7-Hexanoyltaxol–Eluting Stent for Prevention of Neointimal Growth

An Intravascular Ultrasound Analysis From the Study to COmpare REstenosis rate between QueST and QuaDS-QP2 (SCORE)

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Background—Inhibition of neointimal tissue growth has been demonstrated in preliminary human feasibility studies with a stent-based polymer sleeve delivering 7-hexanoyltaxol. The Study to COmpare REstenosis rate between QueST and QuaDS-QP2 (SCORE) trial is a human, randomized, multicenter trial comparing 7-hexanoyltaxol (QP2)-eluting stents (qDES) with bare metal stents (BMS) in the treatment of de novo coronary lesions. The purpose of this substudy was to evaluate the acute expansion property and long-term neointimal responses of qDES compared with BMS as assessed by intravascular ultrasound (IVUS).

Methods and Results—A total of 122 (qDES 66, BMS 56) patients were enrolled into the IVUS substudy. All IVUS images (immediately after the procedure and at 6-month follow-up) were analyzed at an independent core laboratory in a blind manner. At baseline, qDES achieved stent expansion similar to BMS. At follow-up, qDES showed reduced neointimal growth by 70% at the tightest cross section and by 68% over the stented segment ($P<0.0001$ for both), resulting in a significantly larger lumen in qDES than in BMS. Unlike intracoronary brachytherapy, there was no evidence of negative edge effects, unhealed dissections, or late stent-vessel wall malapposition over the stented and adjacent references segments in either group.

Conclusions—Detailed IVUS analysis revealed that qDES had comparable acute mechanical and superior long-term biological effects to BMS. Although the long-term benefits and limitations of this technology require further investigation, the reduction in neointimal thickenings demonstrated that local delivery of 7-hexanoyltaxol through polymer sleeves augments conventional mechanical treatment of atherosclerotic disease. **(*Circulation*. 2002;106:1788-1793.)**

Key Words: cardiovascular diseases ■ drugs ■ restenosis ■ stents ■ ultrasonics

Coronary stents eliminate elastic recoil of target vessels, thereby reducing restenosis rate in percutaneous coronary interventions.[1] However, the occurrence of stent restenosis as the result of intimal hyperplasia remains a clinical challenge. Local drug delivery represents a therapeutic approach that enables high local concentration of drug with minimum systemic adverse effects. Particularly, stent-based delivering of drugs has been considered a promising technique to provide both a highly selective biological and mechanical solution precisely at the target segment. At present, a number of pharmacological agents, in combination with various delivery platforms, are being evaluated for their potential to improve the acute and long-term outcomes.

Paclitaxel (Taxol) and related taxane compounds interfere with the proliferation, signal transduction, and migration of vascular smooth muscle cells, thus contributing to the reduction of neointimal growth.[2,3] These effects primarily derive from the unique agent character that shifts the cytoskeleton

Received March 8, 2002; revision received July 18, 2002; accepted July 18, 2002.

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Circulation **is available at http://www.circulationaha.org** **DOI: 10.1161/01.CIR.0000031734.11420.1C**

equilibrium toward assembly with profound stabilization in the microtubules.[4] Accordingly, several animal studies have demonstrated that stent-based local delivery of paclitaxel could prevent intimal proliferation through the use of an overstretched vessel injury model.[5–7] Preliminary human studies also showed that local delivery of 7-hexanoyltaxol (QP2, a taxane analogue) through polymer sleeves on a balloon-expandable stent reduced neointimal growth after coronary intervention.[8,9] To confirm those pilot results from the small-number, nonrandomized, feasibility registries, a prospective randomized multicenter trial was conducted. The purpose of this intravascular ultrasound (IVUS) substudy was to investigate (1) the acute mechanical properties of this sleeve-based drug-eluting stent and (2) the long-term antiproliferative effectiveness compared with a conventional bare metal stent (BMS).

Methods

Study Design and Patient Population

This study represents an IVUS substudy of the SCORE trial (Study to COmpare REstenosis rate between QueST and QuaDS-QP2): the human, prospective, randomized, multicenter study to evaluate the safety and efficacy of the QP2 drug-eluting stent (QuaDS-QP2 stent, qDES) compared with a BMS (QueSt stent) in the prevention of in-stent restenosis (Quanam Medical/Boston Scientific). Inclusion criteria were de novo lesions in native coronary arteries, patient age ≥50 and ≤80 years, and target vessel reference diameter ≥3.0 and ≤3.5 mm, as assessed by visual estimate. Patients with a recent history of acute myocardial infarction or left ventricular ejection fraction ≤30% were excluded from this trial. All patients gave informed consent before study enrollment. The local Human Subjects Committee at all participating institutions approved the protocols.

Stent Designs and Implantation Procedure

Both qDES and BMS consist of 316L stainless steel and were identified in length (13 or 17 mm) and diameter (3.0 or 3.5 mm). The detailed configuration of qDES was previously reported.[9] In short, the qDES is equipped with multiple polyacrylate sleeves as the platform for drug elution. Each sleeve is 2.4 mm in length and contains 800 μg of QP2. In this study, the number of sleeves was 4 and 5, in 13-mm and 17-mm length stents, respectively. After sheath placement, 10 000 to 15, 000 IU of heparin was administered. The appropriate stent size was selected by using the reference vessel diameter, and the stents were implanted according to a standard implantation technique with predilatation. After the procedure, patients were treated with acetylsalicylic acid (100 mg) indefinitely and with ticlopidine or clopidogrel (500 mg) for either 1 month or 12 months for BMS or qDES, respectively.

Intravascular Ultrasound Imaging

IVUS was performed immediately after stent implantation and at 6-month follow-up with one of two commercially available imaging systems. The first was 3.2-F, 30-MHz or 2.9-F, 40-MHz single-element mechanical ultrasound catheter (Boston Scientific). The second incorporated 3.0-F, 20-MHz phased-array ultrasound catheter (Endosonics/Jomed). At follow-up, the IVUS system used for each patient was identical to the system used after stent implantation. Intracoronary nitroglycerin was injected before image acquisition. Motorized pullback devices (0.5 mm/s) were used during all IVUS data acquisition. All IVUS images were recorded on s-VHS videotape or compact disk for off-line analysis.

Intravascular Ultrasound Analysis

An independent core laboratory at Stanford University Medical Center reviewed all ultrasound images. Two observers, blinded to clinical information and treatment protocol, performed all IVUS analyses.

Qualitative IVUS parameters evaluated in this study included (1) stent apposition (incomplete apposition being defined as ≥1 strut clearly separated from the vessel wall with evidence of blood speckle behind the strut); (2) edge tears (disruption of plaque immediately adjacent to the stent ends where the flap could be clearly differentiated from the underlying plaque); and (3) late stent malapposition (incomplete stent apposition at follow-up not seen immediately after stent implantation).

Quantitative IVUS analysis was performed by using commercially available planimetry software (TapeMeasure/EchoPlaque, Indec Systems and Plus-Plus, Sanders Data Systems), according to previously validated and published protocols.[10] Two-dimensional analysis was performed at the tightest cross section within the stent and the proximal and distal reference segments (defined as the location in the native vessel with minimum disease within 3 to 10 mm from stent margins and before the emergence of any major side branches). Stent and lumen areas were manually traced, and neointimal area was computed as stent minus lumen area. Cross-sectional narrowing (CSN) was calculated as neointimal area divided by stent area. Percent stent expansion was calculated as minimum stent area (MSA) divided by averaged reference lumen area. Three-dimensional analysis was performed by means of Simpson's method. Stent, lumen, and neointimal volumes were computed for the entire stented segment. To adjust for different stent lengths, volume index was calculated as volume data divided by stent length (SVI: stent volume index, LVI: lumen volume index, and NVI: neointimal volume index). The interobserver correlation coefficients for SVI, LVI, and NVI were 0.998, 0.997, and 0.984, respectively.

Quantitative Coronary Angiography

All cineangiograms were independently analyzed by the Cardiovascular Research Foundation Angiographic Core Laboratory. Cine frames from multiple projections were digitized and analyzed with the use of the CMS-GFT algorithm (MEDIS). Image calibration was performed with contrast-filled catheters used as the reference standard.

Statistical Analysis

Qualitative data are presented as mean±SD, and qualitative data are presented as frequencies. Statistical analyses were performed with the StatView 5.0 (SAS Institute). For comparisons of continuous variables between the 2 stent groups, a 2-tailed, unpaired *t* test was used. A 2-way repeated-measures ANOVA was used to evaluate potential differences in serial IVUS measurements between the two stent groups. Categoric data were compared by means of the χ^2 or Fisher exact test. Significance was defined as a threshold of $P=0.05$.

Results

Patient Characteristics

Between April 2000 and January 2001, 122 patients were enrolled in this IVUS substudy from 266 patients in the overall SCORE population on an institutional basis. In this population, 66 patients were assigned to the qDES group and 56 to the BMS group. Baseline patient, lesion, and procedural characteristics were similar in both groups (Table 1). Ninety-six IVUS images (qDES, 48; BMS, 48) were entered into baseline IVUS analysis (26 patients were excluded because of incomplete image acquisition, inadequate image quality, or other technical reasons in the imaging procedure at the catheterization laboratory). Ninety-two IVUS images (qDES, 49; BMS, 43) were available for follow-up IVUS analysis. Primary reasons for reduced follow-up included patient refusal, incomplete image acquisition, and inadequate image quality. In addition, one patient died of suspected pulmonary

TABLE 1. Baseline Clinical and Lesion Characteristics

	BMS	qDES	*P*
Age, y	63.6±7.1	62.6±8.4	NS
Male sex, %	75	77	NS
Diabetes mellitus, %	25	21	NS
Hypertension, %	63	65	NS
Ejection fraction, %	66.3±8.6	63.3±10.0	NS
Vessel treated, %			
LAD	45	50	NS
RCA	43	32	NS
LCX	12	18	NS
Reference lumen diameter, mm	3.07±0.54	2.94±0.42	NS
Minimum lumen diameter, mm	0.97±0.44	0.98±0.40	NS
% Diameter stenosis	68.5±12.3	66.7±12.7	NS
Lesion length, mm	12.44±4.53	11.39±4.85	NS
Stent length, mm	15.79±4.67	15.24±4.36	NS
Inflation pressure, atm	12.2±3.0	11.7±3.4	NS

Values are mean±SD or frequencies.

LAD indicates left anterior descending artery; RCA, right coronary artery; and LCX, left circumflex artery.

embolism during the follow-up period (qDES). Complete volumetric analysis was available in 86% and 93% for baseline and follow-up studies, respectively. Each analysis population had baseline characteristics comparable to the overall enrolled patients, with no significant differences between the two stent groups. Furthermore, characteristics of this substudy subset were comparable to the complete SCORE study population. The follow-up period was also identical in the two groups (qDES, 6.2±0.9 months; BMS, 6.3±1.0 months, *P*=NS).

Acute Results

Immediately after stent implantation, no plaque protrusion was detected in either group. Mild incomplete stent apposition was observed in 8 cases (qDES, 6% versus BMS, 10%, *P*=NS) and mild edge tears in 12 cases (qDES, 13% versus BMS, 13%, *P*=NS), with similar frequencies in the qDES and BMS groups. Two-dimensional and 3-dimensional quantitative analyses showed no significant differences in acute results between the two stent groups, including the average reference lumen area, MSA, SVI, and percent stent expansion (Table 2).

Follow-Up Results

At 6-month follow-up, unhealed edge tear was not observed in either group. On the other hand, the pattern of neointimal growth differed significantly between the two groups (Figure 1). In the BMS group, almost all stent struts were covered with neointima throughout the stented segment, and 7 cases (16%) showed the IVUS catheter nearly wedged in abundant neointima. In contrast, in the majority (94%) of qDES, neointima was either undetectable or observed on the stent struts as a very thin layer only in some part of the stent. No evidence of late stent malapposition or echolucent tissue was detected in either group.

TABLE 2. Postprocedure IVUS Results

	BMS	qDES	*P*
Reference lumen area, mm^2	10.27±2.94	10.00±2.37	NS
Minimum stent area, mm^2	8.15±1.91	7.59±1.62	NS
% Stent expansion	84.0±22.1	78.7±17.6	NS
Stent volume index, mm^3/mm	8.68±1.70	8.52±1.76	NS
Incomplete stent apposition, n (%)	5 (10)	3 (6)	NS
Edge tears, n (%)	6 (13)	6 (13)	NS

Values are mean±SD or frequencies.

In the 2-dimensional quantitative analysis, at the worst cross section, qDES showed a larger minimum lumen area (MLA) by 28%, a reduced neointimal area by 70%, and an improved CSN by 65% compared with BMS (Table 3). There was no significant difference in the average reference lumen area between the two stent groups. Further volumetric analysis of the entire stented segment revealed similar SVI in the two groups (qDES, 8.63±2.25 mm^3/mm; BMS, 8.84±1.83 mm^3/mm, *P*=NS), with no significant chronic recoil during the follow-up period. On the other hand, qDES showed a significantly reduced NVI by 68% than BMS (qDES, 0.79±0.51 mm^3/mm; BMS, 2.48±1.49 mm^3/mm, *P*<0.0001, Figure 2). Consequently, the LVI was significantly larger in qDES than in BMS (qDES, 7.83±2.11 mm^3/mm; BMS, 6.36±2.16 mm^3/mm, *P*=0.0019).

Figure 3 shows the relation between postprocedural MSA and follow-up MLA in the two stent groups. In the BMS group, only a weak correlation was observed (*r*=0.39, *P*=0.02), whereas qDES showed a significant positive relation with a greater correlation coefficient between the two parameters (*r*=0.73, *P*<0.0001).

Discussion

Clinical studies with conventional BMS have shown that certain plaque types have an overwhelming biological response to the acute mechanical injury by stent implantation and/or sustained stimuli from the rigid metal struts. In addition to the classic risk factors for in-stent restenosis, including multivessel disease, small-diameter vessels, long lesions, and bifurcations, recent IVUS studies have demonstrated that excessive arterial remodeling at preintervention,[11] large plaque burden before or after intervention,[12] and diabetes mellitus[13] should be also segregated for their biologically active milieus. After intracoronary brachytherapy as the first biological vector to approach those high-risk lesions, stent-based local drug delivery is considered an emerging breakthrough technology with less technical demand for operators. Among a number of pharmacological agents evaluated, rapamycin (sirolimus)[14–16] and paclitaxel[5–7] on a metal backbone were the front-runners, showing a significant reduction of in-stent neointimal growth in animal models or human studies. Early human registries with sleeve-based delivery of 7-hexanoyltaxol (a taxane analogue) have also shown favorable long-term outcomes after stenting.[8,9] This agent, the same drug used in this study, is highly lipophilic and insoluble in water. Although metabolism and toxicity are similar to paclitaxel, its C-7 portion is esterified with caproic acid to slow drug release from the polymer without altering its biological activity as a microtubule inhibitor. The current study is the first report to compare this particular type of

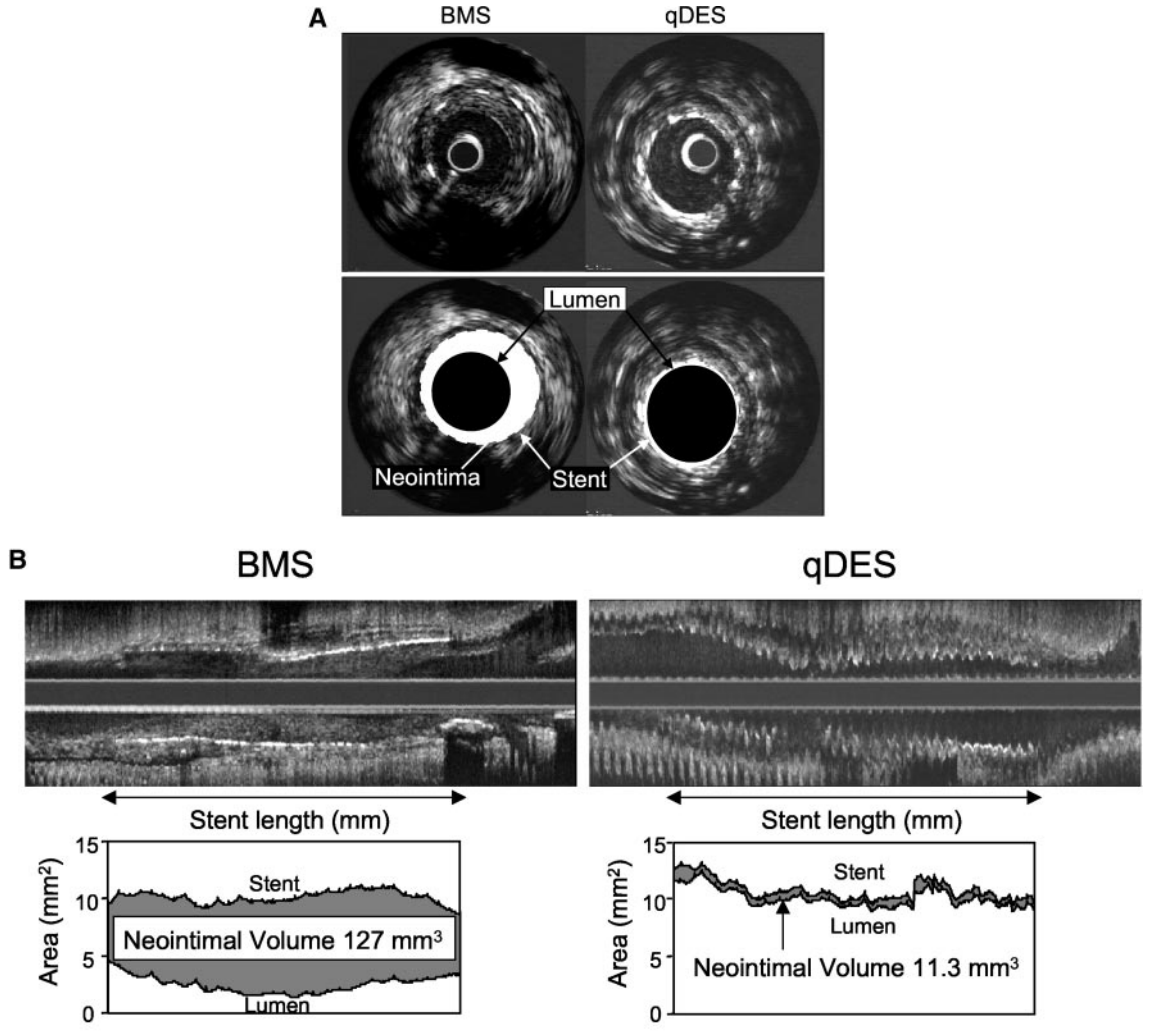

Figure 1. Representative cases. A, Cross-sectional IVUS images at 6-month follow-up show abundant neointima in BMS (left) versus minimal neointima in qDES (right). B, Longitudinal IVUS images at 6-month follow-up. Large amount of in-stent neointima is observed in BMS (left), whereas qDES (right) shows distinct inhibition of neointimal growth along the entire stented segment. Both stent lengths are 17 mm.

drug-eluting stent with BMS in a prospective, randomized, multicenter fashion.

Acute Mechanical Properties

The design of drug-eluting stents can significantly affect the pharmacokinetics as well as the mechanical scaffolding properties. Although metal stents have radial strength superior to newer polymer stents, conventional metal stents had several limitations as a drug reservoir because of limited surface area and drug-binding property of the stainless steel struts. One approach to circumvent these problems is a sleeve-based drug delivery system that allows a relatively uniform application of a desired amount of drug in a

TABLE 3. Follow-Up IVUS Results

	BMS	qDES	*P*
Reference lumen area, mm²	9.20±3.03	9.52±2.82	NS
Minimum lumen area, mm²	4.97±2.22	6.40±1.82	0.001
Neointimal area, mm²	3.57±2.19	1.07±0.90	<0.0001
Cross-sectional narrowing, %	41.5±22.6	14.2±11.1	<0.0001

Values are mean±SD.

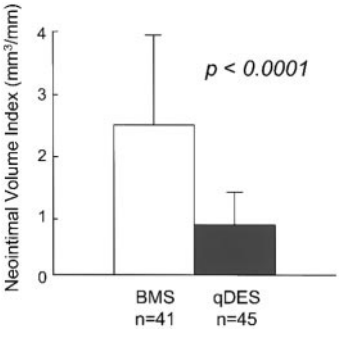

Figure 2. Neointimal volume index in BMS and qDES groups. Results are reported as mean±SD.

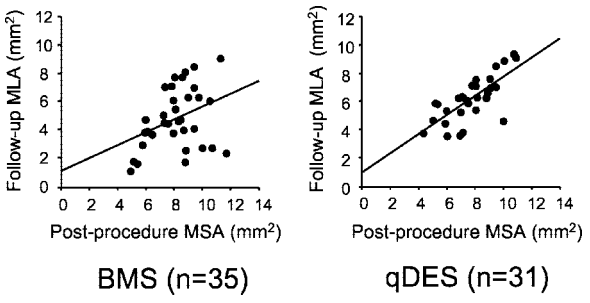

Figure 3. Relation between postprocedural MSA and follow-up MLA. qDES showed higher correlation coefficient (r=0.73, P<0.0001) than in BMS (r=0.39, P=0.02), indicating consistent efficacy of qDES irrespective of variable degrees of biological activity in each individual lesion.

controlled manner. On the other hand, these sleeves may potentially restrict initial stent expansion. Furthermore, complete stent apposition may be critical in antiproliferative drug-eluting stents not only for effective tissue drug uptake but also for the prevention of thrombotic events caused by delayed endothelialization, as observed in the animal models with paclitaxel-eluting stents.[5] In this study, however, qDES achieved an MSA and percent stent expansion comparable to those of BMS with similar lesion and procedural characteristics. Additional volumetric analysis also confirmed these findings over the entire stented segment. More importantly, no difference was observed in the occurrence of incomplete stent apposition between the two groups. Although the unique design of this drug-eluting stent may still call particular attention to major side branch protection, the technical requirement to achieve optimal stent expansion is considered comparable to conventional BMS.

Long-Term Biological Effects

In-stent restenosis is due solely to neointimal hyperplasia in response to stent-induced acute and chronic inflammation in the vessel wall. This process involves several cytokines and growth factors, inducing multiple signaling pathways to activate smooth muscle cell migration and proliferation. Therefore, attention has long been directed at the potential of antiproliferative agents that block cell cycle progression of vascular smooth muscle cells. Among a number of antiproliferative agents, paclitaxel and related compounds have several advantages as a candidate for local drug therapy: (1) a highly lipophilic character that promotes rapid cellular uptake by enabling easy passage through the hydrophobic barrier of cell membranes and (2) a prolonged deposition that supports a long-lasting antiproliferative action even after a brief, single-dose application at low concentrations. On the other hand, the efficacy of paclitaxel in reducing neointimal hyperplasia significantly depends on drug dose, delivery methods, and study models as well. For example, one rabbit iliac artery model demonstrated that a polymer-coated, paclitaxel-eluting stent (200 μg/stent) could reduce neointimal hyperplasia by 59% at 28-day follow-up.[5] In another study that used a pig coronary model, a paclitaxel-eluting stent with a dip-coating technique (187 μg/stent) showed a 39% reduction in neointimal hyperplasia compared with control.[6] On the other hand, local delivery of paclitaxel with a double-balloon local infusion catheter (10 mL; 10 μmol/L) failed to show any benefit after stenting in pig coronaries.[17] In the current study, which used a sleeve-based delivery system of 7-hexanoyltaxol, however, the favorable results of early human feasibility registries[8,9] have been well replicated, achieving a 70% reduction in neointimal hyperplasia compared with the control BMS. Moreover, qDES showed a higher correlation coefficient between postprocedural MSA and follow-up MLA than in BMS, indicating consistent efficacy of qDES, irrespective of various patient/lesion profiles and risk factors, and, therefore, variable degrees of biological activity in each lesion. Further follow-up will be needed to determine whether this particular type of drug-eluting stent may face late "catch-up," as reported in animal models with other agents and delivery platforms.[7]

Complications Assessed by IVUS

Animal studies have demonstrated several important similarities in histological characteristics between antiproliferative drug-eluting stents and intracoronary radiation therapy, which raises the concern of potential negative edge effects,[18] unhealed dissections,[19] or late stent-vessel wall malapposition.[20] In this study population, however, none of those morphological complications were detected at 6-month follow-up. Nevertheless, significant inhibition of neointimal proliferation was accompanied with the undetectable neointimal layer (by IVUS with axial resolution 120 μm) in parts of qDES, which may have a relation to late thrombotic events in the stented vessels. Although it is difficult to discuss the potential relation between the undetectable neointimal layer and adverse follow-up events from IVUS findings, the significantly delayed healing process reported in animal studies with other drug-eluting stents[5,7] may underscore the need for prolonged antiplatelet therapy in this type of stent.

Future Clinical Implications

To date, several multicenter, randomized trials have been initiated worldwide, elucidating the safety and effectiveness of drug-eluting stents. The preliminary results of four trials, including RAndomized study with the sirolimus-eluting VElocity balloon-expandable stent in the treatment of patients with de novo coronary artery Lesions (RAVEL) (rapamycin), ASian Paclitaxel-Eluting stent Clinical Trial (ASPECT), TAXUS, and European evaLUation of pacliTaxel-Eluting Stent (paclitaxel), showed minimum binary restenosis rates (0% to 14%)[16] (Seung-Jung Park, Eberhard Grube, and Anthony H. Gershlick, unpublished data, 2001). Although it is difficult to compare the results of 7-hexanoyltaxol polymer sleeve stent with other coated stents directly, RAVEL and ASPECT showed a significant reduction of neointimal growth (NVI, 0.11 to 1.2 mm^3/mm)[16] (Myeong-Ki Hong, unpublished data, 2002), similar to the magnitude found in this study. On the other hand, the patient population of these early clinical trials may consist of relatively simple lesions or patients at low risk. With more research and advanced technologies of drugs and their delivery, a new era of drug-eluting stent may emerge in the field of real-world, complex coronary interventions, as discussed above. Further

studies will be required to identify appropriate patient/lesion subsets with increased risk of restenosis that may derive true benefit from this technology, from both clinical and cost-effectiveness perspectives. In addition, whether IVUS guidance for these new biological treatments is advantageous will await the cumulative analysis of future trials.

Study Limitations

Several significant issues should be noted. First, enrollment in the IVUS substudy was not performed in a randomized fashion because of technical challenges during the imaging procedure. This may have created a selection bias toward larger lumens, less tortuous vessels, or lower risk patients compared with the entire population of the SCORE trial. Despite this potential bias, baseline patient/lesion and procedural characteristics were identical either between the two randomized treatment groups in this substudy or between the substudy subset and overall study. Second, follow-up IVUS was not available in all patients. Although this was primarily due to several logistic reasons, one patient in the qDES group had noncardiac death (suspected pulmonary embolism) during follow-up. Third, long-term observations beyond 6 months are lacking. Fourth, IVUS data were not directly related to all follow-up events. Finally, there are some intrinsic limitations in IVUS analysis as reported previously.

Conclusions

The detailed IVUS substudy from a human, prospective, randomized multicenter trial revealed that the sleeve-based 7-hexanoyltaxol eluting stent showed comparable acute mechanical and superior long-term biological effects to bare metal stents. Unlike another biological therapy that uses intracoronary radiation, there was no evidence of IVUS-detected adverse vessel response over the stented and adjacent references segments. Although the long-term benefits and limitations of this technology remain to be investigated further, future directions clearly implicate a biological cellular approach to compliment the conventional mechanical treatment of atherosclerotic disease.

Acknowledgments

We are grateful to Drs Mary E. Russell (Boston Scientific Corp), Martha A. Reitman, (Reitman Corp), and Yoshio Kobayashi (Cardiovascular Research Foundation) for their support.

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for the SCORE Investigators

Circulation. 2002;106:1788-1793; originally published online September 9, 2002;
doi: 10.1161/01.CIR.0000031734.11420.1C
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231

Print ISSN: 0009-7322. Online ISSN: 1524-4539