

# Mechanical Prevention of Distal Embolization During Primary Angioplasty

## Safety, Feasibility, and Impact on Myocardial Reperfusion

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**Background**—Effective myocardial reperfusion after primary percutaneous coronary intervention (PCI) may be limited by distal embolization. We tested the safety, feasibility, and efficacy of the FilterWire-Ex (FW), a distal embolic protection device, as an adjunct to primary PCI.

**Methods and Results**—Fifty-three consecutive patients undergoing primary PCI with FW protection were compared with a matched control group treated by primary PCI alone. Successful FW positioning was obtained in 47 patients (89%) without complications. Histological analysis of the content of the last 13 filters showed multiple embolic debris in all cases. FW use was associated with lower postinterventional corrected TIMI frame count ( $22 \pm 14$  versus  $31 \pm 19$ ;  $P=0.005$ ) and higher occurrence of grade 3 myocardial blush (66% versus 36%;  $P=0.006$ ) and early ST-segment elevation resolution (80% versus 54%;  $P=0.006$ ). At multivariate analysis, FW use was the only independent predictor of early ST-segment elevation resolution and of grade 3 myocardial blush. FW patients showed lower peak creatine kinase-MB release ( $236 \pm 172$  versus  $333 \pm 219$  ng/mL;  $P=0.013$ ) and greater improvement at 30 days in left ventricular wall motion score index ( $-0.30 \pm 0.19$  versus  $-0.18 \pm 0.26$ ;  $P=0.008$ ) and ejection fraction ( $+7 \pm 4\%$  versus  $+4 \pm 7\%$ ;  $P=0.012$ ).

**Conclusions**—FW use during primary PCI is feasible and safe. Distal embolization prevention appears to exert a beneficial effect on markers of myocardial reperfusion and on left ventricular function improvement at 30 days. (*Circulation*. 2003;108:171-176.)

**Key Words:** myocardial infarction ■ angioplasty ■ embolism ■ reperfusion

Signs of microvascular hypoperfusion after successful primary percutaneous coronary intervention (PCI) have been observed in up to 80% of cases according to the marker used to assess effective reperfusion, such as angiographic myocardial blush, resolution of ST-segment elevation, or myocardial contrast echocardiography.<sup>1-6</sup> This occurrence, named “no-reflow,” is associated with poorer functional recovery and adverse outcome.<sup>7</sup> Distal embolization of thrombus/plaque components during primary PCI may play a crucial role in limiting effective myocardial reperfusion<sup>8-10</sup>; thus, it can be hypothesized that mechanical prevention of distal embolization might prevent no-reflow during primary PCI.

The FilterWire-EX (FW) is a 0.014-inch guidewire that incorporates a nonoccluding polyurethane porous membrane filter (80- $\mu$ m pores) in the shape of a windsock to allow retention and removal of embolized particles. The filter can be delivered and retrieved through a 3.9F monorail sheath.

We here report on the safety and feasibility of the adjunctive use of the FW during primary PCI performed on native coronary arteries for acute myocardial infarction. The impact of FW use on myocardial reperfusion was compared with a case-matched control group.

## Methods

### Patient Population

Fifty-three consecutive patients with acute myocardial infarction were included in the study and subjected to primary PCI with the FW after written consent was obtained. The inclusion criteria were as follows: (1) presentation within 6 hours from symptom onset; (2) chest pain lasting >30 minutes and resistant to intravenous nitrates; (3)  $\geq 0.2$ -mV ST-segment elevation in at least 2 contiguous leads on a 12-lead ECG; (4) infarct-related native artery with a reference lumen diameter >3.0 mm and with a Thrombolysis In Myocardial Infarction trial (TIMI) flow grade <3. Although FW use is recommended for coronary diameters ranging from 3.5 to 5.5 mm, the inclusion criterion was extended to vessels >3.0 mm because

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unpublished data from the manufacturer's laboratory indicate nearly complete distal protection in vessels 3.0 to 3.5 mm in diameter (data on file, Boston Scientific Corp). The exclusion criteria were significant left main coronary disease, cardiogenic shock at admission, or thrombolytic therapy. The local Institutional Ethics Committee approved the study protocol.

### Primary PCI With Distal Protection

Interventions were performed by 2 high-volume operators (U.L., A.S.P.). Before intervention, patients received standard medical therapy consisting of 7500 IU of unfractionated heparin, 500 mg of aspirin, and  $\beta$ -blockers if not contraindicated. Administration of glycoprotein IIb/IIIa inhibitors was at the discretion of the treating physician. During intervention, the activated clotting time was maintained between 250 and 300 seconds. Poststenting therapy consisted of aspirin and clopidogrel at standard dosages. Primary PCI was performed with 6F radial access unless contraindicated, stent placement without restrictions, and treatment of the infarct-related artery only. The initial attempt to cross the target lesion was performed with the FW guidewire tip. The device was advanced beyond the target lesion proximally to any important bifurcation. In patients with persistent TIMI grade 0 flow, the filter was deployed 2.0 to 3.0 cm beyond the occlusion and repositioned if necessary after predilation with a 1.5-mm balloon. After satisfactory stent deployment, the FW was reinserted into its sheath and retrieved. In case of FW inability to cross the target lesion, a second attempt was made with a traditional guidewire as a "buddy" wire and, if necessary, by predilation with a 1.5-mm balloon. In case of FW delivery failure within 10 minutes, routine PCI was performed, and an intention-to-treat criterion was applied. Successful coronary intervention was defined as residual stenosis <20% with TIMI flow grade  $\geq 2$ .

### Histopathologic Analysis

The last consecutive 13 deployed devices were placed in 10% neutral buffered formalin. The filter content was teased away and processed for histological analysis. The formalin in the test tube was also filtered and processed. Tissue samples were dehydrated in graded series of alcohol and embedded in paraffin. Serial histological sections at 5- $\mu$ m intervals were cut and stained with hematoxylin-eosin or Alcian blue for examination with a light microscope. Morphometric analysis of the size and number of particles was performed with a micrometric grid. If the number of particles exceeded 20 per slide, only the largest 20 particles were analyzed.

### Matched Comparison

To compare markers of effective reperfusion of FW patients (FW group), a case-matched control group of 53 patients undergoing primary PCI without distal protection (PCI group) was selected from our database. Matching was performed through an automatic query on the database, blinded to procedural and clinical outcomes. The database was reviewed sequentially in a chronologically inverse order; for each FW patient, the first patient in the database satisfying the matching parameters and fulfilling the inclusion/exclusion criteria was chosen. The matching parameters in order of sequential selection were as follows: (1) infarct-related artery; (2) pre-PCI TIMI flow grade; (3) gender; and (4) age  $\pm 4$  years.

### Angiographic Analysis

The angiograms were re-read as a single group by 3 experienced observers (G.A., R.R., and M.D.C.). Preprocedure and postprocedure angiograms, the object of analysis, were spliced from the rest of the procedure to blind the investigators to the use of the FW. Quantitative coronary angiography parameters, TIMI flow grade, corrected TIMI frame count (cTFC), and myocardial blush were measured as described previously.<sup>4,11-13</sup> With regard to cTFC, the number of frames was multiplied by 30 and divided by 12.5 to report a cine frame count in accordance with standard methods.

### ECG, Echocardiographic, and Laboratory Data

Preintervention and postintervention 12-lead ECGs were analyzed as a single group by a blinded observer (A.M.). The total ST-segment elevation ( $\Sigma$ STe) was calculated in each ECG from leads exploring the infarct area as described previously.<sup>14</sup> Resolution of  $\Sigma$ STe after PCI was defined as >70% reduction of the initial value.

Analysis of 2D echocardiograms, performed before and 30 days after PCI, was performed by 2 investigators blinded to the treatment (C.P. and V.D.B.). The left ventricular (LV) wall motion score index (WMSI), end-diastolic volume, end-systolic volume, and ejection fraction (LVEF) were calculated by standard methods. Creatine kinase (CK) and CK-MB were assessed every 8 hours during the first day and then daily until discharge.

### Study End Points

The primary end points of the present study were the feasibility and safety of adjunctive use of the FW during primary PCI. Secondary end points were the markers of effective reperfusion ( $\Sigma$ STe resolution, myocardial blush grade, and cTFC). Other secondary end points were peak CK and CK-MB release, change in LVEF and WMSI at 30 days compared with admission, and incidence of major adverse cardiac events, including death, reinfarction, and need for target vessel revascularization at 30 days.

### Statistical Analysis

Data are expressed as mean  $\pm$  SD for continuous variables and as absolute and relative frequencies for categorical variables. Student's unpaired *t* test or Mann-Whitney *U* test was used to compare continuous variables between groups. Student's paired *t* test was used to assess changes from baseline to 30 days. Categorical variables were compared by  $\chi^2$  test or Fisher's exact test, as appropriate. Independent predictors of the occurrence of  $\Sigma$ STe resolution and of grade 3 myocardial blush were identified by entering all variables associated with a probability value <0.10 at univariate analysis into a logistic regression analysis. Probability values <0.05 were considered to be statistically significant (NCSS 2000 Software).

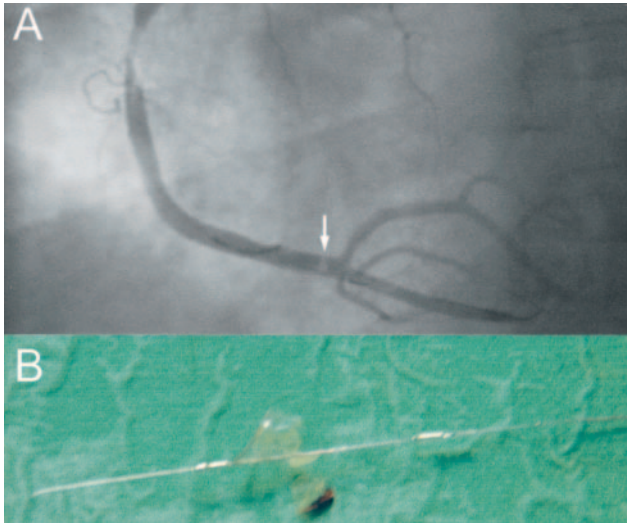
## Results

### Feasibility and Safety of FW Use During Primary PCI

Correct FW delivery was achieved in 47 patients (89%). In 7 patients (15%), FW delivery, initially unsuccessful, was achieved after insertion of a "buddy" wire to reduce vessel tortuosity; in 4 of these patients, predilation with a 1.5-mm balloon was also necessary. Blinded positioning of the FW because of persistent TIMI grade 0 flow occurred in 7 cases (15%); filter repositioning after predilation was necessary in 2 of these cases. Safe retrieval of the filter was obtained in all cases. Coronary dissections attributable to FW delivery were not observed.

After retrieval of the device, direct visual inspection of the filter yielded macroscopic particles in 16 patients (34%), including 7 of the 13 patients in whom histopathologic analysis was performed (Figures 1 and 2). Temporary reduction in coronary flow during FW deployment was observed in 14 cases (30%), followed by TIMI grade 3 flow restoration after FW retrieval in all cases.

In 4 cases (9%), a "kissing" FW technique was performed at bifurcations located just beyond the target lesion and with both branches >3.0 mm in lumen diameter; procedural success was obtained with balloon angioplasty alone in 2 cases, whereas provisional stenting, after removal of one of the devices, was necessary in 2 cases. In 9 patients (19%), a

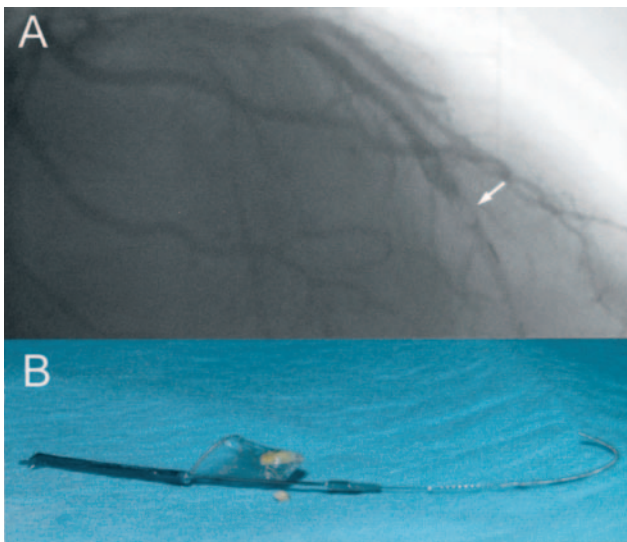


**Figure 1.** A, Angiographic view of FW deployed during PCI of acutely occluded right coronary artery. Filling defect (arrow) is visible in filter. B, Same case, magnified view of retrieved filter with red embolus.

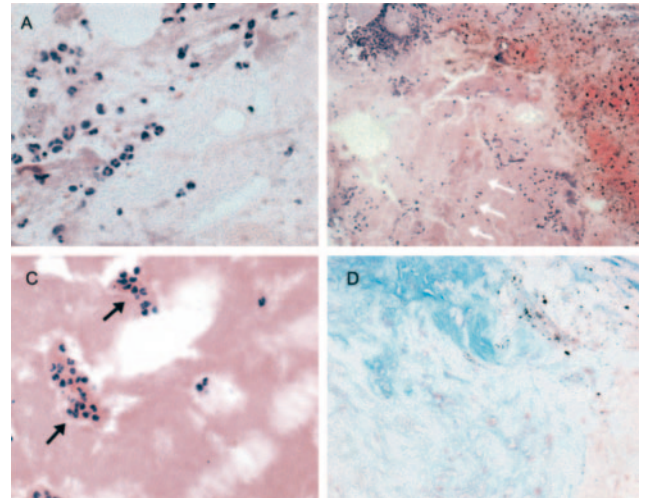
branch 2.5 to 3.0 mm in diameter was left unprotected because of its contiguity to the target lesion.

### Histopathologic Analysis

Particles were recovered in 13 of 13 devices, and their number ranged from 7 to 118 per filter (mean  $45 \pm 40$ ). Distribution of particle major axis dimensions was as follows: 22%  $< 80 \mu\text{m}$ , 30% 80 to  $120 \mu\text{m}$ , 16% 120 to  $250 \mu\text{m}$ , 15% 250 to  $500 \mu\text{m}$ , and 17%  $> 500 \mu\text{m}$ . The majority of particles were composed of platelets, red cells, and fibrin, which led to classification as fresh thrombus (Figure 3A). Cellularity was widely variable, often including polymorphonuclear cells (Figures 3A and 3C). In 7 patients (54%), a necrotic core was observed in the context of a fibrin network, which suggests



**Figure 2.** A, Angiographic view of FW deployed during PCI of acutely occluded left anterior descending artery. Filling defect (arrow) is visible in filter. B, Same case, magnified view of retrieved filter with yellow-white embolus.



**Figure 3.** A, Fresh thrombus; groups of polymorphonuclear cells infiltrate fibrin net (magnification  $\times 40$ ). B, Necrotic area is visualized (arrows) within thrombotic fragment (magnification  $\times 20$ ). C, Cellular clusters (arrows), including polymorphonucleates, surrounded by necrosis (magnification  $\times 20$ ). D, Focal positivity for Alcian blue stain indicating presence of mucopolysaccharides (magnification  $\times 10$ ).

the presence of ongoing thrombus organization and/or plaque remnants (Figures 3B and 3C). Particles with mucopolysaccharidic amorphous extracellular matrix, which stained positive with Alcian blue, were observed in 5 patients (38%), which also supports the presence of plaque components within the embolized material (Figure 3D). Foam cells, smooth muscle cells, cholesterol clefts, and calcifications were not observed.

### Matched Comparison of Procedural Results

Table 1 compares the baseline clinical and angiographic characteristics of the 2 study groups.  $\Sigma\text{STe}$  and WMSI mean values at admission were slightly, although not significantly, higher in the PCI group ( $P=0.054$  and  $P=0.069$ ). Use of glycoprotein IIb/IIIa inhibitors was significantly less frequent in the FW group ( $P<0.001$ ).

Procedural results in the 2 groups are presented in Table 2. The needle-to-balloon time was slightly but significantly longer in the FW group ( $P<0.001$ ). After PCI, TIMI flow less than grade 3, myocardial blush less than grade 3, angiographic signs of distal embolization, and lack of  $\Sigma\text{STe}$  resolution were significantly more frequent in the PCI group, which also showed higher cTFC values ( $P=0.005$ ). Peak CK and CK-MB release values were significantly higher in the PCI group.

Univariate and multivariate analysis indicated that FW use was the only independent predictor of  $\Sigma\text{STe}$  resolution ( $P=0.003$ , OR 0.18, 95% CI 0.06 to 0.56) and of myocardial blush grade 3 after PCI ( $P=0.01$ , OR 0.33, 95% CI 0.13 to 0.81) among the following variables: gender, age, infarct location, diabetes, previous myocardial infarction, preinfarction angina, glycoprotein IIb/IIIa inhibitor use, coronary dimensions, pain onset-to-PCI time, needle-to-balloon time, basal  $\Sigma\text{STe}$ , basal WMSI, and basal LVEF (Table 3).

**TABLE 1. Clinical and Angiographic Characteristics at Admission in Patients in the FW and PCI Groups**

	PCI (n=53)	FW (n=53)	<i>P</i>	Failed FW (n=6)
Age, y	60±11	61±11	0.645	64±7
Gender, male/female, n	44/9	44/9	1.000	6/0
Smoking history, n (%)	31 (58)	28 (53)	0.696	5 (83)
Diabetes, n (%)	6 (11)	9 (17)	0.408	1 (17)
Previous myocardial infarction, n (%)	7 (13)	9 (17)	0.592	2 (33)
Preinfarction angina, n (%)	25 (47)	20 (38)	0.438	2 (50)
Multivessel coronary disease, n (%)	21 (40)	25 (47)	0.557	4 (67)
Systolic blood pressure, mmHg	116±28	111±26	0.404	113±28
Heart rate, bpm	85±22	82±21	0.429	85±31
LVEF, %	45±8	43±6	0.201	42±5
LV WSMI	1.62±0.25	1.72±0.29	0.069	1.75±0.37
Total ST-segment elevation, mV	11±5	13±5	0.054	14±4
Glycoprotein IIb/IIIa inhibitor, n (%)	34 (64)	16 (30)	<0.001	1 (17)
Infarct-related coronary artery, n (%)				
Left anterior descending	23 (43)	23 (43)	1.000	3 (50)
Left circumflex	8 (15)	8 (15)	1.000	2 (33)
Right	22 (41)	22 (41)	1.000	1 (17)
Proximal reference diameter, mm	3.41±0.42	3.43±0.43	0.748	3.32±0.28
Minimal lumen diameter, mm	0.16±0.24	0.12±0.22	0.213	0.03±0.08
Diameter stenosis, %	95±7	97±7	0.179	99±2
TIMI flow grade, 0/1/2	35/7/11	35/7/11	1.000	5/1/0
Pain onset-to-PCI time, min	218±111	228±94	0.601	210±70

Failed FW indicates patients in whom FW delivery failure occurred.

### LV Function and Clinical Course

In both groups, WSMI improved significantly at 30 days with respect to baseline, with a greater increase in the FW group ( $P=0.008$ ; Figure 4A). FW use was also associated with significantly greater improvement in LVEF ( $P=0.012$ ; Figure 4B).

Two patients in the PCI group died in the hospital of late development of refractory cardiogenic shock. The prevalence of major adverse cardiac events at 30 days was not significantly different in the FW versus the PCI group (5% versus 11%;  $P=0.488$ ).

### Discussion

The main findings of the present study are as follows: (1) the FW may be used during primary PCI in selected cases with a high delivery success rate and without significant complications; (2) multiple, distal embolization frequently occurs during primary PCI; and (3) in this clinical setting, mechanical prevention of distal embolization may improve myocardial reperfusion and recovery of LV function.

Embolization has not been considered a common event during PCI, except when PCI was performed on degenerated vein grafts.<sup>15</sup> Recently, a number of clinical studies demonstrated that distal embolization occurs routinely during interventions on native coronary arteries and during primary PCI.<sup>8,10,16–18</sup> Angiographic evidence of distal embolization during primary PCI has been reported to range from 9% to 15%.<sup>10,19</sup> In the present study, visual inspection of the

retrieved filters showed captured emboli in 34% of cases, whereas the histopathologic analysis demonstrated the presence of multiple embolic debris in 13 of 13 cases; the inability to distinguish small emboli from blood staining the device by direct visual inspection may account for this discrepancy. Our histopathologic data are in agreement with those of Grube et al,<sup>16</sup> who also reported microscopic evidence of distal embolization in 100% of patients undergoing elective PCI on native coronary arteries. In the present study, a significant proportion of the analyzed emboli was represented by mucopolysaccharidic components and necrotic cores. This finding, in agreement with previous reports,<sup>16,17,20</sup> may have therapeutic implications, because plaque-containing emboli or emboli derived from partially organized clots might be unresponsive to pharmacological therapy.

Distal embolization during primary PCI has an effect on reperfusion effectiveness and on prognosis, because it brings an increased risk of death at 5 years of 44% compared with 9% in patients without embolization.<sup>10</sup> In acute coronary syndromes, the adjunctive use of an intracoronary thrombectomy system (X-sizer, Endicor, Medical Inc) during PCI significantly improves myocardial reperfusion.<sup>21</sup> Although these data strongly suggest that a substantial benefit can be expected by preventing embolization during primary PCI, the use of distal protection systems in this clinical setting has been discouraged by the technical limitations of the available devices (high profile, occlusive mechanism, low trackability

**TABLE 2. Procedural Results in the 2 Study Groups**

	FW (n=53)	PCI (n=53)	P
Procedural success, n (%)	52 (98)	52 (98)	1.000
Needle-to-balloon time, min	25±6	20±6	<0.001
Stenting, n (%)	51 (96)	53 (100)	0.495
Reference diameter, mm	3.54±0.45	3.52±0.42	0.817
Minimal lumen diameter, mm	3.21±0.58	3.24±0.51	0.758
Diameter stenosis, %	10±9	8±10	0.323
Stent length, mm	18.3±5.4	17.1±4.7	0.215
TIMI flow grade <3, n (%)	1 (2)	8 (15)	0.031
cTFC, frames	22±14	31±19	0.005
Myocardial blush grade,* n (%)			0.006
0–1	5 (9)	13 (28)	
2	13 (25)	16 (36)	
3	35 (66)	16 (36)	
Distal embolization, n (%)	1 (2)	8 (15)	0.031
ST-segment elevation†			
Resolution >70% after PCI, n (%)	41 (80)	27 (54)	0.006
Peak CK, U/L	1698±1109	2493±1644	0.004
Peak CK-MB mass, ng/mL	236±172	333±219	0.013

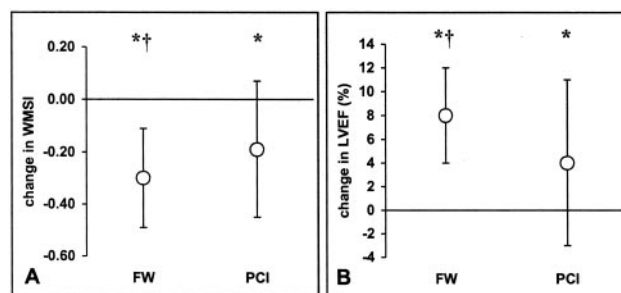
\*Not available in 8 patients.

†Not available in 5 patients.

and maneuverability, and excessive time consumption). Thus, although several studies demonstrate their efficacy during elective interventions, mainly on saphenous vein grafts,<sup>16,22,23</sup> the literature reports on only 8 patients treated by primary PCI plus an occlusive distal protection device (PercuSurge) with good immediate angiographic results and without intra-procedural complications.<sup>17</sup> The FW ensures sufficient blood flow throughout the procedure and 6F and radial access compatibility, together with a degree of maneuverability compatible with the need for prompt vessel recanalization. These theoretical advantages favor the use of FW during primary PCI. We here report a technical success rate in FW delivery and retrieval close to 90% despite the relatively short time (10 minutes) allowed for filter delivery attempts.

**TABLE 3. Variables Associated With  $\Sigma$ STe Resolution and With Grade 3 Blush at Univariate and Multivariate Analysis**

	Univariate Analysis			Multivariate Analysis		
	No	Yes	P	P	OR	95% CI
$\Sigma$ STe resolution						
Left anterior descending artery, n (%)	23 (68)	23 (34)	0.001	0.07	4.2	0.89–19.3
Prior myocardial infarction, n (%)	8 (24)	8 (12)	0.13	...		
Preinfarction angina, n (%)	10 (29)	34 (51)	0.04	...		
Heart rate on admission, bpm	88±26	81±19	0.09	...		
Use of FW, n (%)	10 (29)	26 (61)	0.003	0.003	0.18	0.06–0.56
Grade 3 blush						
Prior myocardial infarction, n (%)	11 (23)	5 (10)	0.07	...		
Pain onset-to-PCI time, min	242±87	211±104	0.13	...		
Needle-to-balloon time, min	21±6	24±6	0.01	...		
Use of FW, n (%)	18 (38)	35 (69)	0.003	0.01	0.33	0.13–0.81

**Figure 4.** Changes in LV WMSI (A) and LVEF (B) during follow-up. \* $P < 0.01$ , day 30 vs baseline. † $P < 0.02$ , FW vs PCI group.

The present study was not structured and powered to demonstrate benefits in terms of clinical outcome. Instead, it evaluated surrogate markers known to be associated with improved LV function and survival. A cTFC cutoff value of 23 has been demonstrated to be highly predictive of clinical and functional outcome<sup>24</sup>; in the present study, a cTFC >23 was observed in 24% of patients treated with FW and in 58% of control patients ( $P < 0.001$ ). Myocardial blush and ST-segment resolution have been validated as surrogate markers of effective myocardial reperfusion and as predictors of clinical outcome.<sup>3,4,14</sup> With regard to these markers, the use of FW was the only independent predictor at univariate-multivariate analysis of  $\Sigma$ STe resolution >70% and myocardial blush grade 3 (Table 3).

### Study Limitations

Among the markers of suboptimal reperfusion, the final TIMI flow grade of <3 achieved in 85% of our control patients is somewhat less than usually described.<sup>25,26</sup> This relatively low rate may be due to chance, differences in interpretation, or, more likely, a selection bias caused by the protocol inclusion criteria requiring infarct-related arteries >3.0 mm and pre-interventional TIMI flow less than grade 3. Indeed, both conditions have been described to favor a final TIMI flow grade <3.<sup>27,28</sup> On the other hand, the case-matched design of the present study allowed a balanced between-group distri-

bution of the main baseline parameters known to affect prognosis after primary PCI (Table 1).

Incomplete embolic protection might have occurred because of pre-PCI embolization and/or embolization induced by the passage of the device; inability to protect branches  $\leq 3.0$  mm; or blinded filter positioning in cases with persistent TIMI flow grade 0. FW efficacy in vessels  $< 3.5$  mm (64% of treated coronary segments) has yet to be determined clinically. Finally, the principal end points of the present study were not evaluated by an independent, validated core laboratory, although the angiographic, echocardiographic, and ECG data were analyzed by reviewers other than the operators who were blinded to the treatment.

### Conclusions and Clinical Implications

Distal embolization during primary PCI is a frequent, if not obligatory, phenomenon. In this setting, adjunctive use of the FW is feasible and safe, and it may improve myocardial reperfusion by reducing the embolic burden.

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