High-Dose 7-Hexanoyltaxol-Eluting Stent With Polymer Sleeves for Coronary Revascularization

One-Year Results From the SCORE Randomized Trial

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OBJECTIVES The Study to COmpare REstenosis Rate between QueST and QuaDDS-QP2 (SCORE) trial was a multicenter, randomized, open-label trial comparing the safety and performance of 13- and 17-mm QuaDDS stents (n = 126) (Quanam Medical Corp., Santa Clara, California/Boston Scientific Corp., Natick, Massachusetts) versus uncoated control stents (n = 140) in focal, de novo coronary lesions.

BACKGROUND The pioneering drug-delivery QuaDDS stent used four to six acrylate polymer sleeves, each loaded with 800 μg of the paclitaxel derivative 7-hexanoyltaxol.

METHODS Clinical end points were assessed at 1, 6, and 12 months post procedure. Quantitative coronary angiography and intravascular ultrasound were performed post procedure and at six-month follow-up.

RESULTS In the QuaDDS group, early stent thrombosis and myocardial infarction (MI) rates were significantly higher, leading to premature cessation of enrollment. For the QuaDDS group, the stent thrombosis rate increased from 3.2% to 10.3% between 1 and 12 months, associated with increased non–Q-wave MI and death rates. The angiographic restenosis rate at six months was reduced from 32.7% (control) to 7.4% (p < 0.0001). However, the primary end point was not met with six-month target vessel revascularization (TVR) rate as well as the composite major adverse cardiac event rates (cardiac death, MI, and TVR) comparable between groups.

CONCLUSIONS Despite angiographic indications of potential anti-restenotic benefit, increased rates of stent thrombosis, MI, and cardiac death associated with the QuaDDS stent show an unacceptable safety profile. (J Am Coll Cardiol 2004;44:1368–72) © 2004 by the American College of Cardiology Foundation

The use of bare metal coronary stents after balloon angioplasty has decreased, but not eliminated, restenosis and the subsequent need for repeat revascularization procedures (1). For this reason, drug-eluting stents that provide antiprolif-
Abbreviations and Acronyms
IVUS = intravascular ultrasound
MACE = major adverse cardiac event
MI = myocardial infarction
QCA = quantitative coronary angiography
TLR = target lesion revascularization
TVR = target vessel revascularization

Committees of participating institutions approved the protocol, and patients provided written informed consent before enrollment.

Enrollment, planned for 400 patients in 19 international sites, began in February 2000. In April 2001, enrollment was terminated prematurely (266 patients, 15 sites, 4 countries) because of unexpectedly high rates of adverse cardiac events (stent thrombosis cardiac death, and myocardial infarction [MI]).

Patient selection. Eligible patients (51 to 79 years of age) had documented de novo lesions in native coronary arteries, objective evidence of ischemia (stable/unstable angina, positive functional study), and clinical, hemodynamic, and angiographic indications for percutaneous transluminal coronary angioplasty. Key angiographic inclusion criteria were lesion length suitable for a single 13- or 17-mm stent with stenosis >50% and location in a native coronary vessel ≥3.0 mm and ≤3.5 mm in diameter.

Key exclusion criteria included excessive tortuosity, involvement of side branch >2.0 mm in diameter, moderate or severe calcification of the target lesion or adjacent vessel, acute MI <1 week before the procedure, stroke or transient ischemic attack <6 months before the procedure, and allergy or contraindication to aspirin, clopidogrel, ticlopidine, heparin, or stainless steel.

End points. Clinical end points included stent thrombosis rate and major adverse cardiac event (MACE), defined as cardiac death, Q-wave and non-Q-wave MI, and revascularization of the target lesion (coronary artery bypass graft or percutaneous coronary intervention). An independent Clinical Events Committee adjudicated MACE. The primary end point six months post procedure was the target vessel revascularization (TVR) rate; secondary end points were MACE, quantitative coronary angiography (QCA), and intravascular ultrasound (IVUS) assessments of restenosis. Successful reduction was predefined as a restenosis rate <20%.

Device. Control devices included commercially available uncoated stents and balloon-expandable (13- or 17-mm long; 3.0- or 3.5-mm diameter) QueST stents made of 316L surgical-grade stainless steel in a slotted tube design and mounted on an over-the-wire balloon catheter delivery system. The test stent (QuaDDS) was the QueST stent mounted with polymer sleeves with 800 μg 7-hexanoyltaxol each (Fig. 1). The 13-mm stent contained 4 sleeves (3.2 mg); the 17-mm had 5 sleeves (4.0 mg).

Procedures. Patients, randomized to QuaDDS or control stents, received a loading dose of ticlopidine (500 mg) or clopidogrel (150 to 300 mg) ≤24 h before the procedure and heparin to maintain an active clotting time of ≥250 s. Post procedure, the protocol mandated aspirin (100 mg daily) indefinitely. Ticlopidine (250 mg twice a day) or clopidogrel (75 mg every day) treatment, initially mandated for either one month (control) or six months (QuaDDS), was amended to one year for the QuaDDS stent.

Follow-up. Clinical follow-up was conducted at 1, 6, and 12 months post procedure. Coronary angiography was performed before and immediately after the index procedure and at six-month follow-up or when a patient presented with cardiac symptoms. An independent core laboratory (Cardiovascular Research Foundation, New York, New York) following established methodology performed QCA analyses. In-stent restenosis assessments included percent diameter stenosis, minimum lumen diameter, reference vessel diameter, acute gain, late loss, and restenosis rate (percent with >50% diameter stenosis). Intravascular ultrasound assessment was performed on 122 patients (66 QuaDDS; 56 control) immediately post procedure and again at six months (6).

Statistical analysis. Final data management and statistical analyses were performed by PAREXCEL International Ltd. (Waltham, Massachusetts). The primary study hypothesis was that the QuaDDS stent would reduce in-stent restenosis rates compared with bare metal stents (7,8). Statistical analyses, performed using SAS version 6.12 (SAS Institute, Cary, North Carolina), were based upon actual stent received to assess the safety performance of the stent. Continuous variables are summarized as mean ± SD and compared between treatment groups using a two-sample t test. Categorical variables are expressed as percentages and compared using two-sided Fisher’s exact test. Survival analyses for freedom from MACE and target lesion revascularization (TLR) were performed using the Kaplan–Meier product-limit method and compared using the log-rank test. A p value <0.05 was considered statistically significant.

RESULTS
The SCORE trial was terminated prematurely (266 patients) in April 2001 owing to a high rate of adverse cardiac
MACE rates were comparable as a result of similar TVR rates (Table 2). However, the QuaDDS group showed higher rates of overall MI and non-Q-wave MI.

Twelve-month MACE rates were similar but the QuaDDS group showed higher rates of MI and cardiac death. The groups had similar survival curves for freedom from MACE and freedom from TLR (Fig. 2).

**QCA and IVUS.** At six-month follow-up, the restenosis rate was reduced from 32.7% (control) to 7.4% (QuaDDS [p < 0.0001]) (Table 3). The QuaDDS group minimum lumen diameter was larger; percent diameter stenosis and late loss were lower (Table 3). The IVUS outcomes showing a 68% reduction in neointimal growth and a 28% increase in minimum lumen area in the QuaDDS group versus control patients were published previously (6).

**DISCUSSION**

The pioneering QuaDDS stent’s unacceptable safety profile and failure to impact revascularization have halted further development of this high-dose, acrylate polymer sleeve delivery system. The safety outcomes from this mode of paclitaxel delivery stand in stark contrast to acceptable results obtained with other paclitaxel-eluting coated stents (2–5,9). Factors that may have contributed to the increased stent thrombosis, non-Q-wave MIs, and death are outlined in the following discussion.

**Drug.** Drug doses loaded on the QuaDDS stent were >10-fold above the TAXUS paclitaxel-eluting stents (e.g., 17-mm QuaDDS stent, 4,000 µg; 16-mm TAXUS stent, 108 µg) (2). Second, release was protracted for QuaDDS, with most (80%) 7-hexanoyltaxol release occurring within 90 days and continuing to six months (Quanam/Boston Scientific preclinical data on file). This contrasts with burst release of the paclitaxel within the first 48 h for the other paclitaxel-eluting stents. Hence, higher drug doses for a longer time may have delayed healing and prevented surface passivation, contributing to the QuaDDS stent’s higher stent thrombosis rate.

**Polymer.** Long-term (90- and 180-day) porcine studies conducted subsequent to SCORE enrollment demonstrated...
an intense inflammatory reaction with frequent granulomas and fibrosis with severe narrowing and occlusion in vessels stented with the QuaDDS stent or polymer-only sleeves (Boston Scientific data on file), indicative of vascular incompatibility of the polymer sleeves alone and with 7-hexanoyltaxol. These proinflammatory findings in the porcine model with the acrylate polymer may suggest additional mechanisms contributing to the poor QuaDDS safety profile in humans.

**Sleeves.** Multiple, relatively thick sleeves could potentially block side branches, leading to higher rates of periprocedural non-Q-wave MI. In contrast, paclitaxel-eluting stents using strut-conforming drug coatings have established safe clinical trial profiles (2,3,5,9).

**CONCLUSIONS**

Despite the limitations of open-label design, the SCORE trial outcomes demonstrate that for the QuaDDS stent, the potential anti-restenotic benefit seen with reduced binary restenosis rates is outweighed by an unacceptable safety profile. Incomplete healing suggested by ongoing stent
thrombosis and associated MACE argue that the goal for paclitaxel delivery is transient and low-level paclitaxel release as opposed to the QuaDDS design with protracted and high-dose release of 7-hexanoyltaxol.

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REFERENCES

APPENDIX
An independent Clinical Events Committee whose members were Stephen G. Ellis, MD, Patrick L. Whitlow, MD, and E. Murat Tuzcu, MD, of the Cleveland Clinic Foundation, adjudicated MACE.

The Clinical Oversight Committee, consisting of Mary E. Russell, MD, David O. Williams, MD, and Simon Stertz, MD, recommended that the SCORE trial be prematurely terminated owing to a high rate of adverse cardiac events.