-evident neointima); QCA follow-up diameter stenosis = 43.9 to 2.76 · (length of stent without IVUS-evident neointima). *Solid diamonds,* placebo patients; *open circles,* low-dose patients; *crosses,* high-dose patients.

been studied in either bare metal or drug-eluting stents. 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 ISR with a single-center (Asan Medical Center) IVUS substudy.[9,10] There were 2 dose densities: −3.1 or 1.3 $\mu g/mm^2$, and a placebo arm. IH volume obstruction measured 29.1 ± 19.2% in patients who receved placebo, 18.7 ± 17.2% in those receiving a low dose, and 11.8 ± 13.0% in those receiving a high dose. The present study used data from ASPECT to assess the length of stent that was free of IVUS-detectable IH in each group and to compare IVUS and quantitative coronary angiographic (QCA) indexes of efficacy with the length of those stents free of IVUS-evident neointima. The 3 groups of the ASPECT allowed comparison across a wide range of neointimal responses.

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All patients gave written, informed consent. This study was approved by 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-dose patients). The details have been previously published.[9,10]

Procedural and follow-up angiograms were submitted to an independent angiographic core laboratory

(Methodist DeBakey Heart Center, Houston, Texas). QCA (CAAS II, Pie Medical, Masstricht, The Netherlands) included standard measures of proximal and distal references and minimum lumen diameters before and after the procedure, and at follow-up.

IVUS imaging was performed after 0.2 mg of intracoronary nitroglycerin was administered using 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). Using computerized planimetry, postintervention and follow-up stent, lumen, and IH (stent minus lumen) areas were measured every 1 mm within the stented segment.[11] Volumes were calculated using Simpson's rule. Mean stent, lumen, and IH areas and IH thicknesses were calculated over the length of the stent. IH volume obstruction was calculated as IH volume divided by stent volume. The length of each stent that was free of IVUS-detectable neointima was determined.

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.

The IVUS neointima-free length of stent was shorter in angiographic restenotic lesions (>50% diameter stenosis) than in nonrestenotic lesions (1.1 ± 1.9 nvs 6.9 ± 6.0 mm, $p = 0.0020$).

The frequency distribution of the length of stents free of IVUS-evident neointima is shown in Figure 1. It 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 ($p = 0.0029$). More than 25% of the stent length was free of IVUS-detectable IH in 20.8% of bare metal stents, in 50.0% of low-dose stents, and in 64.3% of high-dose stents ($p = 0.0065$). More than 50% of the stent length was free of IVUS-detectable IH in 12.5% of bare metal stents, in 35.7% of low-dose stents, and in 46.4% of high-dose stents ($p = 0.0304$). More than 75% of the stent length was free of IVUS-detectable IH in 8.3% of bare metal stents, in 10.7% of low-dose stents, and in 35.7% of high-dose stents ($p = 0.0167$).

IVUS percent IH volume obstruction correlated with the length of this IVUS neointima-free segment ($r = 0.785$, $p < 0.0001$; Figure 2.) An IH volume obstruction <5% appeared to be associated with >75% of the length of the stent being free of IVUS-detectable neointima.

QCA late lumen loss (postintervention minus follow-up minimum lumen diameter) and follow-up diameter stenosis also correlated with the IVUS neointima-free length of stent ($r = 0.670$, $p < 0.0001$ and $r = 0.679$, $p < 0.0001$, respectively) (Figure 3).

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Ideally, to minimize stent thrombosis and maximize antirestenosis potential, drug-eluting stents would permit repeat endothelialization without significant IH. However, assessment of stent repeat endothelialization is below the resolution of IVUS. Thus, the argument has been made that some late loss (by QCA) and some neointima (by IVUS) is good because this suggests less uncovered stent metal—a potential nidus for thrombus formation. Therefore, the present study evaluated the relation between conventional indexes of drug-eluting stent efficacy (QCA late loss and IVUS IH volume obstruction) and the length of stent free of neoitima.

In the present analysis, the length of stent that was free of IVUS-detectable neointima was greater in nonpolymeric paclitaxel-eluting stents than in bare metal stents. QCA late loss, QCA follow-up diameter stenosis, and IVUS IH volume obstruction all correlated inversely with the IVUS-evident neointima-free length of stent. Nevertheless, there was significant patient-to-patient variability, with the greatest variability in the highest dose densities. Thus, neointimal suppression not only affected areas of the stent with the greatest IH but also was heterogeneous, suppressing even a modest amount of IH, and was associated with longer lengths of the stent that were not neointima-covered, at least as detectable using IVUS.

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