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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 antiproliferative drugs to the stented vessel wall have been designed and studied for reducing in-stent restenosis.

The pioneering QuaDDS stent (Quanam Medical Corp., Santa Clara, California/Boston Scientific Corp., Natick, Massachusetts) was designed to control neointimal proliferation through prolonged high-dose delivery of the paclitaxel derivative 7-hexanoyltaxol (QP2) via acrylate polymer membranes mounted on a novel stent design (QueST).This technology differs markedly from subsequent paclitaxel-eluting stents that use drug or drug-polymer coatings to deliver low-dose paclitaxel to inhibit restenosis (2–5).

We report final one-year outcomes from the Study to COmpare REstenosis Rate between QueST and QuaDDS-QP2 (SCORE) trial.

METHODS

Study design. The open-label, randomized, multicenter SCORE trial compared safety and performance of the QuaDDS stent versus the QueST, or other, bare metal stents in focal, de novo coronary lesions. Ethics Review

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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

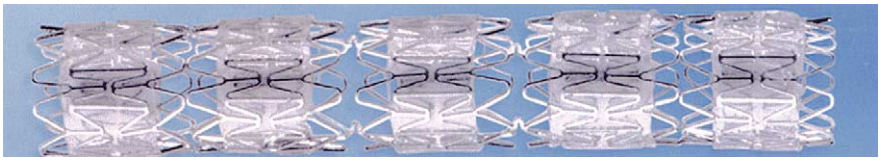

Figure 1. Photograph of the QuaDDS stent with five polymer sleeves.

Table 1. Baseline Demographics and Clinical Characteristics

Characteristic*	QuaDDS (n = 126)	Control (n = 140†)
Gender, male (%)	81	78
Age, yrs (min, max)‡	61 (33, 79)	63 (34, 80)
Diabetes (%)	20	21
Hypertension (%)	68	64
Previous myocardial infarction (%)	39	41
Hypercholesterolemia (%)	72	78
Current smoking (%)	16	18

*No statistically significant differences between groups ($p < 0.05$). †QueST: 111; commercial uncoated: 29. ‡In accordance with the protocol, eligible patients were between 50 and 80 years old but five patients under 50 were enrolled.

events as recommended by the Clinical Oversight Committee. Long-term results were collected for 91% (244 of 266) and 76% (201 of 266) of patients at six-month clinical and angiographic follow-up, respectively, and for 88% (235 of 266) at 12-month clinical follow-up. The Clinical Oversight Committee also recommended that the SCORE trial patients be maintained on clopidogrel and followed in a long-term registry.

Baseline and procedural characteristics. Groups showed no significant differences with respect to baseline demographics and clinical characteristics (Table 1). Mean lesion lengths (QCA) were comparable (11.7 ± 4.4 mm [QuaDDS]; 12.0 ± 4.4 mm). Stent placement with post-procedure percent diameter stenosis <20% was comparable (99.7% [QuaDDS]; 99.8%).

Clinical outcomes. In the QuaDDS group, stent thrombosis rates were higher at 1, 6, and 12 months and were associated with increased rates of cardiac death and MI (Table 2). The risk for cardiac death or MI in QuaDDS patients who had a stent thrombosis was 84.6%, significantly higher than for those who did not ($p < 0.001$). Among QuaDDS patients with a stent thrombosis, 23.1% (3 of 13) had associated death, 76.9% (10 of 13) had associated MI, and 15.4% (2 of 13) had associated cardiac death and MI.

One-month overall MACE rates were higher in the QuaDDS group, attributable in part to an increase in MI, most likely related to polymer sleeve side branch occlusion.

The six-month primary end point was not met. Group 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

Table 2. 1-, 6-, and 12-Month Cumulative MACE and Stent Thrombosis

Event	1 Month			6 Months			12 Months		
	QuaDDS (n = 126)	Control* (n = 140)	p†	QuaDDS (n = 126)	Control* (n = 140)	p†	QuaDDS (n = 126)	Control* (n = 140)	p†
MACE	16 (12.7%)	4 (2.9%)	0.004	26 (20.6%)	20 (14.3%)	0.196	37 (29.4%)	35 (25.0%)	0.490
Cardiac death	2 (1.6%)	0 (0.0%)	0.223	3 (2.4%)	0 (0.0%)	0.105	5 (4.0%)	0 (0.0%)	0.023
MI	15 (11.9%)	3 (2.1%)	0.002	20 (15.9%)	3 (2.1%)	< 0.001	24 (19.0%)	3 (2.1%)	< 0.001
Q-wave MI	1 (0.8%)	0 (0.0%)	0.474	3 (2.4%)	0 (0.0%)	0.105	6 (4.8%)	0 (0.0%)	0.011
Non–Q-wave MI	13 (10.3%)	3 (2.1%)	0.008	15 (11.9%)	3 (2.1%)	0.002	16 (12.7%)	3 (2.1%)	0.001
Target vessel revascularization	3 (2.4%)	1 (0.7%)	0.348	15 (11.9%)	18 (12.9%)	0.854	25 (19.8%)	33 (23.6%)	0.552
Target lesion revascularization	3 (2.4%)	1 (0.7%)	0.348	10 (7.9%)	14 (10.0%)	0.670	18 (14.3%)	26 (18.6%)	0.410
Stent thrombosis	4 (3.2%)	0 (0.0%)	0.049	9 (7.1%)	1 (0.7%)	0.007	13 (10.3%)	1 (0.7%)	< 0.001

*Included two patients randomized to the QuaDDS stent who erroneously received a control stent. †Two-sided Fisher's exact tests; $p < 0.05$ = statistically significant.
MACE = major adverse cardiac events; MI = myocardial infarction.

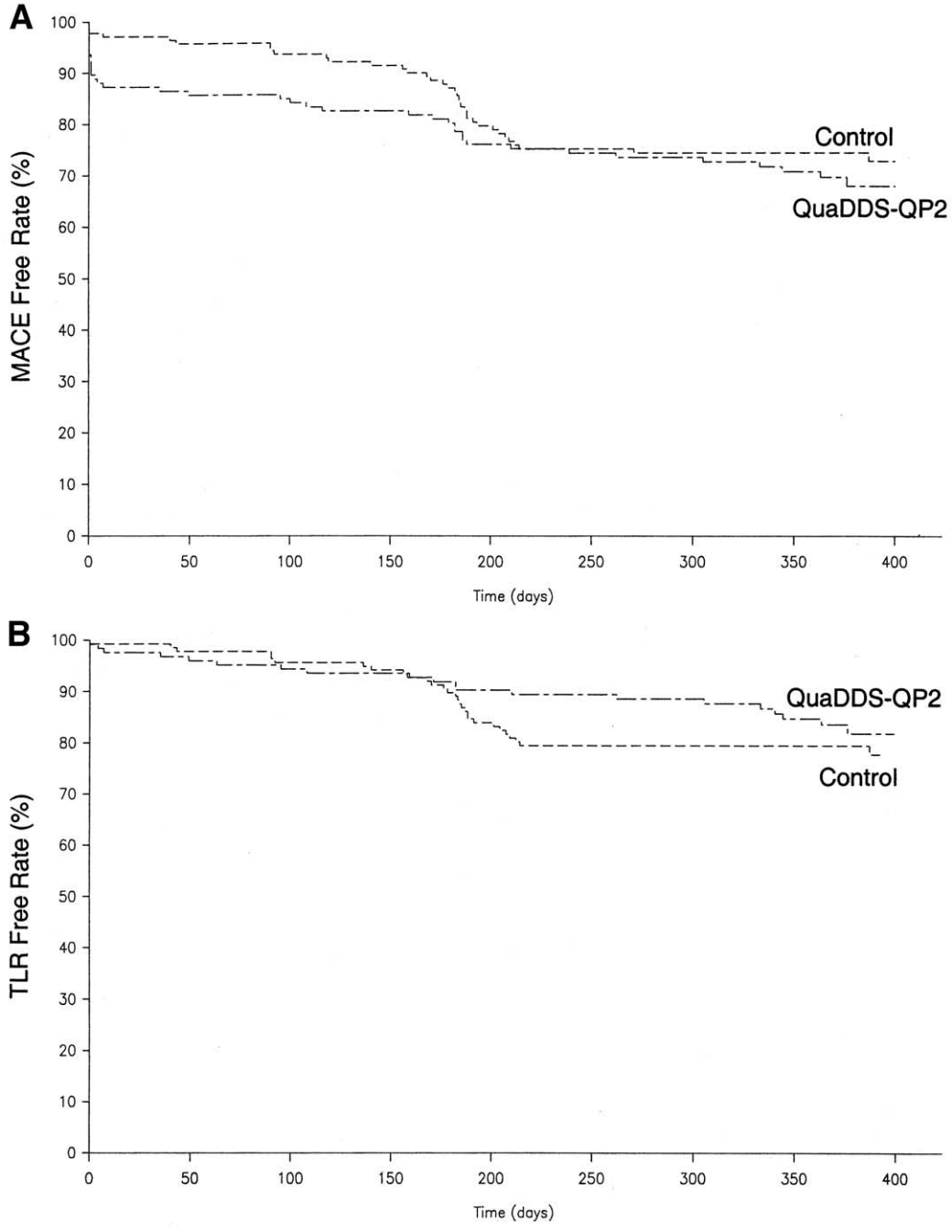

Figure 2. Freedom from **(A)** major adverse cardiac event (MACE) and **(B)** target lesion revascularization (TLR) post-procedure.

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

Table 3. Baseline, Post-Procedure, and Six-Month Angiographic Outcomes in the SCORE Trial

	QuaDDS* (n)	Control* (n)	p†
Baseline‡			
Reference vessel diameter (mm)	2.91 ± 0.43 (116)	3.00 ± 0.48 (132)	0.12
Lesion length (mm)	11.69 ± 4.38 (113)	11.98 ± 4.35 (130)	0.60
Minimum lumen diameter (mm)	0.92 ± 0.38 (116)	0.92 ± 0.46 (133)	0.99
Percent diameter stenosis (%)	68.67 ± 12.17 (116)	69.86 ± 12.95 (132)	0.46
Post-procedure‡			
Reference vessel diameter (mm)	2.97 ± 0.38 (114)	3.06 ± 0.44 (132)	0.11
Minimum lumen diameter (mm)	2.78 ± 0.37 (116)	2.91 ± 0.46 (133)	0.01
Percent diameter stenosis (%)	6.28 ± 10.25 (114)	4.43 ± 10.50 (132)	0.16
Six months‡			
Minimum lumen diameter (mm)	2.43 ± 0.54 (94)	1.79 ± 0.76 (107)	< 0.0001
Percent diameter stenosis (%)	16.4 ± 18.1 (94)	39.5 ± 23.9 (107)	< 0.0001
Binary (>50%) restenosis rate (%)§	7.4% (94)	32.7% (107)	< 0.0001
Late lumen loss (mm)	0.34 ± 0.58 (94)	1.08 ± 0.79 (107)	< 0.0001

*Mean ± SD or %. †Continuous data: two-sample *t* test; binary data: two-sided Fisher's exact test; $p < 0.05$ = statistically significant. ‡Angiographic analyses were carried out on the randomized groups. §>50% in-stent diameter stenosis, excluding patients with thrombosis.
SCORE = Study to COmpare REstenosis Rate between Quest and QuaDDS-QP2.

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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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 Stertzer, MD, recommended that the SCORE trial be prematurely terminated owing to a high rate of adverse cardiac events.