Novel Drug-Delivery Stent
Intravascular Ultrasound Observations From the First Human Experience
With the QP2-Eluting Polymer Stent System
Yasuhiro Honda, MD; Eberhard Grube, MD; Luis M. de la Fuente, MD; Paul G. Yock, MD; Simon H. Stertzer, MD; Peter J. Fitzgerald, MD, PhD

Background—The aim of this study was to use serial intravascular ultrasound (IVUS) to evaluate the long-term effect of stent-based 7-hexanoyltaxol (QP2, a taxane analogue) delivery on neointimal tissue growth within the stent and on vessel dimensions at the adjacent reference segments.

Methods and Results—Serial IVUS analyses (immediately after intervention and at follow-up at 8.3 months) were performed in 15 native coronary lesions treated with the QuaDS-QP2 stent. IVUS measurements were performed at 8 cross-sections in each target segment (4 cross-sections within the stent and 2 cross-sections in each reference segment). At baseline, no significant plaque protrusion or thrombus was detected in the target segment. Mild incomplete stent apposition and edge dissection were observed in one and two cases, respectively. Percent expansion of the stent (minimum stent area/average reference lumen area) was 96.0±21.7%. At follow-up, mean neointimal area within the stent was 1.2±1.3 mm², and mean cross-sectional narrowing (neointimal area/stent area) was 13.6±14.9%. At the vessel segments immediately adjacent to the stent, a significant increase in plaque area (1.9±2.6 mm², P=0.001) was observed, but vessel area remained unchanged. However, no patients showed clinically significant in-stent or edge restenosis (diameter stenosis ≥50%) during the follow-up period.

Conclusions—The first human experience with the new drug-delivery stent showed a minimal amount of neointimal proliferation in the stented segment. Late lumen loss at the reference sites adjacent to the stent was acceptable and predominantly due to plaque proliferation. (Circulation. 2001;104:380-383.)

Key Words: coronary disease ■ drugs ■ stents ■ restenosis ■ ultrasonics

Despite a variety of mechanical approaches, including dilation, debulking, and scaffolding a lesion with a rigid metal, restenosis rates of 20% to 40% across a broad range of lesions continue to represent a significant limitation of percutaneous coronary interventions. Over the last decade, the search for new therapies to reduce restenosis has drawn new attention to adjunctive strategies to impact the biological component of coronary plaque. Although intracoronary radiation therapy is one of the promising biological approaches, recent studies have also raised the concerns of lumen narrowing in the adjacent reference segments and increased late thrombosis rates.1,2 The local delivery of antiproliferative drugs with a drug-eluting stent is considered a potential alternative to provide both a biological and mechanical solution.3,4

Preclinical studies have shown that local administration of paclitaxel (Taxol), a microtubular inhibitor, or its analogues significantly reduces smooth muscle cell migration and proliferation for months after balloon angioplasty or stenting.5 However, the effect of this agent on the diseased human coronaries and the influence of the long-term stimulus from the drug-eluting stent on the adjacent vessel wall remain unknown.

The aims of this pilot study were to use serial (after intervention and at follow-up) intravascular ultrasound (IVUS) imaging (1) to evaluate the long-term effect of stent-based 7-hexanoyltaxol (QP2, a taxane analogue) delivery on neointimal tissue growth within stents and (2) to characterize the vessel and plaque changes in the adjacent coronary artery segments.

Methods From January 1999 to August 2000, 20 patients successfully underwent QuaDS-QP2 stent (Quanam Medical Corp) implantation with serial IVUS evaluation (Figure 1). This stent is a slotted-tube, 316L stainless steel, balloon-expandable stent with multiple polymer sleeves that slowly release QP2. The drug is loaded into the biocompatible polyacrylate sleeve at 800 μg of QP2 per 2.4 mm of sleeve. The number of sleeves can vary with the size of the stent.
with a maximum number of 5 sleeves on the 21-mm stent. In this pilot study, either 13- or 17-mm stents were used. Patients were studied after giving written, informed consent. Protocols were approved by the local Human Subjects Committee.

Procedure
All patients were premedicated with aspirin (325 mg/d) and received heparin (100 U/kg) before the procedures. After predilatation of the target lesion, stents were deployed using a standard implantation technique guided by IVUS. Postdeployment high-pressure dilatation was allowed, with balloon selection and inflation pressure at the discretion of the individual operator. After stent implantation, aspirin was continued indefinitely and ticlopidine (500 mg/d) was prescribed for 30 days in all cases.

Angiographic and IVUS Analyses
Serial angiography and IVUS imaging were performed after intracoronary administration of nitroglycerin (200 μg) immediately after the procedure and at follow-up. All cineangiograms and IVUS images were independently analyzed by the Stanford University Cardiovascular Core Analysis Laboratory.

Qualitative IVUS parameters assessed in the study included stent apposition (incomplete apposition being defined as ≥1 strut clearly separated from the vessel wall with evidence of blood speckle behind the strut) and edge tears (defined as disruptions of plaque immediately adjacent to the stent ends where the flap could be clearly differentiated from the underlying plaque).

Quantitative IVUS measurements were performed at 8 cross-sections in each target segment (4 cross-sections within the stent and 2 cross-sections in each reference segment) as follows: the tightest cross-sections within the stent at baseline and at follow-up, the proximal and the distal stent edges (the stent segments within 1 mm of the proximal and distal stent ends), the proximal and distal peri-stent margins (the reference segments immediately adjacent to the proximal and distal stent ends), and the proximal and distal reference sites. Cross-sectional narrowing was calculated as neointimal area divided by stent area. Validation of qualitative and quantitative assessment by IVUS has been reported previously.

Statistical Analysis
Statistical analysis was performed using StatView 5.0. Quantitative data are presented as mean±SD and were compared using a 2-tailed, paired t test or Wilcoxon signed-rank test, as appropriate. P<0.05 was considered significant.

Results
Two patients received both a drug-eluting stent and a standard bare-metal stent. For the purpose of this analysis, these cases were not included. Due to incomplete image acquisition or inadequate image quality, 4 patients were excluded from the serial IVUS analysis. In total, 15 lesions in 14 patients were enrolled in this study. Baseline demographics and procedural characteristics for the en-

TABLE 1. Baseline Clinical and Procedural Characteristics

<table>
<thead>
<tr>
<th></th>
<th>Age, y</th>
<th>Male sex, n (%)</th>
<th>Previous conditions, n (%)</th>
<th>Risk factors, n (%)</th>
<th>Vessel treated, n (%)</th>
<th>Coronary angiography</th>
<th>Intravascular ultrasound</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age, y</td>
<td>61±14</td>
<td>9 (64)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Male sex, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Previous conditions, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Myocardial infarction</td>
<td>6 (43)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary angioplasty</td>
<td>2 (14)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Coronary artery bypass</td>
<td>0 (0)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Risk factors, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Currently smoker</td>
<td>3 (21)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypercholesterolemia</td>
<td>12 (86)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Hypertension</td>
<td>6 (43)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Diabetes</td>
<td>1 (7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Vessel treated, n (%)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LAD</td>
<td>5 (33)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>RCA</td>
<td>9 (60)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>LCx</td>
<td>1 (7)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Restenotic lesion, n (%)</td>
<td>2 (13)</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>No. of stents per lesion</td>
<td>1.1±0.3</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Mean stent length, mm</td>
<td>16.0±4.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Final balloon size, mm</td>
<td>3.3±0.4</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Maximum inflation pressure, atm</td>
<td>15.5±2.6</td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
</tbody>
</table>

Values are mean±SD or n (%). LAD indicates left anterior descending artery; RCA, right coronary artery; and LCx, left circumflex artery.
rolled patients are shown in Table 1. In the entire population enrolled in this registry (n=20), 2 patients underwent target vessel revascularization at a segment in the same vessel that was proximal or distal to the QuaDS-QP2 stent (follow-up period, 8.3±4.1 months). No patient died or experienced myocardial infarction. Serial quantitative coronary angiography data are shown in Table 2.

**Stented Segments**

At baseline, no significant plaque protrusion or thrombus was detected in the stented segment. Mild incomplete stent apposition and edge tear were observed in one and two cases, respectively. Percent expansion of the stent (minimum stent area/average reference lumen area) was 96±22%. At follow-up, mean neointimal area within the stent was 1.2±1.3 mm², and mean cross-sectional narrowing (neointimal area/stent area) was 13.6±14.9%. Serial changes in quantitative IVUS parameters are shown in Table 2.

**Peri-Stent Margins**

During the follow-up period, plaque area in the peri-stent margins increased significantly, from 8.7±2.2 mm² to 10.7±3.0 mm² (P<0.05) and from 7.5±3.7 mm² to 9.4±4.2 mm² (P<0.05) for the proximal and distal margins, respectively (Figure 2). No significant change in vessel area was observed in either the proximal or the distal margins. Consequently, late lumen loss at the peri-stent margins was 1.3±2.6 mm² (P=0.09) for the proximal margin and 1.4±2.2 mm² (P<0.05) for the distal margin. The proximal and the distal reference sites showed no significant change in vessel, plaque, or lumen area.

**Discussion**

This study presents serial IVUS observations from the first human trial with the QP2-eluting polymer stent system. In the stented segments, a minimal amount of neointimal proliferation was observed at follow-up. The peri-stent margins (the vessel segments immediately adjacent to the stent ends) showed a degree of lumen narrowing similar to conventional metal stents that was predominantly due to plaque proliferation. No patients showed clinically significant in-stent or edge restenosis (diameter stenosis ≥50%) during the follow-up period.

Previous IVUS studies have reported that mean cross-sectional narrowing after conventional bare-metal stent implantation ranges from 20% to 48%. The lesser amount of neointima observed in the present study (13.6%) was comparable to the numbers reported for radioactive stents (7.4% to 16.7%)⁶ and sirolimus-coated stents (10.4% to 11.0%).⁴ Importantly, animal studies have demonstrated that the histological characteristics of paclitaxel-eluting stents are similar to those after intracoronary radiation therapy in several aspects, which raises the concern of potentially increased late thrombosis rates and lumen narrowing in the vessel segments adjacent to the drug-eluting stent. In this initial experience with the QP2-eluting stent, however, late thrombotic events were not observed, although clinical trials with a larger study population will be required to confirm this preliminary result.

After radioactive stent implantation, the mechanism responsible for the accelerated restenosis at the stent margins is a combination of tissue growth and negative vessel remodeling, presumably due to radiation dose fall-off coupled with balloon injury during stent deployment. In theory, drug dose fall-off and the long-term stimulus from polymer materials in drug-eluting stents may also potentially provoke sustained inflammation at the unscaffolded, balloon-injured, peri-stent vessel segments. In this preliminary study, however, the degree of late lumen loss at the peri-stent margins of the QP2-eluting stent was similar to the numbers reported for conventional bare-metal stents. This phenomenon resulted primarily from tissue growth, with no significant vessel shrinkage or local dilatation. Considering the striking anti-proliferative effect of drug-eluting stents in the stented segment, aggressive postdeployment dilatation with high pressures may no longer be necessary, thereby minimizing vessel wall injury and subsequent neointimal proliferation at stent margins. Further investigation will be needed to determine the appropriate vessel and/or lesion subset and optimal implantation technique for this particular type of stent.

**Study Limitations**

First, this study is based on a registry of a small, select patient population, raising the possibility of selection bias and low statistical power. Second, automated pullback was not used in all cases. To circumvent this limitation, quantitative IVUS analysis was performed with a semivolumetric technique. Finally, longer follow-up periods might be necessary for drug-eluting stents than for conventional metal stents, as has been suggested for intracoronary radiation therapy.

**Conclusion**

The first experience in humans with a new drug-delivery stent showed favorable outcomes in the stented segment, with no evidence of significant marginal exacerbation.
References


Novel Drug-Delivery Stent: Intravascular Ultrasound Observations From the First Human Experience With the QP2-Eluting Polymer Stent System
Yasuhiro Honda, Eberhard Grube, Luis M. de la Fuente, Paul G. Yock, Simon H. Stertz and Peter J. Fitzgerald

Circulation. 2001;104:380-383
doi: 10.1161/hc2901.094149

Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
Copyright © 2001 American Heart Association, Inc. All rights reserved.
Print ISSN: 0009-7322. Online ISSN: 1524-4539

The online version of this article, along with updated information and services, is located on the World Wide Web at:
http://circ.ahajournals.org/content/104/4/380

Permissions: Requests for permissions to reproduce figures, tables, or portions of articles originally published in Circulation can be obtained via RightsLink, a service of the Copyright Clearance Center, not the Editorial Office. Once the online version of the published article for which permission is being requested is located, click Request Permissions in the middle column of the Web page under Services. Further information about this process is available in the Permissions and Rights Question and Answer document.

Reprints: Information about reprints can be found online at:
http://www.lww.com/reprints

Subscriptions: Information about subscribing to Circulation is online at:
http://circ.ahajournals.org/subscriptions/