JACC: CARDIOVASCULAR INTERVENTIONS VOL. 2, NO. 10, 2009

ISSN 1936-8798/09/$36.00
PUBLISHED BY ELSEVIER INC. DOI: 10.1016/j.jcin.2009.07.013

Randomized Comparison of Primary Percutaneous Coronary Intervention With Combined Proximal Embolic Protection and Thrombus Aspiration Versus Primary Percutaneous Coronary Intervention Alone in ST-Segment Elevation Myocardial Infarction

The PREPARE (PRoximal Embolic Protection in Acute myocardial infarction and Resolution of ST-Elevation) Study

Joost D. E. Haeck, MD,* Karel T. Koch, MD, PhD,* Luc Bilodeau, MD,† René J. Van der Schaaf, MD,* José P. S. Henriques, MD, PhD,* Marije M. Vis, MD,* Jan Baan, Jr, MD, PhD,* Allard C. Van der Wal, MD, PhD,‡ Jan J. Piek, MD, PhD,* Jan G. P. Tijssen, PhD,* Mitchell W. Krucoff, MD,§ Robbert J. De Winter MD, PhD*

Amsterdam, the Netherlands; Montréal, Québec, Canada; and Durham, North Carolina

Objectives The purpose of this study was to evaluate the effectiveness of combined proximal embolic protection with thrombus aspiration (Proxis Embolic Protection System [St. Jude Medical, St. Paul, Minnesota]) in ST-segment elevation myocardial infarction patients.

Background Embolization during primary percutaneous coronary intervention (PCI) may result in microvascular obstruction, reduced myocardial perfusion, and impaired prognosis.

Methods Two hundred eight-four patients were randomized to primary PCI with the Proxis system versus primary PCI alone after angiography. The primary end point was the occurrence of complete (≥70%) ST-segment resolution (STR) at 60 min measured by continuous ST-segment Holter.

Results There was no significant difference in the occurrence of the primary end point (80% vs. 72%, p = 0.14). However, immediate complete STR (at time of last contrast) occurred in 66% of Proxis-treated patients and 50% in control patients (absolute difference, 16.3%; 95% confidence interval: 4.3% to 28.2%; p = 0.009). A significant lower ST-segment curve area (0 to 3 h after primary PCI) was observed in the Proxis arm (5,192 μV/min vs. 6,250 μV/min, p = 0.037). Major adverse cardiac and cerebral events at 30 days occurred with similar frequency in both groups (6 vs. 10).

Conclusions There was no significant difference in complete STR at 60 min in this proof-of-concept study. However, we observed a significant difference in immediate complete STR in Proxis-treated patients, better STR at later time points, and a reduction of electrocardiogram injury current over time, compared with control patients. The results suggest that primary PCI with the Proxis system may lead to better immediate microvascular flow in ST-segment elevation myocardial infarction patients. (The PREPARE Study; ISRCTN71104460) (J Am Coll Cardiol Intv 2009;2:934–43) © 2009 by the American College of Cardiology Foundation

From the *Department of Cardiology and the ‡Department of Pathology, Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands; †Department of Cardiology, Institut de Cardiology de Montréal, Montréal, Quebec, Canada; and the §Duke Clinical Research Institute, Duke University Medical Center, Durham, North Carolina. This study is supported by grants from St. Jude Medical and from the University of Amsterdam.

Manuscript received June 29, 2009; accepted July 9, 2009.

Primary percutaneous coronary intervention (PCI) has been shown to be the superior treatment for ST-segment elevation myocardial infarction (STEMI) and effectively restores perfusion of the infarct-related artery (1). Despite its value, primary PCI using balloons and stents alone may dislodge atherothrombotic material adherent to the ruptured plaque, causing microvascular obstruction and limiting myocardial salvage. Embolization of atherothrombotic material during primary PCI is considered an important determinant of microvascular obstruction and is associated with impaired ST-segment resolution, increased infarct size, reduced recovery of ventricular function, and a 5-fold increase in 5-year mortality (2–6). Most randomized trials of thrombus aspiration catheters and distal embolic protection devices did not show a treatment benefit, thereby not supporting the use of any embolic protection device or thrombus aspiration catheter in the setting of STEMI (7–15). Recently, the TAPAS (Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study) showed that thrombus aspiration before stenting of the infarct-related artery resulted in improved myocardial blush grade (MBG) and clinical outcome 1-year after primary PCI (16,17).

The Proxis device (St. Jude Medical, St. Paul, Minnesota) (Fig. 1) is a novel system of combined proximal embolic protection and thrombus aspiration. In a registry of 172 patients, we showed that the Proxis system was feasible and safe in the setting of primary PCI in patients with STEMI. The results demonstrated good angiographic outcomes, excellent ST-segment resolution, and low 1-year mortality (18). On the basis of these findings, the randomized, controlled PREPARE (Proximal Embolic Protection in Acute Myocardial Infarction and Resolution of ST-Elevation) trial was designed to evaluate the effectiveness of combined proximal embolic protection with thrombus aspiration during mechanical reperfusion therapy in STEMI.

Methods

Patient selection and treatment. The PREPARE trial is an investigator-initiated, randomized, open trial with blinded evaluation of end points, in which 2 hospitals with 24/7 coronary intervention facilities in the Netherlands (Academic Medical Center, University of Amsterdam, Amsterdam, the Netherlands) and in Canada (Institut de Cardiologie de Montréal, Montréal, Canada) participated. The institutional review board of both hospitals approved the study. Written informed consent was obtained from all patients.

Patients were eligible for the trial if they had symptoms of myocardial infarction <6 h after onset, electrocardiographic evidence of persistent ST-segment elevation of at least 200 μV in 2 or more contiguous leads. Exclusion criteria were individuals younger than 18 years of age, contraindications to the use of glycoprotein IIb/IIIa receptor antagonists, coexistent condition associated with a limited life expectancy, prior coronary artery bypass grafting or lytics, recurrence of myocardial infarction in the same myocardial area, an electrocardiogram (ECG) unsuitable for ST-segment resolution evaluation (left bundle branch block, ventricular pacemaker, and atrial fibrillation). Patients were included after the first angiogram provided Thrombolysis In Myocardial Infarction (TIMI) flow grade 0 to 1 and a coronary anatomy suitable for treatment with the Proxis system. Patients were not included if any of the following applied: left main occlusion, left main stenosis of more than 30%, heavy proximal calcifications, a small infarct-related artery (<2.5 mm in diameter), and a proximal location of the lesion leading to an insufficient "landing zone" for the Proxis system (generally <10 to 12 mm). Informed consent was obtained after suitability of coronary anatomy of the patient for the treatment with the Proxis system had been established. Patients who consented were subsequently randomized 1:1 to a strategy of primary PCI with combined embolic protection and thrombus aspiration or to primary PCI alone.

Abbreviations and Acronyms

CI = confidence interval
CK-MB = creatine phosphokinase myocardial band isoenzyme
MACCE = major adverse cardiac and cerebral events
MBG = myocardial blush grade
PCI = percutaneous coronary intervention
STEMI = ST-segment elevation myocardial infarction

The Proxis system was used in patients randomized to primary PCI with combined embolic protection and thrombus aspiration. The Proxis system is a single-operator full-length flexible catheter (6- or 7-F guiding catheter compatible) and based on a carbon dioxide gas (CO_2) inflation system. It was deployed proximal to the target lesion before crossing. Inflation of the sealing balloon suspends antegrade flow during the period of lesion intervention. Stagnated blood and emboli liberated after each lesion intervention were retrieved by gentle aspiration. Crossing of the coronary occlusion with the wire, balloon dilation, and stent placement was performed through the Proxis system and carried out under full proximal blockade of the vessel. Aspiration and embolic protection by temporary proximal vessel occlusion were repeated during each step of the PCI procedure (18).

Primary PCI was performed in a standard manner with approved wires, balloons, and stents in patients randomized to primary PCI alone. All patients received 300 mg of aspirin, clopidogrel (600 mg followed by 75 mg/24 h), unfractionated heparin (70 U/kg) before PCI. Use of glycoprotein IIb/IIIa receptor antagonists was left to operator discretion. After the procedure, patients were transferred to the coronary care unit. Standard therapies after PCI included aspirin (at least 80 mg daily), clopidogrel (75

JACC: CARDIOVASCULAR INTERVENTIONS, VOL. 2, NO. 10, 2009
OCTOBER 2009:934–43

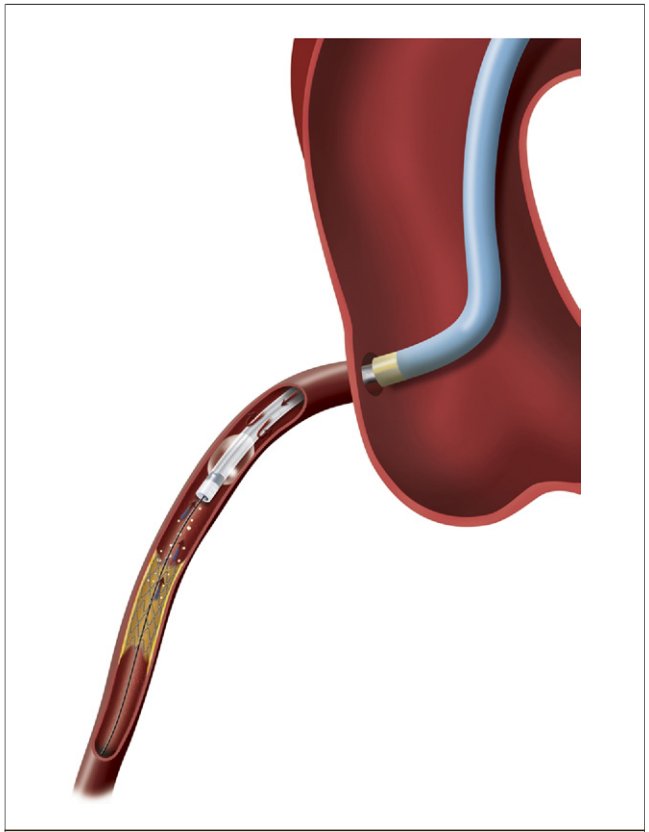


Figure 1. The Proxis Embolic Protection System

The Proxis Embolic Protection System in a native coronary artery.

mg daily), beta-blockers, lipid-lowering agents, and angiotensin-converting enzyme inhibitors or angiotensin II receptor blockers, according to European Society of Cardiology guidelines (19). Stabilized patients from referring hospitals were transferred back after a minimum of 6 h.

Data collection. Continuous digital 12-lead ECG/Holter monitoring (Northeast Monitoring 180+, Natick, Massachusetts) for ST-segment analysis was started on arrival at the catheterization laboratory before PCI. Continuous ECG monitoring was continued a minimum of 6 h after PCI. Continuously updated ST-segment resolution analysis was performed by a central core laboratory (eECG Core Laboratory, Duke Clinical Research Institute/Duke University Medical Center, Durham, North Carolina) using previously published methodology (20,21). In brief, ST-segment levels were measured 60 ms after the J-point in the most abnormal lead. ST-segment recovery was determined over serial time points by comparing ECGs recorded at each specified time interval with the most abnormal "peak" ECG in the data recorded between study enrollment and arrival in the catheterization laboratory. The 12-lead summated ST-segment deviation versus time trend curves were used to calculate ST-segment injury curve areas. Changes during the interventional procedure were excluded from analysis. All ST-segment recovery end points were read blinded to any treatment assignment or clinical information.

After the PCI procedure, a coronary angiogram was obtained, and TIMI-graded coronary flow, MBG, and angiographic signs of distal embolization were estimated as previously described (5,22,23). Two experienced investigators (K.T.K., R.J.dW.), blinded to all other data, assessed all angiograms. In case of any discrepancies, a third experienced investigator (J.P.S.H.) determined the angiographic parameters. Cardiac creatine phosphokinase-myocardial band isoenzyme (CK-MB) levels were measured at admission, and after 5, 7, 10, 12, 18, and 24 h. Retrieved debris before and after target lesion intervention was collected in separate filters. Aspirated material was assessed by inspection and histopathologic analysis of the filter content. A pathologist (A.C.VdW.), blinded to the angiographic findings and the result of PCI, performed the histopathologic analyses. Information about clinical events was obtained from hospital records and from telephone interviews with the study participants at 30 days.

End point definitions. The primary end point of the study was the occurrence of complete (≥70%) resolution of ST-segment elevation 60 min after last contrast injection. Complete ST-segment resolution (dichotomous) was defined as a reduction of at least 70% of the ST-segment deviation of the most deviated lead relative to the peak ST-segment deviation before PCI. Secondary ECG end points were the occurrence of complete (≥70%) resolution of ST-segment elevation immediately after PCI (at the time of last contrast injection) and at 30, 90, and 120 min after last contrast injection; percentage of ST-segment elevation resolution (continuous) immediately after PCI and at 30, 60, 90, and 120 min after last contrast injection; and ST-segment curve area. Percentage of ST-segment elevation resolution was defined as the percentage change between the most abnormal lead in the most abnormal ECG in the recording session before the PCI (the "peak" ECG) and the ST-segment level in that same lead at each of the designated time points (immediate end PCI, 30, 60, 90, and 120 min after last contrast injection). ST-segment curve area was defined as the area under the summated 12-lead absolute ST-segment deviation versus time trend curve from the last contrast injection to 3 h after PCI, reported as μV/min. Angiographic end points were TIMI-graded coronary flow, MBG, and the presence of angiographic signs of distal embolization (5,22). The enzymatic end point was infarct size measured by a biochemical biomarker of myocardial necrosis (CK-MB). Clinical end points were overall major adverse cardiac and cerebral events (MACCE). Overall MACCE included death, spontaneous or procedural myocardial infarction, stroke, and percutaneous or surgical target vessel revascularization. All deaths were cardiovascular unless an unequivocal noncardiac cause could be identified. The myocardial infarctions and target vessel revascularize-

tions were classified according to standardized definitions of the Academic Research Consortium (24). Stroke was defined as a new focal neurologic deficit of vascular origin lasting more than 24 h. Stroke was further classified as the result of intracranial hemorrhage, ischemia (if a computed tomography or MRI scan was available), or uncertain cause. All suspected clinical events were adjudicated by a blinded critical events adjudication committee.

Statistical analyses. The main clinical analysis consists of a single comparison between the treatment groups of the percentage of patients with more than 70% resolution of the ST-segment elevation at the time of last contrast injection. We designed our study to have a power of beta = 80% to detect an improvement in percentage of patients with complete (>70%) ST-segment resolution by 15% with a level of significance of alpha <0.05. These assumptions yielded a sample size of 140 patients in each treatment arm.

All data were analyzed on an intention-to-treat basis. Discrete variables are reported as counts and continuous variables, mean ± SD, or median and interquartile range. Chi-square and Fisher exact probability test were used to test equality of the event rates. The 95% confidence interval (CI) for the rate difference is calculated via the exact method. Data are expressed as mean ± SD or as medians, whenever appropriate. Student *t* test or Mann-Whitney *U* test were used accordingly. For all statistical analyses, we used the SPSS software package, version 16.0 (SPSS Inc., Chicago, Illinois). A value of $p < 0.05$ in the 2-tailed test was regarded as significant. Because the study was not powered for clinical outcomes, the event rates are presented for descriptive purposes only, and no statistical comparisons were done.

Results

Patients and treatment. Between March 1, 2006, and June 27, 2008, 284 STEMI patients, at 2 centers in the Netherlands and Canada, were randomized to receive either primary PCI with combined proximal embolic protection and thrombus aspiration (n = 141) or primary PCI alone (n = 143). Randomization flow is shown in Figure 2. Baseline demographic and angiographic characteristics were well matched between the 2 randomized cohorts, except for a higher incidence of current smoking in the control group and an older population in the Proxis-treated group (Table 1). Almost all patients had a complete occlusion of the infarct-related artery at the first angiogram: there was a TIMI flow grade of 0 to 1 in 274 of the 281 patients (98%).

Procedural results. The procedural results are summarized in Table 2. The Proxis system was adequately positioned in 132 of 141 patients (94%). As shown in Table 2, combined proximal embolic protection and thrombus aspiration resulted in a 3-min delay in arterial puncture to first balloon inflation compared with the control group. Direct stenting

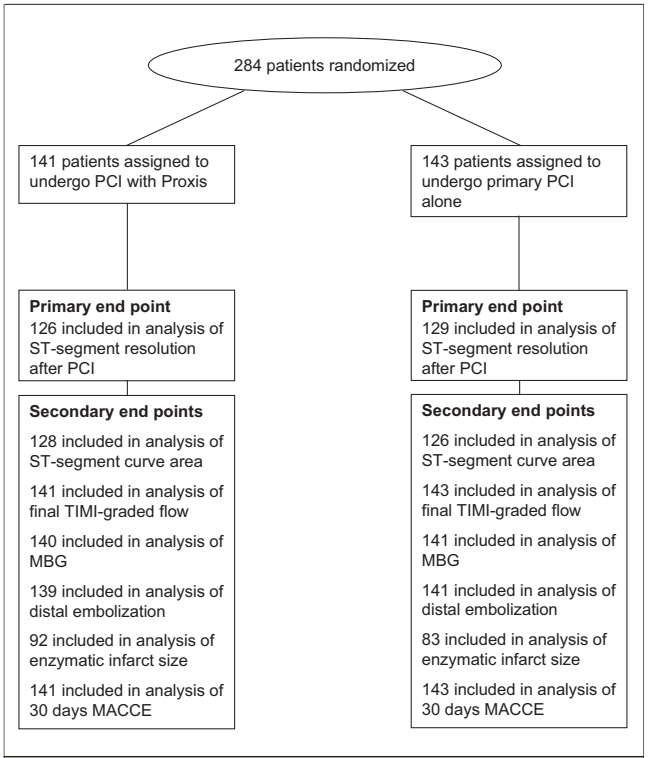


Figure 2. Randomization Flow

MACCE = major adverse cardiac or cerebral events; MBG = myocardial blush grade; PCI = percutaneous coronary intervention; TIMI = Thrombolysis In Myocardial Infarction.

was performed in a minority of patients (15%). No emergency coronary artery bypass graft surgery was required, and there were no intraprocedural deaths or strokes. Furthermore, no dissection or vessel trauma at the site where the Proxis system had been inflated was observed.

ST-segment recovery. Complete ST-segment resolution at 60 min after last contrast injection occurred in 101 of the 126 patients (80%) in the Proxis arm and in 72% (93 of 129) of patients in the control group (absolute difference, 8.1%, 95% CI: −2.4% to 18.6%; p = 0.14). Complete ST-segment resolution at the end of PCI occurred in 85 of 129 patients (66%) receiving combined proximal embolic protection and thrombus aspiration and in 67 of 135 patients (50%) in the control group (absolute difference, 16.3%; 95% CI: 4.3% to 28.2%; p = 0.009), with a median percent ST-segment resolution of 79% versus 69% respectively (p = 0.015) as shown in Table 3 and no evidence of heterogeneity. The difference between the 2 groups evanesced over time, as shown in Figure 3; however, the overall ST-segment curve area (0 to 3 h after primary PCI) was still significantly lower in the Proxis arm versus the control arm (5,192 μV/min vs. 6,250 μV/min, p = 0.037) (Table 3). Faster and more complete ST-segment resolution with the Proxis system was observed in a host of subgroups evaluated, including subgroups according to infarct-related artery and

Table 1. Baseline Characteristics of the Patients

	PCI With Proxis (n = 141)	Primary PCI Alone (n = 143)	p Value
Age, yrs	62 ± 11	59 ± 11	0.03
Male sex	112 (80%)	114 (80%)	0.95
History of			
Diabetes mellitus*	17 (12%)	9 (6%)	0.09
Hypertension†	44 (31%)	33 (23%)	0.12
Hypercholesterolemia†	29 (21%)	19 (13%)	0.10
Myocardial infarction	8 (6%)	13 (9%)	0.27
PCI	9 (6%)	10 (7%)	0.84
Cerebrovascular disease	8 (6%)	6 (4%)	0.57
Cardiovascular disease in family	49 (35%)	54 (38%)	0.60
Smoking	21 (15%)	18 (13%)	0.56
Current smoking	70 (50%)	93 (65%)	0.01
Pre-infarction angina	10 (7%)	7 (5%)	0.44
SBP, mm Hg	135 ± 29	129 ± 26	0.08
DBP, mm Hg	77 ± 17	77 ± 16	0.93
Heart rate, beats/min	72 ± 18	75 ± 20	0.32
Maximal ST-segment deviation, μV	468 (306–781)	572 (337–703)	0.52
Number of diseased vessels			0.68
1	95 (67%)	99 (69%)	
2	40 (28%)	31 (22%)	
3	6 (4%)	13 (9%)	
Infarct-related vessel			0.86
Left anterior descending artery	41 (29%)	42 (29%)	
Left circumflex artery	14 (10%)	15 (11%)	
Right coronary artery	86 (61%)	86 (60%)	
Baseline TIMI flow grade			0.52
0	127 (90%)	127 (89%)	
1	12 (9%)	11 (8%)	
2	2 (1%)	5 (4%)	
Visible thrombus	107 (76%)	95 (66%)	0.08
Lesion type			0.29
B1	21 (15%)	22 (15%)	
B2	88 (62%)	99 (69%)	
C	32 (23%)	22 (15%)	

Data are expressed as mean ± SD, n (%), or median (interquartile range). Data for maximal ST-segment deviation were available for 131 subjects in the percutaneous coronary intervention (PCI) with Proxis group and 136 subjects in the primary PCI alone group. *Diabetes was defined as that diagnosed before admission and managed with diet, oral hypoglycemic agents, or insulin; †hypertension and hypercholesterolemia were defined as that requiring prescription medication. Lesion type was classified according to the Lesion Complexity Classification of the American College of Cardiology and the American Heart Association.

DBP = diastolic blood pressure; SBP = systolic blood pressure; TIMI = Thrombolysis In Myocardial Infarction.

the use of glycoprotein IIb/IIIa receptor antagonists. The absolute differences varied between 9.8% and 28.6% (Table 4).

Angiographic, enzymatic, histopathologic, and 30-day clinical outcomes. Combined proximal embolic protection and thrombus aspiration tended to improve post-procedural TIMI flow grade ($p = 0.06$). No statistical difference in MBG was observed. The rates of angiographically documented signs of distal embolization were slightly less frequent and infarct size measured by peak of CK-MB was smaller in the Proxis-treated patients. But none of these differences reached statistically significance (Table 5).

Debris was confirmed on pathology in 84 of the 112 patients (75%). In 73 of the 84 patients (87%), debris was extracted before dilation or stent placement. In 29 of the 84 patients (35%), debris was aspired before and after target lesion intervention and in 11 of the 84 patients (13%) only after target lesion intervention. Histopathologic analysis of the filter content showed in 42 of the 84 patients (50%) only thrombus, in 41 of the 84 patients (49%) thrombus and plaque components, and in only 1 patient (1%) only plaque components. No difference in the composite of debris before and after target lesion intervention was observed.

Table 2. Procedural Results

	PCI With Proxis (n = 141)	Primary PCI Alone (n = 143)	p Value
Procedural success	141 (100%)	141 (99%)	
Direct stenting	15 (11%)	27 (19%)	0.05
Balloon angioplasty	4 (3%)	8 (6%)	0.25
Proxis placed	132 (94%)	—	
Length of stented segment, mm	25 ± 10	24 ± 10	0.08
Diameter of stented segment, mm	3.5 ± 0.4	3.5 ± 0.4	0.21
Additional thrombus aspiration	8 (6%)	8 (6%)	0.97
Left ventricular support	6 (4%)	5 (4%)	0.74
GP IIb/IIIa receptor antagonists	61 (43%)	50 (35%)	0.15
Symptom onset to balloon, min	170 (132–234)	153 (126–212)	0.07
Arterial puncture to balloon, min	17 (13–23)	14 (10–18)	<0.01
Total procedure time, min	45 (36–58)	31 (25–40)	<0.01
Cath lab call to arterial puncture, min	46 (37–56)	45 (35–53)	0.37

Data are expressed as n (%), mean ± SD, or median (interquartile range). Data for catheterization laboratory call to arterial puncture were available for 133 subjects in the percutaneous coronary intervention (PCI) with Proxis group and 139 subjects in the primary PCI alone group.
GP = glycoprotein.

As shown in Table 6, overall MACCE occurred with similar frequency with or without combined proximal embolic protection and thrombus aspiration (4% vs. 7%). Two patients died in each treatment group of progressive heart failure. None of the repeat angiograms showed evidence of a (re)stenotic lesion or complication at the site where the Proxis system had been inflated.

Discussion

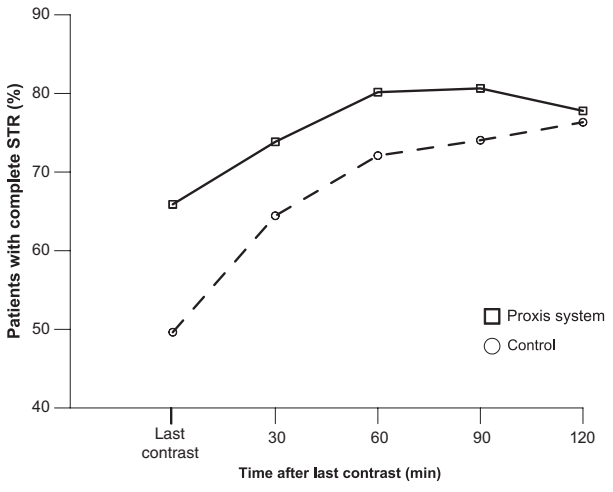
The PREPARE trial is the first proof-of-concept trial to test the effectiveness of primary PCI with combined proximal embolic protection and thrombus aspiration compared with primary PCI.

The difference in the pre-specified primary end point, 80% versus 72% of patients with complete (≥70%) ST-segment resolution at 60 min, did not reach statistical significance. Yet, the intention-to-treat analysis showed a significantly higher immediate ST-segment resolution in favor of Proxis-treated patients and a significant reduction of overall injury current over time. While ST-segment recovery parameters are ultimately surrogate electrocardiographic biomarkers, they reflect intensity and duration of myocardial ischemia and have consistently been associated with infarct size, ejection fraction, and mortality in patients with myocardial infarction (2–4,25). Although the primary end point of ≥70% ST-segment resolution at 60 min and important secondary end points, such as MBG, were not statistically significant different between the 2 groups, there was a measurable effect very early with reperfusion that then equilibrated across groups over time. Mechanistically, this very early measurable difference in ST-segment recovery is conceptually consistent with prevention of distal embolization. Although the difference in ST-segment resolution with the Proxis system was transient, improved microcirculatory reperfusion within the first hour after restoration of

Table 3. Continuous ST-Segment Recovery Parameters

	PCI With Proxis (n = 141)	Primary PCI Alone (n = 143)	p Value
ST-segment resolution, %			
Immediate	79 (63–98)	69 (43–92)	0.015
At 30 min	83 (70–97)	78 (63–93)	0.13
At 60 min	88 (72–100)	84 (67–97)	0.15
At 90 min	87 (75–99)	85 (67–98)	0.45
At 120 min	86 (72–99)	87 (73–97)	0.74
ST-segment curve area,* μV/min	5,192 (3,793–7,626)	6,250 (4,221–9,186)	0.037

Data are expressed as median (interquartile range). Data for immediate ST-segment resolution were available for 129 subjects in the PCI with Proxis group and 135 subjects in the primary percutaneous coronary intervention (PCI) alone group; for at 30 min, 130 and 135 subjects, respectively; for at 60 min, 126 and 129 subjects; for at 90 min, 124 and 131 subjects; for at 120 min, 126 and 131 subjects; and for ST-segment curve area, 128 and 126 subjects. *Area under the ST-segment deviation versus time trend curve is from the last contrast injection to 3 h after the procedure.



Proxis system					
Complete STR, *n*	85	96	101	100	98
Total, *n*	129	130	126	124	126
Control					
Complete STR, *n*	67	87	93	97	100
Total, *n*	135	135	129	131	131
***P*-value**	**0.009**	0.11	0.14	0.23	0.88

Figure 3. Rates of Complete (>70%) ST-Segment Resolution at Different Time Periods After Primary PCI With Proxis System or Alone

PCI = percutaneous coronary intervention; STR = ST-segment resolution.

epicardial flow may translate into a clinically relevant reduction in infarct size and clinical outcomes, although the current study was underpowered to answer this question definitively.

Multiple explanations may be proposed as to why combined proximal embolic protection and thrombus aspiration leads to enhance myocardial reperfusion as observed by early ST-segment recovery. In contrast to distal protection devices and manual thrombus aspiration devices, the Proxis system provides embolic protection before wire crossing of the thrombotic coronary occlusion. Inflation of the sealing balloon suspends antegrade flow in the infarct-related artery during every manipulation and engagement of the thrombotic occlusive lesion with wires, balloons, and also later with stents. Hence, the Proxis system prevents both embolization during lesion crossing and protects the distal side branches of the infarct-related artery. In the PREPARE trial, debris was extracted in 48% of patients at the time of target lesion stent placement, which likely provides additional protection against distal embolization. In addition to embolic protection and thrombus aspiration, the intracoronary evacuation of biologically active inflammatory mediators produced at the site of the plaque could contribute to improvement of microcirculatory flow (26). Pathophysiological mechanisms that involve thrombus composition (i.e., platelets, inflammatory cells, and plaque components), myocardial perfusion, and microvascular obstruction are still

Table 4. Subgroup Analyses for the Complete ST-Segment Resolution at Time of Last Contrast Injection

	Rate of Complete ST-Segment Resolution			
	PCI With Proxis (n = 129)	Primary PCI Alone (n = 135)	Absolute Difference (95% CI)	p Value
All patients	85/129 (66%)	67/135 (50%)	16.3 (4.3 to 28.2)	0.009
Infarct-related artery				
Anterior	16/38 (42%)	7/40 (18%)	24.6 (4.2 to 45.0)	0.03
Nonanterior	69/91 (76%)	60/95 (63%)	12.7 (−0.6 to 26.0)	0.08
Lesion				
Proximal	29/42 (69%)	19/47 (40%)	28.6 (7.8 to 49.5)	0.01
Nonproximal	56/87 (64%)	48/88 (55%)	9.8 (−4.8 to 24.4)	0.22
Baseline thrombus				
Yes	64/98 (65%)	46/92 (50%)	15.3 (1.2 to 29.4)	0.04
No	21/31 (68%)	21/43 (49%)	18.9 (−4.1 to 41.9)	0.15
Symptom onset to balloon, h				
<3	47/69 (68%)	43/87 (49%)	18.7 (3.0 to 34.4)	0.02
≥3	38/60 (63%)	24/48 (50%)	13.3 (−5.5 to 32.2)	0.18
Use of GP IIb/IIIa antagonists				
Yes	29/52 (56%)	13/46 (28%)	27.5 (7.8 to 47.2)	0.008
No	56/77 (73%)	54/89 (61%)	12.1 (−2.4 to 26.5)	0.14
Current smoking				
Yes	47/63 (75%)	47/89 (53%)	21.8 (6.1 to 37.5)	0.007
No	38/66 (58%)	20/46 (44%)	14.8 (−4.8 to 33.0)	0.18

Data are expressed as n (%).

CI = confidence interval; other abbreviations as in Table 2.

Table 5. Angiographic Outcomes and Infarct Size

	PCI With Proxis (n = 141)	Primary PCI Alone (n = 143)	p Value
TIMI flow grade			0.06
0–1	0 (0%)	3 (2%)	
2	10 (7%)	15 (11%)	
3	131 (93%)	125 (87%)	
Myocardial blush grade			0.93
0–1	5 (4%)	9 (6%)	
2	22 (16%)	15 (11%)	
3	113 (81%)	117 (83%)	
Angiographic signs of distal embolization	14 (10%)	20 (14%)	0.36
Infarct size by peak CK-MB, μg/l*	204 (136–378)	246 (154–413)	0.22

Data are expressed as n (%) or median (interquartile range). Data for myocardial blush grade were available for 140 subjects in the PCI with Proxis group and 141 subjects in the PCI alone group; for angiographic signs of distal embolization, 139 and 141 subjects, respectively; and for infarct size by peak creatine kinase-myocardial band (CK-MB), 92 and 83 subjects. *The CK-MB upper limit of normal is 6.5 μg/l for Academic Medical Center Amsterdam and 5.0 μg/l for Institut de Cardiologie de Montréal, respectively.

Abbreviations as in Table 1.

unknown and need further investigation (27). Another interesting although unproven explanation for our results may be ischemic post-conditioning (28). The sequential and repetitive inflations of the sealing balloon of the Proxis system may have prevented reperfusion injury by inducing repetitive transient episodes of ischemia at the time of myocardial reperfusion.

The success of this randomized multicenter study was enhanced by the fact that technical success rates with the Proxis system in primary PCI were high. In 94% of the cases, combined proximal embolic protection and thrombus aspiration were performed. Atheromatous and/or thrombotic debris was retrieved in 75% of patients, similar to the 77% rate of histologically confirmed material demonstrated in our registry. The use of the Proxis system resulted in only a 3-min delay in arterial puncture to first balloon inflation time.

Our findings support the beneficial effect of the Proxis system. In addition, the favorable outcome in immediate ST-segment resolution occurred despite a lower frequency of direct stenting with the Proxis system, which is associated with reduction of microvascular injury (29). Notably, the percentage of patients with complete ST-segment resolution in the control arm of our study was comparable at all time points to that in the treatment and control arms of the EMERALD (Enhanced Myocardial Efficacy and Recovery by Aspiration of Liberated Debris) trial (15). In that study, ST-segment resolution over time was superimposable for the control and distal protection arms.

The PROXIMAL (Proximal Protection During Saphenous Vein Graft Intervention) trial recently demonstrated equivalent effectiveness of the Proxis system compared with distal embolic protection in PCI of saphenous vein grafts (30). The PREPARE trial identifies another application of combined proximal embolic protection and thrombus aspiration. Our study was designed to include a selection of STEMI patients (i.e., TIMI flow grade 0 to 1, ≥200 μV ST-segment elevation). Since the Proxis system demonstrated the ability to aspirate atherothrombotic material after target lesion intervention, other subset of patients, in particular myocardial infarction patients with "spontaneously reperfused arteries," may also benefit from combined proximal embolic protection and thrombus aspiration, which were not included in our trial. Larger prospective randomized trials with relevant clinical end points are needed to demonstrate an effect of proximal protection with the Proxis system on patient outcome in primary PCI.

Study limitations. First, the PREPARE trial was underpowered to detect differences in clinical events. The study measured surrogate end points, which may provide insight into a mechanistic impact that may translate into clinical

Table 6. Clinical End Points 30 Days

	PCI With Proxis (n = 141)	Primary PCI Alone (n = 143)
Death	2	2
Spontaneous myocardial infarction	1	2
Procedural myocardial infarction*	1	1
Urgent percutaneous TLR	2	3
Urgent percutaneous TVR	2	4
Surgical TVR	1	2
Acute stent closure	2	2
Stroke	0	1
Overall MACCE	6	10
Percutaneous non-TVR	9	8
Surgical non-TVR	0	0

Data are expressed as number of patients. *Myocardial infarction related to additional percutaneous coronary intervention (PCI).

MACCE = major adverse cardiac or cerebral events; TLR = target lesion revascularization; TVR = target vessel revascularization.

benefit. Second, our study was conducted in 2 high-volume centers with experienced operators, proficient with the Proxis system. Therefore, the results may not be extrapolated to settings with less experienced operators and/or to low-volume centers. Third, the results of our study may not be applicable to other patient and lesion subtypes. Mainly due to the necessity of a "landing zone" for the Proxis system (>10 to 12 mm), patients with a myocardial infarction related to an ostial left anterior descending coronary artery were excluded. The slight preponderance of myocardial infarctions related to the right coronary artery in our trial may be due to this necessity for a "landing zone." Finally, because most patients were referred from other non-PCI hospitals and were transferred back after a relatively short observation time, CK-MB values were complete in only 62% of the patients.

Conclusions

There was no significant difference in complete (>70%) ST-segment resolution at 60 min in this proof-of-concept study. However, we observed a significant difference in immediate complete ST-segment resolution in Proxis-treated patients, better ST-resolution at later time points, and a reduction of ECG injury current over time, compared with control patients. The results of the PREPARE trial suggest that primary PCI with combined proximal embolic protection and thrombus aspiration may lead to better immediate microvascular flow in STEMI patients.

Acknowledgments

The authors gratefully acknowledge the technical and nursing staff of the Cardiac Catheterization Laboratories and Coronary Care Units of the 2 centers (Heads Martin G. H. Meesterman, Danielle Larocque, and Ronald Schmeddes); Wim J. Rohling, Dr. Krischan D. Sjauw, Nathalie Hardy, and Maguy Shabani for the data management; and Dr. Cindy Green, Senior Statistician to the Duke eECG Core Laboratory.

Reprint requests and correspondence: Dr. Karel T. Koch, Department of Cardiology, Cardiac Catheterization Laboratory B2-125, Academic Medical Center, University of Amsterdam, Meibergdreef 9, 1105 AZ Amsterdam, the Netherlands. E-mail: k.t.koch@amc.uva.nl.

REFERENCES

1. Keeley EC, Boura JA, Grines CL. Primary angioplasty versus intravenous thrombolytic therapy for acute myocardial infarction: a quantitative review of 23 randomised trials. Lancet 2003;361:13–20.
2. McLaughlin MG, Stone GW, Aymong E, et al. Prognostic utility of comparative methods for assessment of ST-segment resolution after primary angioplasty for acute myocardial infarction: the Controlled Abciximab and Device Investigation to Lower Late Angioplasty Complications (CADILLAC) trial. J Am Coll Cardiol 2004;44:1215–23.
3. Poli A, Fetiveau R, Vandoni P, et al. Integrated analysis of myocardial blush and ST-segment elevation recovery after successful primary angioplasty: Real-time grading of microvascular reperfusion and prediction of early and late recovery of left ventricular function. Circulation 2002;106:313–8.
4. van't Hof AW, Liem A, de Boer MJ, Zijlstra F. Clinical value of 12-lead electrocardiogram after successful reperfusion therapy for acute myocardial infarction. Zwolle Myocardial Infarction Study Group. Lancet 1997;350:615–9.
5. Henriques JP, Zijlstra F, Ottervanger JP, et al. Incidence and clinical significance of distal embolization during primary angioplasty for acute myocardial infarction. Eur Heart J 2002;23:1112–7.
6. Kotani J, Nanto S, Mintz GS, et al. Plaque gruel of atheromatous coronary lesion may contribute to the no-reflow phenomenon in patients with acute coronary syndrome. Circulation 2002;106:1672–7.
7. Ali A, Cox D, Dib N, et al. Rheolytic thrombectomy with percutaneous coronary intervention for infarct size reduction in acute myocardial infarction: 30-day results from a multicenter randomized study. J Am Coll Cardiol 2006;48:244–52.
8. Beran G, Lang I, Schreiber W, et al. Intracoronary thrombectomy with the X-sizer catheter system improves epicardial flow and accelerates ST-segment resolution in patients with acute coronary syndrome: a prospective, randomized, controlled study. Circulation 2002;105:2355–60.
9. Cura FA, Escudero AG, Berrocal D, et al. Protection of distal embolization in high-risk patients with acute ST-segment elevation myocardial infarction (PREMIAR). Am J Cardiol 2007;99:357–63.
10. Gick M, Jander N, Bestehorn HP, et al. Randomized evaluation of the effects of filter-based distal protection on myocardial perfusion and infarct size after primary percutaneous catheter intervention in myocardial infarction with and without ST-segment elevation. Circulation 2005;112:1462–9.
11. Kaltoft A, Bottcher M, Nielsen SS, et al. Routine thrombectomy in percutaneous coronary intervention for acute ST-segment-elevation myocardial infarction: a randomized, controlled trial. Circulation 2006; 114:40–7.
12. Kelbaek H, Terkelsen CJ, Helqvist S, et al. Randomized comparison of distal protection versus conventional treatment in primary percutaneous coronary intervention: the drug elution and distal protection in ST-elevation myocardial infarction (DEDICATION) trial. J Am Coll Cardiol 2008;51:899–905.
13. Lefevre T, Garcia E, Reimers B, et al. X-sizer for thrombectomy in acute myocardial infarction improves ST-segment resolution: results of the X-sizer in AMI for negligible embolization and optimal ST resolution (X AMINE ST) trial. J Am Coll Cardiol 2005;46:246–52.
14. Silva-Orrego P, Colombo P, Bigi R, et al. Thrombus aspiration before primary angioplasty improves myocardial reperfusion in acute myocardial infarction: the DEAR-MI (Dethrombosis to Enhance Acute Reperfusion in Myocardial Infarction) study. J Am Coll Cardiol 2006;48:1552–9.
15. Stone GW, Webb J, Cox DA, et al. Distal microcirculatory protection during percutaneous coronary intervention in acute ST-segment elevation myocardial infarction: a randomized controlled trial. JAMA 2005;293:1063–72.
16. Svilaas T, Vlaar PJ, van der Horst, I, et al. Thrombus aspiration during primary percutaneous coronary intervention. N Engl J Med 2008;358: 557–67.
17. Vlaar PJ, Svilaas T, van der Horst I, et al. Cardiac death and reinfarction after 1 year in the Thrombus Aspiration during Percutaneous coronary intervention in Acute myocardial infarction Study (TAPAS): a 1-year follow-up study. Lancet 2008;371:1915–20.
18. Koch KT, Haeck JD, Van Der Schaaf RJ, et al. Proximal embolic protection with aspiration in percutaneous corononary intervention using the proxistrade mark device. Rev Cardiovasc Med 2007;8:160–6.
19. Van de Werf F, Ardissino D, Betriu A, et al. Management of acute myocardial infarction in patients presenting with ST-segment elevation. The Task Force on the Management of Acute Myocardial Infarction of the European Society of Cardiology. Eur Heart J 2003;24:28–66.
20. Krucoff MW, Croll MA, Pope JE, et al. Continuously updated 12-lead ST-segment recovery analysis for myocardial infarct artery patency

assessment and its correlation with multiple simultaneous early angiographic observations. Am J Cardiol 1993;71:145–51.
21. Roe MT, Green CL, Giugliano RP, et al. Improved speed and stability of ST-segment recovery with reduced-dose tenecteplase and eptifibatide compared with full-dose tenecteplase for acute ST-segment elevation myocardial infarction. J Am Coll Cardiol 2004;43:549–56.
22. TIMI Study Group. The Thrombolysis in Myocardial Infarction (TIMI) trial. The Thrombolysis in Myocardial Infarction (TIMI) trial. Phase I findings. N Engl J Med 1985;312:932–6.
23. van't Hof AW, Liem A, Suryapranata H, Hoorntje JC, de Boer MJ, Zijlstra F. Angiographic assessment of myocardial reperfusion in patients treated with primary angioplasty for acute myocardial infarction: myocardial blush grade. Zwolle Myocardial Infarction Study Group. Circulation 1998;97:2302–6.
24. Cutlip DE, Windecker S, Mehran R, et al. Clinical end points in coronary stent trials: a case for standardized definitions. Circulation 2007;115:2344–51.
25. Moons KG, Klootwijk P, Meij SH, et al. Continuous ST-segment monitoring associated with infarct size and left ventricular function in the GUSTO-I trial. Am Heart J 1999;138:525–32.
26. Maier W, Altwegg LA, Corti R, et al. Inflammatory markers at the site of ruptured plaque in acute myocardial infarction: locally increased interleukin-6 and serum amyloid A but decreased C-reactive protein. Circulation 2005;111:1355–61.
27. Kramer MC, Van Der Wal AC, Koch KT, et al. Presence of older thrombus is an independent predictor of long-term mortality in patients with ST-elevation myocardial infarction treated with thrombus aspiration during primary percutaneous coronary intervention. Circulation 2008;118:1810–6.
28. Thibault H, Piot C, Staat P, et al. Long-term benefit of postconditioning. Circulation 2008;117:1037–44.
29. Loubeyre C, Morice MC, Lefevre T, Piechaud JF, Louvard Y, Dumas P. A randomized comparison of direct stenting with conventional stent implantation in selected patients with acute myocardial infarction. J Am Coll Cardiol 2002;39:15–21.
30. Mauri L, Cox D, Hermiller J, et al. The PROXIMAL trial: proximal protection during saphenous vein graft intervention using the Proxis Embolic Protection System: a randomized, prospective, multicenter clinical trial. J Am Coll Cardiol 2007;50:1442–9.

Key Words: ST-segment elevation myocardial infarction ■ primary percutaneous coronary intervention ■ combined proximal embolic protection and thrombus aspiration.