Randomized Evaluation of Polytetrafluoroethylene-Covered Stent in Saphenous Vein Grafts : The Randomized Evaluation of polytetrafluoroethylene COVERed stent in Saphenous vein grafts (RECOVERS) Trial

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The Randomized Evaluation of polytetrafluoroethylene COVERed stent in Saphenous vein grafts (RECOVERS) Trial

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Background—Treatment of lesions located in saphenous vein grafts (SVGs) is associated with increased procedural risk and a high rate of restenosis.

Methods and Results—We conducted a randomized, multicenter trial to evaluate the usefulness of a polytetrafluoroethylene (PTFE)-covered stent compared with a bare stainless steel (SS) stent for prevention of restenosis and major adverse cardiac events (MACE) in patients undergoing SVG treatment. The primary end point was angiographic restenosis at 6 months. Secondary end points were 30-day and 6-month MACE rates, defined as the cumulative of death, myocardial infarction (MI), and target lesion revascularization. Between September 1999 and January 2002, 301 patients with SVG lesions were randomized to either the PTFE-covered JoStent coronary stent graft (PTFE group, n=156) or the SS JoFlex stent (control group, n=145). Angiographic and procedural success rates were similar between the 2 groups (97.4% versus 97.9% and 87.3% versus 93.8%, respectively). The incidence of 30-day MACE was higher in the PTFE group (10.9% versus 4.1%, $P=0.047$) and was mainly attributed to MI (10.3% versus 3.4%, $P=0.037$). The primary end point, the restenosis rate at 6-month follow-up, was similar between the 2 groups (24.2% versus 24.8%, $P=0.237$). Although the 6-month non–Q-wave MI rate was higher in the PTFE group (12.8% versus 4.1%, $P=0.013$), the cumulative MACE rate was not different (23.1% versus 15.9%, $P=0.153$).

Conclusions—The study did not demonstrate a difference in restenosis rate and 6-month clinical outcome between the PTFE-covered stent and the SS stent for treatment of SVG lesions. However, a higher incidence of nonfatal myocardial infarctions was found in patients treated with the PTFE-covered stent. **(*Circulation*. 2003;108:37-42.)**

Key Words: polytetrafluoroethylene ■ grafting ■ restenosis

Treatment of lesions located in saphenous vein grafts (SVGs) is still a challenge. Repeat surgical revascularization (CABG) is feasible but is associated with higher morbidity and mortality and less symptomatic improvement than the initial operation.[1,2] Attempts at percutaneous revascularization in SVG lesions with balloon angioplasty were limited by a relatively low procedural success rate and a high incidence of angiographic recurrence.[3,4] A randomized, saphenous vein de novo trial (the SAVED trial) showed that stent implantation in patients with focal SVG lesions improved procedural success and clinical outcome compared with balloon angioplasty.[5] However, even with the use of stents, treatment of SVG lesions is associated with a high incidence of acute complications, principally distal embolization and periprocedural myocardial infarction (MI), because of the more friable atherosclerotic or thrombotic components of the SVG lesions.[6–12] The polytetrafluoroethylene (PTFE)-covered stent was recently proposed as a new treatment option for SVG lesions with the rationale that a covered stent would be able to entrap friable degenerated material, decrease the probability of distal embolization, and reduce neointimal proliferation.[13–16]

We therefore designed the Randomized Evaluation of polytetrafluoroethylene COVERed stent in Saphenous vein grafts (RECOVERS) trial to compare angiographic restenosis rates and early and late clinical outcome between the PTFE-

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covered stent and the bare stent in patients undergoing SVG intervention.

Methods

Patient Population

The study was a prospective, randomized trial conducted from September 1999 to January 2002 at 20 medical centers, primarily located in Europe (see Appendix). The protocol was reviewed and approved by the medical ethics committee at each participating center, and all patients gave written informed consent.

Patients were eligible for the study if they were at least 18 years old, were not pregnant, had a diagnosis of stable or unstable angina or documented silent ischemia, and had an ejection fraction >35%. The angiographic criteria for inclusion were the presence of a maximum of 2 de novo lesions in an SVG or in 2 vein grafts, with a reference diameter between 2.5 and 5.5 mm and a stenosis of ≥50% and <100%, that required no more than one 26-mm-long covered or bare stent each, as estimated visually.

Patients were not eligible for enrollment if they had an MI within the past 3 days or had a known allergy to the study medications. Angiographic exclusion criteria were a single remaining bypass graft (single remaining circulation), intention to treat native vessels, presence of large thrombus (>50% vessel diameter) in the target lesion, or a lesion located close to side anastomosis.

Randomization

Treatment assignment was determined by computer-generated randomization codes distributed in sealed envelopes to each participating center. Patients were randomly assigned to the groups in a 1:1 ratio. Separate envelopes permitted stratification according to operator's decision to use glycoprotein IIb/IIIa receptor blockers on an elective basis.

Study Device and Interventional Procedure

The JoStent coronary stent graft (Jomed) consists of 2 coaxially aligned stainless steel stents (surgical 316 L) that encompass a microporous PTFE membrane between them in a sandwich-like configuration.[13] Overall wall thickness is 0.30 mm, and mounted profile is 1.6 mm. The stent graft was available in lengths of 9, 12, 16, 19, and 26 mm and a maximum achievable diameter of 5.0 mm. The longitudinal shortening of the stent on expansion is <3%.

In either arm, lesion predilatation was performed with an undersized balloon. The PTFE-covered stent was then hand-crimped on a balloon sized 1.1:1 to SVG diameter based on angiography. High-pressure postdilatation was suggested, and the criterion for optimal stent deployment was a final residual diameter stenosis of <20%.

If dissection or plaque shift occurred at the edge of the stent, additional stents were implanted according to initial randomization. Use of intravascular ultrasound to guide the procedure was left to the discretion of the operator.

Concomitant Medications

All patients were premedicated with aspirin 325 mg/d and ticlopidine 500 mg/d or clopidogrel 75 mg/d, which was begun at least at the time of randomization. During the procedure, patients received intravenous heparin to maintain an activated clotting time of 250 to 300 seconds. Platelet glycoprotein IIb/IIIa receptor blockers were used at the discretion of the operator.

All patients received aspirin (at least 100 mg/d) indefinitely. Patients who received the PTFE-covered stent were treated with ticlopidine 500 mg/d or clopidogrel 75 mg/d for 3 months, whereas patients who received the bare stainless steel (SS) stent were treated for 1 month.

Angiographic Analysis

From 2 orthogonal views, the diameter of the reference vessel, minimal luminal diameter, and target lesion length were determined at baseline, after procedure, and at follow-up with a validated edge-detection program (CMS version 4.0, MEDIS). In addition, the acute gain, late loss, and late-loss index were calculated. Lesions were characterized according to the modified American College of Cardiology/American Heart Association classification. Long lesions were defined as a single continuous narrowing longer than 15 mm. Tandem lesions were defined as lesions in the same vessel that were separated by <15 mm of nondiseased segment. Degenerated SVG was defined as a graft that had a lesion longer than 30 mm and was associated with the presence of thrombus or irregular lumen contours. Distal embolization was defined as angiographic cutoff of a distal branch or vessel at any point during the procedure or decreased flow in a distal vessel that was previously patent in the absence of an occlusion at the site of the target lesion.[17] No reflow was defined as Thrombolysis In Myocardial Infarction (TIMI) flow grade ≤1 that was not due to dissection or high-grade residual stenosis adjacent to the target lesion.

Study End Points and Definitions

The primary end point was angiographic restenosis, defined as stenosis of ≥50% by quantitative coronary angiography at 6-month follow-up angiography or earlier. Secondary end points were 30-day and 6-month major adverse cardiac events (MACE), defined as the composite of death, non–Q-wave MI, Q-wave MI, and target lesion revascularization (CABG and repeat percutaneous coronary intervention).

Angiographic success was defined as final diameter stenosis of <50%. Procedural success was defined as angiographic success without in-hospital MACE.

MI was defined as the occurrence of an elevated creatine kinase (CK)–MB fraction >3 times the upper limit of normal (standardized to the normal range of each clinical site). Patients with enzymatic elevation were further stratified into those with and without appearance of pathological Q waves on serial ECGs. Cardiac enzymes (total CK and CK-MB) were measured before treatment and at 4 to 8 hours after the procedure; further determinations were required if either CK or CK-MB was elevated.

Statistical Analysis

The study was designed to have a power of 80% to reject the null hypothesis of no difference between the treatment groups, with a 5% level of significance in 2-tailed tests. On the assumption that the angiographic restenosis rate would be 35% in the SS stent group[5] and 17% in the PTFE-covered stent group,[14] it was determined that 300 patients would be needed to detect that difference. Comparisons between the 2 treatment groups were performed on an intention-to-treat basis.

The data are presented as numbers and percentages or mean±SD. Categorical variables were compared with the χ^2 test or Fisher's exact test when appropriate. Continuous variables were compared with the use of Student's *t* test or ANOVA. A stepwise multivariable logistic model of the primary and secondary end points was constructed in which the dependent variables were angiographic restenosis or incidence of MACE at 6-month follow-up and the independent variables selected were clinical, angiographic, and procedural covariates. The results are presented as odds ratios with 95% CIs. A 2-tailed probability value of 0.05 or less was considered significant. All statistical analysis was performed with SAS version 6.12 (SAS Institute).

Results

Between September 1999 and January 2002, 301 patients were enrolled at 20 medical centers, primarily in Europe. One hundred fifty-six patients were randomized to the PTFE-covered stent and 145 patients to the SS stent.

Baseline clinical characteristics of the 2 groups were well matched (Table 1). Overall, 85% of the patients were men, and the mean age was 66 years. The clinical profile showed a high percentage of patients with a history of MI (57%) and unstable angina (48%), with the expected prevalence of

TABLE 1. Baseline Clinical Characteristics

	PTFE Group (n=156)	SS Group (n=145)	P
Age, y (range)	66±9 (37–87)	67±8 (42–85)	0.62
Male gender	136 (87.2)	121 (83.4)	0.36
Diabetes mellitus	39 (26.2)	39 (28.0)	0.82
Hypercholesterolemia*	114 (73.1)	103 (71.0)	0.80
Hypertension	96 (61.5)	90 (62.1)	0.82
Family history of CAD	66 (42.3)	55 (37.9)	0.62
Current or ex-smoker	93 (59.6)	89 (61.4)	0.58
Prior MI	90 (57.7)	80 (55.2)	0.56
Prior stroke	10 (6.4)	5 (3.4)	0.37
Prior PTCA	46 (29.5)	37 (25.5)	0.47
Clinical presentation			0.58
Unstable angina	76 (48.8)	69 (47.6)	
Stable angina	62 (39.7)	62 (42.8)	
Silent ischemia	18 (11.5)	14 (9.6)	
Ejection fraction, %	56±12	55±12	0.82
Age of the SVG, y	9.9±5.0	9.1±5.5	0.21

CAD indicates coronary artery disease.
Values are numbers and percentages of patients or mean±SD.
*Total cholesterol >6.5 mmol/L.

diabetes, hypercholesterolemia, and hypertension. The age of the treated grafts was 9.9 years in the PTFE group and 9.1 years in the SS group ($P=0.21$).

Angiographic and procedural characteristics are shown in Tables 2 through 4. Except for a higher prevalence of ostial lesion location in the control group, baseline lesion characteristics were similar in the 2 groups. Stents were successfully implanted in 152 patients in the PTFE group (97.4%) and 142 patients in the SS group (97.9%), with a mean balloon diameter of 3.9±0.6 and 3.8±0.5 mm, respectively, ($P=0.08$) and an average maximum inflation pressure of 18.2±3.9 and 16.0±3.7 atm, respectively ($P=0.0001$). Postdilatation after stent deployment was performed in 97 lesions of PTFE group and 80 lesions of the control group. The final minimal luminal diameter and acute gain were similar in the 2 groups. There was also no difference in the incidence of dissections and transient occlusions or in the occurrence of thrombus, distal embolization, or angiographic "no reflow." Glycoprotein IIb/IIIa inhibitors were used in 31% of patients in the PTFE group and 29% in the SS group ($P=0.73$). Procedural success was comparable between the 2 groups (87.3% versus 93.8% in the PTFE and SS group, respectively; $P=0.08$). There were no patients with acute stent thrombosis, whereas subacute stent thrombosis occurred in 2 patients in the PTFE group (1 of them had non–Q-wave MI) and none of the patients in the SS group.

TABLE 2. Baseline Angiographic Characteristics

	PTFE Group (n=166)	SS Group (n=156)	P
Target graft distribution			0.40
SVG–LAD	53 (31.9)	39 (25.0)	
SVG–RCA	48 (28.9)	42 (26.9)	
SVG–LCx	51 (30.7)	59 (37.8)	
SVG–sequential	14 (8.5)	16 (10.3)	
Target lesion location			0.02
Ostial	51 (30.7)	68 (43.6)	
Body	115 (69.3)	88 (56.4)	
Tandem lesions	31 (18.7)	20 (12.8)	0.20
ACC/AHA type B2/C*	107 (64.5)	96 (61.5)	0.67
Degenerated graft	68 (40.9)	51 (32.7)	0.22
TIMI flow grade			0.79
1	7 (4.2)	9 (5.8)	
2	49 (29.5)	47 (30.1)	
3	110 (66.3)	100 (64.1)	

LAD indicates left anterior descending coronary artery; LCx, left circumflex coronary artery; and RCA, right coronary artery.
Values are numbers and percentages of lesions or mean±SD.
*Modified American College of Cardiology/American Heart Association (ACC/AHA) lesion classification.

TABLE 3. Procedural Characteristics

	PTFE Group (n=166)	SS Group (n=156)	P
Stent length, mm	16.9±5.4	16.6±5.4	0.59
Balloon diameter, mm	3.93±0.65	3.81±0.55	0.08
Inflation pressure, atm	18.2±3.9	16.4±3.7	0.0001
Dissection	14 (8.4)	7 (4.5)	0.18
Transient occlusion	2 (1.2)	0	0.49
Thrombus	18 (10.8)	10 (6.4)	0.22
Distal embolization	4 (2.4)	4 (2.6)	0.99
No reflow	9 (5.4)	3 (1.9)	0.14

Values are mean±SD and numbers and percentages of lesions.

TABLE 4. Quantitative Coronary Angiography Analysis

	PTFE Group (n=166)	SS Group (n=156)	P
Baseline			
Reference diameter, mm	3.36±0.75	3.28±0.71	0.73
MLD, mm	1.11±0.54	1.13±0.54	0.74
Diameter stenosis, %	67.7±13.4	65.6±14.0	0.17
Mean lesion length, mm	11.97±6.7	11.83±7.86	0.86
After procedure			
Reference diameter, mm	3.73±0.69	3.61±0.69	0.12
MLD, mm	3.31±0.57	3.18±0.69	0.07
Diameter stenosis, %	10.9±8.5	12.0±8.2	0.24
Acute gain, mm	2.19±0.68	2.08±0.67	0.16
Six-month follow-up, n/n (%)	132/166 (79.5)	125/156 (80.1)	
Reference diameter, mm	3.54±0.61	3.40±0.63	0.07
MLD, mm	2.37±1.27	2.20±1.09	0.26
Diameter stenosis, %	34.1±34.1	36.7±28.3	0.51
Late loss, mm	0.95±1.15	0.98±1.03	0.86
Loss index	0.47±0.64	0.51±0.62	0.65
Binary restenosis rate, n/n (%)	32/132 (24.2)	31/125 (24.8)	0.24

MLD indicates minimal luminal diameter.
Values are mean±SD, except where otherwise indicated.

TABLE 5. Clinical Outcome

	PTFE Group (n=156)	SS Group (n=145)	P
In-hospital MACE	16 (10.3)	6 (4.1)	0.069
Death	0	1 (0.7)	0.970
MI	15 (9.6)	5 (3.4)	0.055
Non–Q-wave	13 (8.3)	4 (2.8)	0.065
Q-wave	2 (1.3)	1 (0.7)	0.605
TLR	2 (1.3)	0	0.511
PCI	2 (1.3)	0	0.511
CABG	0	0	NA
30-Day MACE*	17 (10.9)	6 (4.1)	0.047
Death	0	1 (0.7)	0.971
MI	16 (10.3)	5 (3.4)	0.037
Non–Q-wave	14 (8.9)	4 (2.8)	0.042
Q-wave	2 (1.3)	1 (0.7)	0.605
TLR	2 (1.3)	0	0.511
PCI	2 (1.3)	0	0.511
CABG	0	0	NA
6-Month MACE†	36 (23.1)	23 (15.9)	0.153
Death	4 (2.6)	4 (2.8)	0.917
MI	22 (14.1)	8 (5.5)	0.022
Non–Q-wave	20 (12.8)	6 (4.1)	0.013
Q-wave	2 (1.3)	2 (1.4)	0.941
TLR	15 (9.6)	12 (8.3)	0.838
PCI	13 (8.3)	10 (6.9)	0.811
CABG	2 (1.3)	2 (1.4)	0.941

PCI indicates percutaneous coronary intervention; TLR, target lesion revascularization.

Values are numbers and percentages of patients.

*Cumulative 30-day MACE; †cumulative 6-month MACE.

Early and 6-Month Outcome

Clinical events that occurred in the hospital, during the first month after intervention, and at 6-month follow-up are listed in Table 5. The incidence of 30-day MACE was higher in the PTFE group (10.9% versus 4.1%, $P=0.047$) and was mainly attributed to a higher incidence of MI (10.3% versus 3.4%, $P=0.037$).

Six-month clinical follow-up was obtained for all patients. Although the cumulative incidence of MACE was not different between the 2 groups (23.1% versus 15.9%, $P=0.153$), the incidence of MI was higher in the PTFE group (14.1% versus 5.5%, $P=0.022$) and was mainly accounted for by the incidence of non–Q-wave MI (12.8% versus 4.1%, $P=0.013$).

A total of 242 patients (81%) with 257 lesions (80%) underwent repeat angiography at 6-month follow-up. The primary end point, the binary restenosis rate, was similar in the 2 groups (25.0% versus 27.2% of patients, $P=0.809$, and 24.2% versus 24.8% of lesions, $P=0.237$, in the PTFE and control groups, respectively). The pattern of restenosis in lesions treated with the PTFE and SS stents, respectively, was as follows: edge (37.5% versus 6.5%, $P=0.008$), diffuse (9.4% versus 45.2%, $P=0.004$), and occlusive (53.1% versus 48.3%, $P=0.799$). Among the 14 patients in the PTFE group with occlusive restenosis, 6 patients had follow-up MACE (4 patients had non–Q-wave MI after discontinuation of ticlopidine after 3 months, and 2 patients had re-PTCA). Among the 13 patients in the SS group, only 1 had follow-up non–Q-wave MI ($P=0.077$).

Multivariate Analysis

Multivariate regression analysis identified the following predictors of the occurrence of cumulative 6-month MACE: use of PTFE stents (OR 2.19, 95% CI 1.16 to 4.13, $P=0.02$) and lesion length (OR 1.95, 95% CI 1.92 to 1.99, $P=0.02$). There were no predictors of angiographic restenosis.

Discussion

The results of this trial show similar 6-month outcomes with regard to restenosis rate, death, and need for repeat revascularization in patients with SVG disease treated with a PTFE-covered stent or an SS stent. However, 30-day MACE and the 6-month MI rate were higher in patients treated with the PTFE-covered stent.

Treatment of SVG lesions is associated with a high incidence of acute complications, principally periprocedural MI.[6–12] The risk of developing CK-MB elevation is higher during SVG than during native coronary intervention, mainly because of friable atherosclerotic or thrombotic components of the SVG lesions. Thrombus has been documented by angioscopy in up to 70% of vein graft lesions undergoing treatment.[18] Hong et al[10] reported in their study that after an otherwise successful SVG intervention, major CK-MB elevation (defined as >5 times the normal range) occurred in 15% of patients and was associated with a significantly increased 1-year cardiac mortality rate compared with a minor rise or normal postprocedural CK-MB values (11.7% versus 6.5% and 4.8%, $P<0.05$, respectively).

In an attempt to improve the outcome of intervention in stenotic vein grafts, several approaches and adjunctive pharmacological regimens have been studied, but with the exception of distal protection devices, none showed a clear benefit in reducing the incidence of distal embolization, especially in complex lesions.[8,19–23] The PTFE-covered stent was recently proposed as a new treatment option for SVG lesions, with the rationale that a covered stent would entrap friable degenerated material and decrease the risk of distal embolization.[13–16] Another important finding derived from observational studies was a reduction of angiographic restenosis after SVG treatment with PTFE-covered stents compared with historical controls.[13,14] A possible explanation for this reduction was that endoluminal sealing of the vessel wall with a membrane-covered stent prevents the exposure of underlying atheromatous tissue to circulatory macrophages, the role of which is important in initiating the restenotic process.[13]

However, the present study failed to support those preliminary data. Although the 10.9% 30-day event rate in patients treated with the PTFE-covered stent was similar to that expected from historical controls, the inferiority compared with the control group is disturbing. Our ability to discern the mechanism is unclear, but possible explanations for the lack of the reduction in restenosis and MACE rate could be edge

proliferation, which is able to extend into the stent, or small disruptions of the PTFE membrane during stent deployment. Edge restenosis, which was a predominant pattern of restenosis in the PTFE group compared with diffuse restenosis in the control group, may imply a more favorable clinical outcome with further refinement in the delivery system to limit any trauma outside the stent.

In the present study, mean balloon size and inflation pressure were higher in the PTFE group, but according to prior experience, high-pressure inflations (16 to 20 atm) are necessary to achieve full expansion of the hand-mounted PTFE stent.[13] The aggressive approach used to deploy and postdilate the PTFE stents may have contributed to the increase in the incidence of in-hospital MIs in the PTFE group. Elsner et al[13] reported that follow-up intravascular ultrasound interrogation demonstrated that neointimal proliferation occurs predominantly at the stent edges, without evidence of gross PTFE membrane disruption. However, possible microscopic alterations of the membrane structure during balloon expansion and late accumulation of the thrombotic material cannot be ruled out.[24]

A disturbing feature has been the late occurrence of non–Q-wave MI in the PTFE group. Between the first month and the sixth month, 6 patients had non–Q-wave MI in the PTFE group (4 of whom had angiographically documented total occlusions). Delayed reendothelialization of the PTFE-covered stents[25] predisposing to thrombotic occlusion can help to explain this finding.

Conclusions

Unlike previous experiences in observational studies, this trial did not demonstrate a beneficial effect of the PTFE stent for SVG treatment. In the present study, SVG interventions with PTFE-covered stents had similar procedural success and in-hospital major complication rates, as well as similar 6-month clinical outcomes compared with bare SS stents. However, a higher incidence of nonfatal MIs was found in patients treated with the PTFE-covered stent.

Appendix

List of Study Committees

Steering Committee

Antonio Colombo, MD, Centro Cuore Columbus, Milan, Italy; Luigi Inglese, MD, Ospedale Clinicizzato, San Donato, Milan, Italy; Nicholaus Reifart, MD, Kardiologisches Institut Main-Taunus, Bad Soden, Germany.

Data Safety and Monitoring Board

Simonetta Blengino, MD; Giovanni Ferrari, MD; Luigi Villa, MD; Issam Moussa, MD.

Clinical Events Committee

Sergio Repetto, MD; Carmelo Cernigliaro, MD; Corrado Vassanelli, MD; Joseph De Gregorio, MD; Issam Moussa, MD.

Core Angiographic Laboratory

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Data Coordinating Center

Mediolanum Cardiovascular Research, Milan, Italy.

Participating Centers, Principal Investigators, and Patients Enrolled

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