Relation of Intimal Hyperplasia Thickness to Stent Size in Paclitaxel-Coated Stents

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

To determine the relation of intimal hyperplasia thickness to stent size in nonpolymeric paclitaxel-coated stents, intravascular ultrasound was performed after stent implantation and at 6 months. Similar to bare metal stents, this study demonstrated that intimal hyperplasia thickness is independent of stent size. There was no deleterious effect of the increased concentration associated with using the same stent design in a smaller artery, and these results suggested that stent strut density may be a more important concept than drug concentration. ©2004 by Excerpta Medica, Inc.

The Asian Paclitaxel-Eluting Stent Clinical Trial (ASPECT) was a 3-center, triple-blind, randomized, placebo-controlled trial of nonpolymer paclitaxel-coated stents to reduce in-stent restenosis; there was 1 single-center serial intravascular ultrasound (IVUS) substudy. The objective of the present analysis was to determine whether the thickness of the neointimal hyperplasia layer that accumulates within nonpolymeric paclitaxel-coated stents is dependent on stent size.

Single de novo lesions in 177 patients were randomized to placebo (bare metal stents) or 1 of 2 paclitaxel dose densities (low dose, 1.28 μg/mm² stent surface area; high dose, 3.10 H9262/μg/mm² stent surface area). Paclitaxel was applied to the stent metal surface without using a polymer; after release of paclitaxel, only a bare metal stent remained. Patients were treated with antiplatelet agents for 6 months. ASPECT included 1 single-center IVUS substudy. Complete serial (poststent implantation and 6-month follow-up) IVUS was available in 81 patients, including 25 control patients, 28 low-dose patients, and 27 high-dose patients. No differences were seen in baseline characteristics when comparing patients in the IVUS substudy with the total cohort or when comparing patients who received the paclitaxel-coated stents with those who received placebo in the IVUS substudy. All IVUS imaging studies were performed after intracoronary administration of 0.2 mg of nitroglycerin. Imaging was acquired using motorized transducer pullback (0.5 mm/s) and a commercial scanner (Boston Scientific, Maple Grove, Minnesota), consisting of a 30-MHz transducer within 3.2Fr imaging sheath. Quantitative volumetric IVUS analysis was performed at an independent core laboratory (Washington Hospital Center). Using computerized planimetry (Tapemeasure, Indec Systems, Mountain View, California) the following measurements were obtained every 1 mm after deployment and at follow-up: (1) stent cross-sectional area (CSA), (2) lumen CSA, and (3) intimal hyperplasia CSA (follow-up stent minus lumen CSA). The image slice with the maximum intimal hyperplasia CSA within the stent was identified. Maximum intimal hyperplasia thickness was measured as the maximum distance between the lumen and the stent along a line that passed through the lumen centroid. Mean intimal hyperplasia thickness for each image slice was calculated. These methods have all been previously described.

Previous studies in bare metal stents have shown that intimal hyperplasia CSA increases with increasing stent CSA, because the same intimal hyperplasia thickness accumulates over a larger circumference. Therefore, it was important to assess not only the relation between stent size and intimal hyperplasia CSA, but also the relation between stent size and intimal hyperplasia thickness. The following relations were analyzed on a per-stent basis: (1) mean intimal hyperplasia thickness versus mean stent CSA, and (2) mean intimal hyperplasia CSA versus mean stent CSA. The following relations were analyzed for the total cohort of 1,400 image slices: (1) intimal hyperplasia CSA versus stent CSA, and (2) mean intimal hyperplasia thickness versus stent CSA. These also allowed determination of the mean intimal hyperplasia CSA and thickness in each cohort.

Statistical analysis was performed with StatView 4.5 software (SAS Institute, Cary, North Carolina). Continuous data are presented as mean ± 1 SD, and categorical data are presented as frequencies. Continuous variables were compared using regression analysis or factorial analysis of variance with post hoc analysis using Fisher’s protected least-significant difference. A p value ≤0.05 was considered statistically significant.

Mean intimal hyperplasia thickness was 0.26 ± 0.22 mm for the high-dose group, 0.39 ± 0.19 mm for...
the low-dose group, and 0.50 ± 0.28 mm for the control group (analysis of variance, p = 0.0002). Post hoc mean intimal hyperplasia thickness was less in the high-dose group than in controls (p = 0.0005); it also tended to be less in the high- versus low-dose (p = 0.056) groups and in the low-dose versus control groups (p = 0.08).

Mean intimal hyperplasia CSA was 0.82 ± 0.90 mm$^2$ for the high-dose group, 1.16 ± 0.92 mm$^2$ for the low-dose group, and 2.16 ± 1.52 for the control group.

FIGURE 1. On a per-stent basis, there was no correlation between mean intimal hyperplasia (IH) CSA or thickness versus mean stent CSA in the control, low-dose, or high-dose groups.

FIGURE 2. On a per-image slice basis, there was a weak correlation between mean intimal hyperplasia (IH) CSA versus stent CSA, but no correlation between mean IH thickness versus stent CSA in the control, low-dose, or high-dose groups.
(p = 0.0002). Post hoc analysis showed that mean intimal hyperplasia CSA was similar with the 2 doses (p = 0.3), and that both the high and low doses had less intimal hyperplasia than the control groups (p <0.0001 and p = 0.0018, respectively).

On a per-stent basis, there was no significant correlation between mean intimal hyperplasia CSA versus mean stent CSA, or between mean intimal hyperplasia thickness versus mean stent CSA (Figure 1).

Similarly, on a per-slice basis, there was a weak relationship between intimal hyperplasia CSA versus stent CSA for each of the 3 groups, but not between mean intimal hyperplasia thickness versus stent CSA (Figure 2).

The present analysis shows that with nonpolymeric paclitaxel-coated stents, intimal hyperplasia thickness is independent of stent size. Only 1 stent design was used in ASPECT: the Supra-G stent (Cook Corp., Bloomington, Indiana). This stent has 0.11-mm-thick struts, with a metal surface area of 42 mm² for the 15-mm-long stent used. Surface coverage will vary depending on vessel size. Theoretically, a 2.5-mm artery has a 15-mm-long lumen surface area of 118 mm²; 36% of the lesion would be covered by stent metal. This increases to 141 mm² and 30% surface coverage for a 3.0-mm artery and to 165 mm² and 25% surface coverage for a 3.5-mm artery. Because the drug is applied to the stent in fixed doses (low dose, 1.28 µg/mm² stent surface area; high dose, 3.10 µg/mm² stent surface area), smaller vessels that have a greater metal surface coverage should receive a greater concentration of the drug. The present analysis showed that this did not impact the neointimal response.

The present study supports the concept that stent strut density may be more important than "total dose" density or "concentration." This is also illustrated when the European evaLUation of paclitaxel Eluting Stent (ELUTES) study is compared with ASPECT. Both studies used the same nonpolymeric paclitaxel coating, but different stent designs. In ASPECT, the total dose delivered was 130 µg at the 3.1 µg/mm² dose density. Conversely, in ELUTES, which used a V-FLEX stent (Cook Corp.) with only a 22- mm² surface area, the total dose was 60 µg at the 2.7-µg/ mm² dose density. The follow-up diameter stenosis in the highest dose groups were 14.1% (ELUTES) and 14% (ASPECT). Thus, there were identical biologic responses despite different overall amounts of drug, but similar dose densities.

The present study supports the concept that stent strut density may be more important than "total dose" density or "concentration." This is also illustrated when the European evaLUation of paclitaxel Eluting Stent (ELUTES) study is compared with ASPECT. Both studies used the same nonpolymeric paclitaxel coating, but different stent designs. In ASPECT, the total dose delivered was 130 µg at the 3.1 µg/mm² dose density. Conversely, in ELUTES, which used a V-FLEX stent (Cook Corp.) with only a 22- mm² surface area, the total dose was 60 µg at the 2.7-µg/ mm² dose density. The follow-up diameter stenosis in the highest dose groups were 14.1% (ELUTES) and 14% (ASPECT). Thus, there were identical biologic responses despite different overall amounts of drug, but similar dose densities.