

# Protection of Distal Embolization in High-Risk Patients With Acute ST-Segment Elevation Myocardial Infarction (PREMIAR)

Fernando A. Cura, MD<sup>a,\*</sup>, Alejandro Garcia Escudero, MD<sup>b</sup>, Daniel Berrocal, MD<sup>c</sup>, Oscar Mendiz, MD<sup>d</sup>, Marcelo S. Trivi, MD<sup>a</sup>, Juan Fernandez, MD<sup>e</sup>, Alejandro Palacios, MD<sup>e</sup>, Mariano Albertal, MD<sup>a</sup>, Ruben Piraino, MD<sup>f</sup>, Miguel Angel Riccitelli, MD<sup>b</sup>, Luis Gruberg, MD<sup>k</sup>, Miguel Ballarino, MD<sup>g</sup>, Jose Milei, MD<sup>h</sup>, Ricardo Baeza, MD<sup>i</sup>, Jorge Thierer, MD<sup>a</sup>, Liliana Grinfeld, MD<sup>c</sup>, Mitchell Krucoff, MD<sup>i</sup>, William O'Neill, MD<sup>l</sup>, and Jorge Belardi, MD<sup>a</sup>,  
on behalf of the PREMIAR Investigators

Distal embolization may decrease myocardial reperfusion after primary percutaneous coronary intervention (PCI). Nonetheless, results of previous trials assessing the role of distal protection during primary PCI have been controversial. The Protection of Distal Embolization in High-Risk Patients with Acute ST-Segment Elevation Myocardial Infarction Trial (PREMIAR) was a prospective, randomized, controlled study designed to evaluate the role of filter-based distal protection during PCI in patients with acute ST-segment elevation myocardial infarction at high risk of embolic events (including only baseline Thrombolysis In Myocardial Infarction grade 0 to 2 flow). The primary end point was continuous monitoring of ST-segment resolution. Secondary end points included core laboratory analysis of angiographic myocardial blush, ejection fraction measured by cardiac ultrasound, and adverse cardiac events at 6 months. From a total of 194 enrolled patients, 140 subjects were randomized to PCI with or without embolic protection, and 54 were included in a registry arm due to the presence of angiographic exclusion criteria. Baseline characteristics were comparable between arms. The rate of complete ST-segment resolution ( $\geq 70\%$ ) at 60 minutes was similar in patients treated with or without distal protection (61.2% vs 60.3%, respectively,  $p = 0.85$ ). Angiographic myocardial blush (67% vs 70.7%,  $p = 0.73$ ), in-hospital ejection fraction ( $47.4 \pm 9.9\%$  vs  $45.3 \pm 7.3\%$ ,  $p = 0.29$ ), and combined end point of death, heart failure, or reinfarction at 6 months (14.3% vs 15.7%,  $p = 0.81$ ) were consistently achieved in a similar proportion in the 2 groups. In conclusion, the use of filter-based distal protection is safe and effectively retrieves debris; however, such use does not translate into an improvement of myocardial reperfusion, left ventricular performance, or clinical outcomes. © 2007 Elsevier Inc. All rights reserved. (Am J Cardiol 2007;99:357–363)

Inadequate myocardial reperfusion at the tissue level is a frequent finding after primary percutaneous coronary intervention (PCI) and has been associated with subsequent poor clinical outcomes.<sup>1–4</sup> Several factors may have an effect on this phenomenon, such as microvascular vasoconstriction, reperfusion injury, or endothelial damage; however, embolization of atheromatous and thrombotic debris distally to the microcirculation occurs frequently and may have a major role in myocardial reperfusion.<sup>1,5,6</sup> Although pilot studies and small randomized trials have suggested a certain

degree of benefit for patients undergoing primary angioplasty with various antiembolic devices,<sup>7–9</sup> other randomized trials have not proved the concept.<sup>10,11</sup> Two factors may have limited the benefit of distal protection in those trials: inclusion of patients with ST-elevation myocardial infarction (STEMI) who are at low risk for embolic events and technical limitations of devices. We therefore examined the safety and efficacy of a novel low-profile, filter-based, distal embolic device (SpideRX, ev3, Inc., Minneapolis, Minnesota) as an adjunct to routine primary or rescue (i.e., after failed thrombolysis) angioplasty of patients with STEMI at high risk for embolic events (infarct-related artery with baseline Thrombolysis In Myocardial Infarction [TIMI] grade  $\leq 2$  flow<sup>3</sup>).

## Methods

**Study design and population:** The Protection of Distal Embolization in High-Risk Patients with Acute Myocardial Infarction (PREMIAR) study was a prospective, randomized, controlled clinical trial performed at 20 institutions in 3 countries. Investigators were selected after demonstration of experience using the device. Patients 21 to 80 years old

<sup>a</sup>Instituto Cardiovascular de Buenos Aires, <sup>b</sup>Hospital Argerich, <sup>c</sup>Hospital Italiano de Buenos Aires, <sup>d</sup>Fundación Favaloro, <sup>e</sup>Sanatorio Trinidad, <sup>f</sup>Sanatorio Plaza de Rosario, <sup>g</sup>Hospital Privado de Cordoba, and <sup>h</sup>Instituto de Investigaciones Cardiológicas, Buenos Aires, Argentina; <sup>i</sup>Duke Clinical Research Institute, Durham, North Carolina; <sup>j</sup>Beaumont Hospital, Royal Oak, Michigan; and <sup>k</sup>Technion, Israel Institute of Technology, Haifa, Israel. Manuscript received June 29, 2006; revised manuscript received and accepted August 22, 2006.

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\*Corresponding author: Tel: 5411-4787-7570; fax: 5411-4787-7571.

E-mail address: fcura@icba-cardiovascular.com.ar (F.A. Cura).

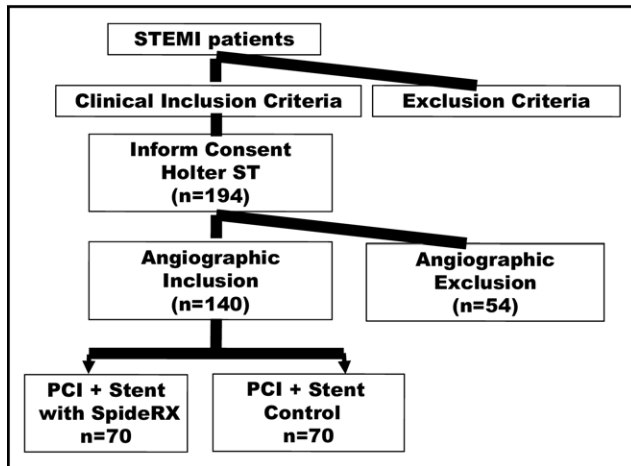


Figure 1. PREMIAR trial flowchart.



Figure 2. SpiderRX distal filter.

continued for 12 months and 80 to 160 mg of aspirin indefinitely.

**Description of the SpiderRX distal embolic protection system:** The SpiderRX embolic protection device (ev3, Inc.) consists of a Teflon-coated 0.014-inch stainless-steel capture wire for use with rapid-exchange systems and a dual-end rapid-exchange delivery-recovery catheter (Figure 2). The capture wire has an atraumatic floppy tip and a heparin-coated nitinol mesh filter available in 5 sizes of 3 to 7 mm. The diameter of the capture wire was selected to be ~0.5 mm larger than the vessel diameter at the site of filter deployment. Unlike other distal protection devices, the capture wire in the SpiderRX device is not used to cross the target lesion. Instead, the operator selects an independent 0.014-inch guidewire to cross the target lesion and access the distal coronary artery based on anatomic and morphologic considerations or personal preference. Once the coronary guidewire is positioned distal to the target lesion, the 3.2Fr delivery catheter is advanced en bloc; once the embolic protection device is 1.5 to 2 cm distal to the target coronary lesion, the guidewire is removed. The delivery catheter is then retracted and removed to deploy the nitinol filter. After angioplasty and stent deployment, the 4.2Fr recovery end of the catheter is advanced to recapture the filter and remove it from the patient.

**Primary end point:** Continuously updated ST-segment resolution analysis using 24-hour digital 12-lead electrocardiographic recordings quantifying the speed, completeness, and stability of reperfusion was performed for all patients in a blinded manner at the Catholic University (Santiago, Chile)/Duke Clinical Research Institute Virtual Electrocardiogram Core Laboratory (Durham, North Carolina). Detailed definitions of standard parameters of ST-segment recovery analysis have been previously published.<sup>12</sup> In brief, peak ST elevation before PCI was compared with ST-segment levels 60 minutes after the final contrast injection in the most abnormal single lead of the standard 12-lead electrocardiogram. Percent resolution of ST-segment elevation was categorized as complete (>70%), partial (30% to 70%), or absent (<30%).<sup>13</sup> The primary end point of the study was the dichotomous rate of complete ST-segment resolution at 60 minutes, defined as  $\geq 70\%$  recovery compared with baseline during continuous ST-segment monitoring.

**Secondary end points:** A combined clinical end point of death, reinfarction, or presence of heart failure at 6 months after the procedure was calculated. Reinfarction was defined as previously described.<sup>11</sup> Heart failure was defined as pulmonary edema documented radiographically or requiring intubation, insertion of an intra-aortic balloon pump, or requirement of pharmacologic pressor support. All adverse events were adjudicated by a clinical events committee blinded to treatment group after review of original

who presented with continuous chest pain for  $\geq 30$  minutes and within 12 hours of onset of pain and ST-segment elevation  $\geq 2$  mm (0.2 mV) in  $\geq 2$  contiguous leads on 12-lead electrocardiography consistent with acute MI and referred to primary or rescue angioplasty were approached for inclusion in the study. Clinical exclusion criteria included presence of cardiogenic shock, aortic dissection, cardiac tamponade, myocarditis, revascularization by coronary bypass surgery or percutaneous intervention within 6 months, oral anticoagulation, pregnancy, known renal failure (defined as creatinine level  $>2$  mg/dl), and allergy to nitinol, stainless steel, aspirin, or thienopyridine. Patients were included only in the absence of conditions precluding evaluation of ST-segment changes on the admission electrocardiogram, such as sustained idioventricular rhythm, presence of a ventricular pacemaker, left bundle branch block, Wolff-Parkinson-White syndrome, or a technically inadequate electrocardiogram.

Before the procedure, 24-hour, continuous, digital, high-fidelity 12-lead electrocardiographic ST-segment monitoring (Northeast Monitoring 180+, Boston, Massachusetts) was initiated. Enrolled subjects underwent coronary catheterization to evaluate them against angiographic exclusion criteria, such as baseline TIMI grade 3 flow, culprit lesion with  $<50\%$  diameter stenosis, target lesion in a saphenous vein graft, or a vessel  $<2.5$  mm, left main trunk disease, bifurcation lesion (side branch  $>2.5$  mm), excessive proximal tortuosity, or need for treatment of  $>1$  vessel during the index procedure (Figure 1). After diagnostic angiography, subjects were further randomized in a 1:1 ratio, according to infarct-related coronary artery (left anterior descending coronary artery) and the physician's intention to use glycoprotein IIb/IIIa inhibitors, to PCI with adjunctive SpiderRX or PCI alone.

All patients received 325 mg of aspirin and a loading oral dose of 300 to 600 mg of clopidogrel before or immediately after the procedure. After catheter introduction, all subjects received intravenous boluses of heparin in sufficient doses to prolong the activated clotting time to  $>250$  seconds. Use of glycoprotein IIb/IIIa inhibitors was at the discretion of the investigator. Clopidogrel was recommended to be

Table 1  
Baseline clinical and angiographic characteristics

Variable	Distal Protection (n = 70)	Control (n = 70)	p Value
Age (yrs)	60.2 ± 9.9	60.4 ± 10.4	0.20
Men	86%	77%	0.19
Diabetes mellitus	19%	20%	0.75
Current smoker	33%	47%	0.08
Hypertension	56%	49%	0.40
Body mass index (kg/m <sup>2</sup> )	28.6 ± 4.1	27.6 ± 5.1	0.15
Previous MI	21%	13%	0.18
Previous coronary revascularization	13%	9%	0.44
Primary coronary angioplasty	97%	96%	0.65
Killip class ≥II	26%	19%	0.31
Symptom onset to angiography (min)	150 (80–270)	146 (75–236)	0.45
Baseline peak ST-segment elevation in most abnormal lead (mV)	6.04 ± 4.9	6.19 ± 4.3	0.85

Values are means ± SDs, percentages of patients, or medians (IQRs).

source documentation. Blinded angiographic evaluation was performed to assess TIMI flow grade, TIMI myocardial perfusion grade, and TIMI frame count before and after PCI.<sup>14</sup> Cardiac ultrasound was performed within 48 to 72 hours, and ejection fraction and end-diastolic and end-systolic volumes were assessed by blinded reviewers.<sup>15</sup>

**Statistical analysis:** The subject sample size was calculated based on the demonstration of a 24% improvement in the proportion of patients with complete ST-segment resolution (defined as ≥70%). For this end point, with  $\alpha = 0.05$  and 80% power, the number of subjects required per group was 62 (total of 124 patients). To account for attrition, the assumed sample size calculated was 140 patients, 70 patients for each group. Simple descriptive statistics were used to summarize baseline characteristics of the randomized treatment group. Abnormal distributions were expressed as medians (interquartile ranges [IQRs]). Chi-square, Fisher's exact test, or Student's *t* test was used to compare groups, as appropriate. All analyses were completed as intention to treat, and all comparisons are 2-sided.

## Results

From December 2004 to November 2005, 194 patients with STEMI were included in the study. Fifty-four patients were excluded due to the presence of angiographic exclusion criteria, such as presence of TIMI grade 3 flow (n = 17), target lesion in a saphenous vein graft (n = 2), excessive tortuosity (n = 11), vessel <2.5 mm (n = 8) and bifurcation lesion (n = 9), or need for treatment of >1 vessel during the index procedure (n = 7). Therefore, 140 high-risk patients (including only those with baseline TIMI grade 0 to 2 flow) were randomized to undergo PCI with distal protection or PCI alone (Figure 1). Baseline demographic and angiographic characteristics were comparable between the 2 randomized groups (Tables 1 and 2).

Table 2  
Procedural and core laboratory angiographic characteristics

Variable	Distal Protection (n = 70)	Control (n = 70)	p Value
Baseline TIMI flow			0.89
0	80%	77%	
1	5%	6%	
2	15%	17%	
Reference vessel diameter (mm)	3.05 ± 1.24	3.09 ± 1.34	0.87
Baseline diameter stenosis (%)	96.1 ± 9.5	95.1 ± 14.6	0.62
Lesion length (mm)	19.54 ± 8.67	17.58 ± 7.85	0.60
Angiographic thrombosis	90%	97%	0.12
≥2 diseased coronary arteries	45%	50%	0.86
Stents used	99%	97%	0.55
Need for predilatation before stenting	81%	74%	0.31
Glycoprotein IIb/IIIa inhibitors used	26%	26%	0.92
Left anterior descending artery target	53%	56%	0.73
Total amount of contrast (ml)	268 ± 102	245 ± 105	0.20
Total procedure time (min)	52 (43–70)	43.5 (30–54)	<0.001
Final TIMI flow			0.49
0–1	3%	5%	
2	19%	9%	
3	78%	86%	
Final corrected TIMI frame count	28.2 ± 22.4	25.5 ± 20.1	0.50
Final perfusion grade			0.51
0–1	18%	18%	
2	15%	7%	
3	67%	71%	
Angiographic complications	10%	17%	0.26
Distal embolization	7%	11%	
Coronary dissection	0%	0%	
Side branch closure	0%	2%	
No-reflow phenomenon	3%	3%	
Coronary thrombosis	3%	12%	
Spasm	0%	0%	
Perforation	0%	0%	

Values are percentages of patients, means ± SDs, or medians (IQRs).

The distal protection device was used successfully in 66 of 70 patients (94%) allocated to the filter group, although predilatation was required to facilitate delivery in 33 of 66 (44%). Visible macroscopic atherothrombotic debris was noted in the filters by visual assessment in 48% of patients from the filter arm. The procedural time was 10.1 ± 6.2 minutes longer in patients treated with distal protection compared with the control arm (Table 2). In patients treated with the filter, there was no significant difference in the feasibility and efficacy between treatment of anterior and nonanterior infarct-related arteries. Filter sizes of choice were 3 mm in 54.3% and 4 mm in 45.7% of patients.

**Myocardial reperfusion and salvage:** The primary end point of complete ST-segment resolution at 60 minutes after the final contrast injection occurred in similar proportions in the 2 groups (Table 3 and Figure 3). Mean 60-minute percent ST-segment resolutions were also similar between arms (74.7 ± 19.5 vs 74.6 ± 20.4, respectively, p = 0.95). Moreover, there was no difference in degree of ST-segment resolution at any postprocedural period (Figure 3). Further,

Table 3  
Subgroup analysis for primary endpoint of complete ST-segment resolution ( $\geq 70\%$ ) at 60 minutes

Variable	Rate of Complete ST-Segment Resolution at 60 min		Difference (95% CI)	p Value
	Distal Protection (n = 70)	Control (n = 70)		
All patients	61%	60%	1 (-15 to 17)	0.91
Infarct-related artery				
Left anterior descending	45%	40%	5 (-18 to 27)	0.66
Non-left anterior descending	81%	87%	-6 (-24 to 12)	0.52
Use of glycoprotein IIb/IIIa inhibitors	81%	60%	21 (-10 to 57)	0.19
Men	58%	60%	-2 (-20 to 17)	0.85
Women	80%	62%	17 (-17 to 52)	0.34
Time to admission (according to median)				
Shorter (<150 min)	58%	65%	-7 (-31 to 17)	0.57
Longer ( $\geq 150$ min)	66%	59%	7 (-16 to 30)	0.56
Diabetes mellitus	46%	50%	-4 (-41 to 34)	0.56
Baseline thrombosis	60%	59%	1 (-18 to 19)	0.96
Baseline TIMI flow				
0/1	63%	62%	1 (-19 to 19)	0.98
2	50%	55%	-5 (-50 to 39)	0.80
Current smoking	82%	73%	9 (-13 to 32)	0.43

CI = confidence interval.

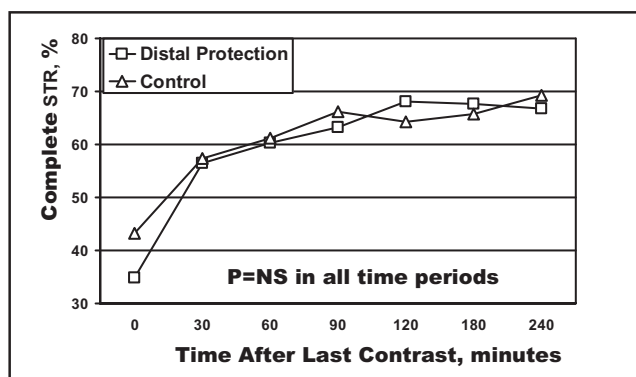


Figure 3. Complete ST-segment resolution (STR;  $\geq 70\%$ ) in different periods after primary angioplasty in the 2 arms.

no subgroup was identified in which ST-segment resolution was more profound with distal protection compared with the control group (Table 3).

Angiographic core laboratory data was obtained in 89% of patients. Final angiographic flow parameters were similar between groups as was the incidence of angiographic complications (Table 2).

Between the distal protection group and the control group, we found no significant difference in left ventricular ejection fraction ( $47.4 \pm 9.9\%$  vs  $45.3 \pm 7.3\%$ ,  $p = 0.29$ ; median 49%, IQR 42 to 53, vs 46%, IQR 43 to 50,  $p = 0.15$ ), end-diastolic volume ( $105.5 \pm 23.2$  vs  $108.7 \pm 32.6$  ml,  $p = 0.62$ ; median 107 ml, IQR 93 to 119, vs 104 ml, IQR 87 to 125,  $p = 0.93$ ), or end-systolic volume ( $57.5 \pm 19.6$  vs  $60.9 \pm 23.2$  ml,  $p = 0.49$ ; median 57 ml, IQR 46 to 62, vs 57 ml, IQR, 46 to 70,  $p = 0.62$ ). Peak creatinine kinase values were 2,302 U/ml (IQR 1,345 to 3,658) in the distal protection group and 2,657 (IQR 1,298 to 4,245) in the control group ( $p = 0.54$ ).

**Particulate analysis:** Histopathologic analysis was performed in 12 consecutive cases from 1 site. Particles were recovered in all filters. Number of particles analyzed ranged from 8 to 48 per filter. Particles ranged from 101 to 1,299  $\mu\text{m}$  in maximum diameter and from 212 to 1,487  $\mu\text{m}^2$  in area. Most particles were composed of platelet clumps, red cells, and fibrin, which led to the diagnosis of fresh thrombus (Figure 4). Cellularity was widely variable, often including monocytes, polymorphonuclear cells, and lymphocyte clusters. Amorphous areas were observed within the fibrin network, which suggested the presence of ongoing thrombus organization and/or plaque remnants. Particles with a mucopolysaccharide amorphous extracellular matrix, which stained positive with Alcian blue, were observed in 4 cases, which also supports the presence of plaque components within the detached material. Lipid vacuoles, foam cells, smooth muscle cells, cholesterol clefts, and calcified areas were rarely observed.

**Clinical outcome:** Although the 30-day and 6-month rates of mortality and heart failure were similar between arms, reinfarction and consequent urgent reintervention events were more frequent in the control group compared with the distal protection arm. However, the predefined combined end point of death, reinfarction, or heart failure at 6 months was similar in the 2 arms (Table 4). Elective target vessel revascularization rate was identical in the 2 groups (8.6%).

## Discussion

In this prospective, randomized, controlled, clinical trial of patients with STEMI who underwent primary or rescue PCI, a filter-based distal protection device did not improve myocardial reperfusion as demonstrated by quantitative biomarkers, such as continuous ST-segment resolution or angiographic blush grade. Left ventricular performance, peak

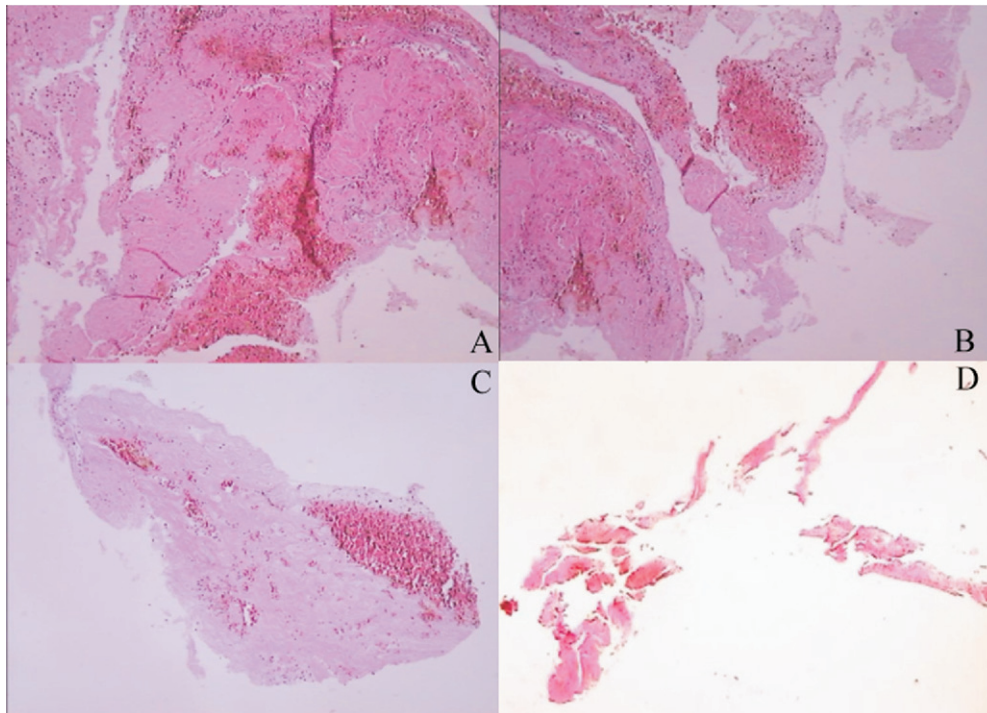


Figure 4. Different views of particulate obtained from filters and panoramic views of a recent thrombus are shown. (A) An extensive thrombus is compared with very small particles in (D). (B, C) Some areas stained light pink are suspicious of being plaque remnants. Hematoxylin and eosin stain, 40 $\times$ .

Table 4  
Clinical outcome at six months

Variable	Distal Protection (n = 70)	Control (n = 70)	p Value
Death			
30 d	5.7%	5.7%	1
6 mos	7.1%	5.7%	0.73
Heart failure			
30 d	11.4%	10.0%	0.78
6 mos	12.8%	11.4%	0.79
Reinfarction			
30 d	0%	7.1%	0.02
6 mos	0%	7.1%	0.02
Combined end point			
30 d	14.3%	14.3%	1
6 mos	14.3%	15.7%	0.81

creatinine kinase release, and clinical outcomes were essentially identical in the 2 arms, showing no improvement in STEMI from distal protection.

Several previous reports demonstrating retrieval of macroscopic atherothrombotic debris of patients with STEMI using thrombectomy or distal protection devices have suggested a beneficial effect during primary PCI.<sup>7-9,16-20</sup> Nevertheless, these early encouraging results contrasted with the results of other larger recent randomized trials.<sup>10,11</sup> Our findings are consistent with and extend those of previous large randomized studies in 2 ways. First, we tested the performance of a low-profile, user-friendly distal filter device, the SpideRX embolic protection device, demonstrating its safety and feasibility as an adjunct during primary PCI in the native coronary circulation, even in the setting of

STEMI with poor visualization of the distal vessel. The selection of the filter size and device deployment was performed without clear visualization of the distal vessel in 80% of subjects who had baseline TIMI grade 0 flow. Second, this study intended to select a subgroup of patients with STEMI at higher risk of distal embolization. Because angiographic detection and measurement of thrombus burden are very subjective with a wide interobserver variability, we used a more reliable variable to select the study population at higher risk based on baseline TIMI flow. Therefore, only patients with baseline TIMI grade 0 to 2 flow were included to represent a group that may derive a more profound benefit from distal protection.<sup>3</sup>

The increment in procedural time, the frequent need to predilate the lesion to position the filter device, the presence of unprotected side branches proximal to the distal system, the potential risk of device-triggered embolization while crossing the lesion, and the limited amount of captured debris may explain the lack of a protective effect of different distal protection systems in the STEMI setting.<sup>21,22</sup> Although the capability of the SpideRX device to capture emboli debris has been demonstrated repeatedly,<sup>23</sup> the captured material was mainly thrombotic, with a broad range of debris volume from extremely few and small particles to very numerous and large atherothrombotic debris.

The present study was unable to identify any specific STEMI subgroup that might profit from adjunctive distal protection. Of note, only 26% of patients enrolled in the PREMIAR trial received glycoprotein IIb/IIIa inhibitors compared with most patients in previous randomized trials.<sup>10,11</sup> However, no benefit of distal protection was seen, even when analysis was confined to the subgroup of patients

without glycoprotein IIb/IIIa inhibitors. An unexpected finding from our study was the reinfarction rate, which was significantly lower in patients treated with adjunctive use of a distal protection device. The association with a higher incidence of final intraluminal thrombosis in the control group might partly explain this phenomenon. However, this result is not consistent with any previous distal protection studies in acute myocardial infarction<sup>10,11</sup> and needs further confirmation in a larger cohort of patients.

We have to recognize several limitations. The present study focused on assessment of clinical surrogates of myocardial reperfusion; hence, it was underpowered to detect small differences in clinical events. Nonetheless, similar results in the combined clinical end point strongly suggest a lack of clinical benefit from distal protection during primary PCI. Assignment of study treatment was not blinded for the investigators or patients, and we cannot exclude bias on the part of the investigators as a factor influencing outcomes. However, continuous ST-segment resolution, cardiac ultrasound variables, and angiographic flow characteristics were assessed by independent core laboratories blinded to treatment assignment, and the clinical adverse events were adjudicated by an independent committee after reviewing original documents.

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## Appendix

**Clinical Sites and PREMIAR Investigators:** ARGENTINA: Instituto Cardiovascular Buenos Aires (F. Cura, MD, M. Albertal, MD, L. Padilla, MD, J. Belardi, MD); Sanatorio Itoiz, Buenos Aires (A. Palacios, MD, J. Fernandez, MD); Hospital Italiano de Buenos Aires (L. Grinfeld, MD, D. Berrocal, MD); Fundación Favalaro, Buenos Aires (O. Mendiz, MD); Instituto Cardiovascular de Corrientes (J. Baccaro, MD); Instituto Cardiovascular de Rosario, Santa Fe (A. Damonte, MD); Sanatorio Parque, Santa Fe (A. Damonte, MD); Policlínica Bancaria, Buenos Aires (J. Blugermann, MD); Sanatorio Plaza de Rosario, Santa Fe (R. Piraino, MD); Hospital Argerich, Buenos Aires (M. Riccitelli, MD); Sanatorio Trinidad, Buenos Aires (A. Palacios, MD); Sanatorio Quilmes, Buenos Aires (A. Palacios, MD); Clínica del Sol, Buenos Aires (J. Gagliardi, MD); Sanatorio Británico de Rosario, Santa Fe (C. Cigalini, MD); Hospital Militar, Buenos Aires (O. Carlevaro, MD, R. Kevorkian, MD); Hospital Privado de Córdoba (M. Ballarino, MD); Sanatorio Quemes, Buenos Aires (M. Bettinotti, MD).

CHILE: Hospital Clínico de la Universidad Católica de Chile, Santiago (R. Corvalan, MD, A. Martinez, MD).

ISRAEL: Technion, Israel Institute of Technology, Haifa (L. Gruberg, MD, R. Beyar, PhD).

HISTOLOGY SUBSTUDY: Instituto de Investigaciones Cardiológicas (A.C. Taquini, MD, J. Milei, MD).

ANGIOGRAPHIC CORE LABORATORY: Hospital Argerich, Buenos Aires, Argentina (A. Garcia Escudero, MD).

CARDIAC ULTRASOUND CORE LABORATORY: Instituto Car-

diovascular Buenos Aires, Buenos Aires, Argentina (M. Trivi, MD).

CONTINUOUS ELECTROCARDIOGRAPHIC MONITORING CORE LABORATORY: Duke Clinical Research Institute, Durham, North Carolina (R. Baeza, MD, M. Krucoff, MD).

ELECTROCARDIOGRAPHIC CORE LABORATORY: Instituto Cardiovascular Buenos Aires, Buenos Aires, Argentina (M. Resk, MD).

CLINICAL EVENTS ADJUDICATION COMMITTEE: Instituto Cardiovascular Buenos Aires, Buenos Aires, Argentina (J. Thierer, MD).

DATA ANALYSIS AND MANAGEMENT: Instituto Cardiovascular Buenos Aires, Buenos Aires, Argentina (M. Resk, MD, D. Bazzino).

STATISTICAL ANALYSIS: J. Thierer, MD.

EXECUTIVE COMMITTEE: J. Belardi, MD (chair), F. Cura, MD, D. Berrocal, MD, O. Mendiz, MD, L. Grinfeld, MD.

ADVISORY COMMITTEE: G. Stone, MD, M. Krucoff, MD, W. O'Neill, MD.

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