

Safety and Efficacy of the FilterWire EZ in Acute ST-Segment Elevation Myocardial Infarction

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Primary percutaneous coronary intervention (PCI) for ST-segment elevation myocardial infarction (STEMI) achieves a high epicardial reperfusion rate; however, it is often suboptimal in achieving myocardial reperfusion due to distal embolization of atherothrombotic particles. The present study assessed whether the capture of embolic particles during PCI would improve myocardial reperfusion outcome. In a multicenter, prospective, randomized, controlled study, 100 patients with STEMI and coronary angiographic evidence of thrombotic occlusion were randomly assigned to PCI using the FilterWire EZ (n = 51) or a control group (n = 49) using regular guidewires. The FilterWire EZ was successfully delivered across the lesion in 84% of patients in the FilterWire EZ group. Primary efficacy end points, including markers of epicardial (Thrombolysis In Myocardial Infarction grade flow) and myocardial reperfusion (myocardial blush score and percent early resolution of ST-segment elevation), did not differ between the 2 study groups. Further, 60- and 90-minute percent ST-segment resolutions were identical in the 2 groups. In a subgroup analysis, a blush score of 3 was achieved in 94% of patients in whom the filter's landing zone was in a vessel diameter >2.5 mm compared with only 55% in those with smaller vessel diameter (p = 0.04). This corresponds to a better debris capture in filters located in large versus small vessels (p = 0.08). In conclusion, in patients with STEMI, use of the FilterWire EZ as an adjunct to primary PCI did not improve angiographic or electrocardiographic measurements of reperfusion compared with conventional PCI only. © 2007 Elsevier Inc. All rights reserved. (Am J Cardiol 2007;99:911–915)

Within the range of devices designed for protection of distal embolization, filter-based catheters are particularly “attractive” due to their ease of use, safety, and theoretical effectiveness.^{1,2} The present study was designed to explore the effect of a filter-based catheter during urgent ST-segment elevation myocardial infarction (STEMI) stent-based percutaneous coronary intervention (PCI) on tissue perfusion.

Methods and Results

This multicenter, prospective, randomized study (Use of Protective FilterWire to improve Flow in Acute Myocardial Infarction [UpFlow MI] study) was conducted in 5 interventional cardiology sites in Israel. Patients with STEMI undergoing revascularization <24 hours of chest pain onset were enrolled. Inclusion criteria were (1) ≥ 1 episode of typical anginal pain lasting >30 minutes within the preceding 24 hours, (2) ST-segment elevation ≥ 1 mm in 2 con-

tiguous leads, (3) coronary artery lesion deemed suitable for PCI and filter device application, and (4) coronary artery occlusion or angiographic appearance of fresh thrombus. Exclusion criteria were (1) a presumed distal vessel size <2.5 mm, (2) relevant coronary left main involvement, (3) vessel anatomy interfering with a safe placement of the filter device (e.g., extreme tortuosity or heavily calcified vessel proximal to the culprit lesion), (4) culprit lesion in a saphenous vein graft, (5) contraindication to glycoprotein IIb/IIIa inhibitors, aspirin, clopidogrel, or heparin, (6) cardiogenic shock, and (7) inability to provide informed consent. The study was approved by the institutional review board, and all participants gave written informed consent.

Immediately after diagnostic angiography, eligible patients were allocated to the FilterWire EZ or control group using a computer-generated, permuted blocks, random sequence selected by a statistician unknown to the investigators and attending medical team. After establishment of eligibility criteria, patients were randomized using sealed opaque envelopes prepared in advance by the study statistician who was not involved in performing the study. In patients allocated to the filter device group, the culprit lesion was crossed with a FilterWire EZ (Boston Scientific, Natick, Massachusetts), which was deployed at a distance closest to the culprit lesion to facilitate safe balloon dilation and stent placement. Details of the design and deployment technique of the filter have been previously described.^{1,3} If the filter device failed to cross the lesion, a second wire

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and/or predilation with a 2.0-mm balloon was introduced followed by additional attempts to cross the lesion with the FilterWire EZ. The filter device was left in place until the PCI procedure was completed. After retrieval, the filter was fixed in 4% formaldehyde (pH 7.0) and subjected to microscopic inspection by the same pathologist. In the 2 groups, PCI was performed with a bare metal stent as previously described.⁴ All patients received aspirin 500 mg intravenously or 200 mg orally before PCI, 70 U/kg of unfractionated heparin, and a loading dose of 300 mg of clopidogrel. Use of glycoprotein IIb/IIIa inhibitors was encouraged but left to the discretion of the operator.

Angiographic images were stored on compact disks and analyzed offline by an independent angiographic core laboratory (Cardiovascular Research Foundation, New York, New York). Thrombolysis In Myocardial Infarction (TIMI) flow grades and myocardial blush were assessed visually according to standard definitions.^{5,6} Quantitative coronary angiographic analysis was performed as previously described.^{7,8} Measurements of minimal luminal diameter, reference diameter, percent diameter stenosis, and diameter of the vessel at the "landing zone" of the filter wire were obtained. Acute gain was calculated as the difference between minimal luminal diameter after stenting and that before dilatation. Time to treatment was defined as the time elapsing from emergency room arrival to the wire crossing of the lesion. Major adverse cardiac events, including death, nonfatal myocardial reinfarction, and congestive heart failure, were monitored throughout the study. Diagnosis of recurrent myocardial infarction was based on typical chest pain, new ST-segment changes, and an increase in creatine kinase >50% over the previous level in ≥ 2 blood samples.^{9,10}

ST-segment resolution was determined by an independent electrocardiographic core laboratory (DCRI, Duke University, Durham, North Carolina) from paper electrocardiogram (ECG) at 0 minutes (enrolling ECG) and at 60 and 90 minutes in 34 patients and from continuous 24-hour digital 12-lead electrocardiographic recordings (Northeast Monitoring 180, Boston, Massachusetts) in 53 patients. The continuous electrocardiographic recording was initiated before catheterization and continued for 24 hours. Instrumentation and core laboratory analysis methods employed have been previously published.^{6,7} ST-segment levels were measured 60 ms after the J-point in the lead with maximal ST-segment elevation. ST-segment recovery was determined by comparing ECGs recorded at different intervals after the last contrast injection, with the most abnormal ECG in the data recorded between study enrollment and arrival in the catheterization laboratory. Changes during the interventional procedure were excluded from analysis. Percent ST-segment resolution was categorized using the Schroeder classification as complete (>70%), partial (30% to 70%), or absent (<30%).^{4,11} The primary end point was prespecified as the dichotomous rate of complete ST-segment resolution measured 60 and 90 minutes after the last contrast injection.

All data were analyzed on an intention-to-treat basis and according to protocol (patients who actually received the filter). Discrete variables are reported as percentages and continuous variables as means \pm SDs or medians and in-

Table 1

Baseline demographic, clinical, and angiographic characteristics of the study population

Variable	Filter Wire (n = 51)	Controls (n = 49)	p Value
Age (yrs)	60 \pm 12	57 \pm 10	0.28
Women	18%	18%	0.96
Diabetes mellitus	22%	23%	0.87
Hypertension	44%	51%	0.27
Hypercholesterolemia (>200 mg/dl)	48%	50%	0.84
Smokers	43%	44%	0.92
Previous myocardial infarction	12%	11%	0.89
Previous coronary bypass grafting	0%	2%	0.31
Previous PCI	12%	14%	0.71
Chest pain to emergency room (h)	3.0 (1.5–7.0)	2.0 (1.1–3.0)	0.004
Emergency room to wire cross (h)	1.5 (0.8–2.3)	1.5 (1.2–2.3)	0.27
Peak ST-segment elevation (mm)	3.0	3.4	
Use of glycoprotein IIb/IIIa inhibitors	74%	77%	0.72
Left ventricular ejection fraction*	47%	44%	0.56

Values are means \pm SDs, percentages of patients, or medians (interquartile ranges).

* First evaluation after the procedure by ventriculography or echocardiography.

terquartile ranges. To test differences between treatment groups, we used Fisher's exact test or chi-square test, as appropriate, for discrete variables and 1-way analysis of variance for continuous variables. Some analyses of continuous variables were corroborated by nonparametric testing with the Mann-Whitney U test. The same models were used to assess the interaction of the study treatment with time from onset of pain to PCI with regard to our primary end point. SAS 8.2 (SAS Institute, Cary, North Carolina) was used for all statistical analyses. In the 2-tailed test, $p = 0.05$ was regarded as statistically significant.

The study comprised 100 consecutive patients with STEMI, 51 of whom were assigned to the FilterWire EZ and 49 to conventional PCI (control group) using a standard 0.014-inch floppy guidewire. There were no significant differences between groups regarding baseline demographic, clinical, and angiographic characteristics (Tables 1 and 2), except for preprocedural TIMI grade flow and time to treatment. Median time from chest pain onset to emergency room admission of all 100 study participants was significantly (1 hour) longer in the filter than in the control group ($p = 0.004$); however, the time lapse from emergency room arrival to wire crossing of the lesion was the same ($p = 0.27$; Table 1). Nevertheless, median time from chest pain onset to emergency room in the 63 patients who arrived <6 hours or 80 patients who arrived <12 hours from chest pain onset to the emergency room was not significantly different between groups (1.8 vs 1.5 hours, $p = 0.29$; 1.8 vs 1.8 hours, $p = 0.18$, respectively). Further, time lapse from emergency room admission to wire crossing of the lesion was similar in the 2 study groups who arrived at the emergency room <6 or <12 hours from onset of chest pain.

Although most patients in the 2 groups had an occluded infarct-related artery (TIMI grade 0/1 flow), the rate was higher in those assigned to the usual therapy than in those

Table 2
Procedural and quantitative angiographic data of target lesion

Variable	Filter Wire (n = 51)	Controls (n = 49)	p Value
Infarct coronary artery			
Left anterior descending	51%	53%	0.32
Left circumflex	14%	10%	0.77
Right	35%	37%	0.58
Vessel diameter (mm)	3.0 ± 0.5	3.1 ± 0.5	0.78
Minimal luminal diameter (mm)	0.18 ± 0.4	0.19 ± 0.3	0.92
Lesion location			
Proximal	49%	39%	0.31
Middle	49%	55%	0.55
Lesion length (mm)	22.8 ± 9	23.3 ± 9	0.69
Wire technical success*	84%	100%	
Cross as first wire	56%	—	
Cross with buddy wire	12%	—	
Cross after balloon dilatation	16%	—	
Debris present	52%	—	
Procedural success†	88%	94%	0.22

Data are expressed as mean ± SD or percentage of patients.

* Technical success was defined as successful delivery of the wire to the intended target site.

† Procedural success was defined as a final diameter stenosis <50% and TIMI grade ≥2 flow.

— = no information.

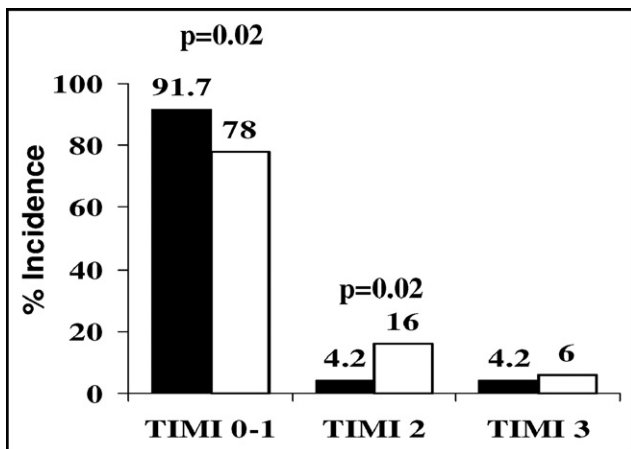


Figure 1. Preprocedural epicardial TIMI grade flow of the control group (n = 49) (black bars) and FilterWire group (n = 51) (white bars).

assigned to the filter wire (92% vs 78%, $p = 0.02$, respectively; Figure 1). However, TIMI grade 0/1 flow was similar in the 2 study groups in the 63 patients arriving at the emergency room <6 hours or the 80 patients who arrived <12 hours from chest pain onset.

The FilterWire EZ was successfully placed as the first and only wire used in only 23 patients (56%). Six patients (12%) required a second “buddy wire” and 8 (16%) underwent predilatation using an undersized balloon. However, in 8 patients (16%), the device could not be advanced beyond the lesion despite several technical maneuvers, mainly due to vessel tortuosity and/or calcification.

Although microscopic inspection showed captured debris in 52% of filters, there were no differences in postprocedural TIMI flow grade or myocardial blush score (Figures 2 and 3) in the 2 study groups, even when analyzing data of

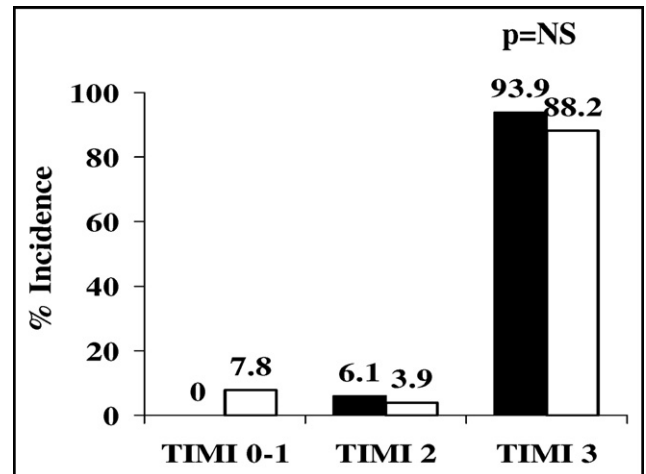


Figure 2. Final procedural epicardial TIMI grade flow of the control group (n = 48) (black bars) and FilterWire group (n = 49) (white bars).

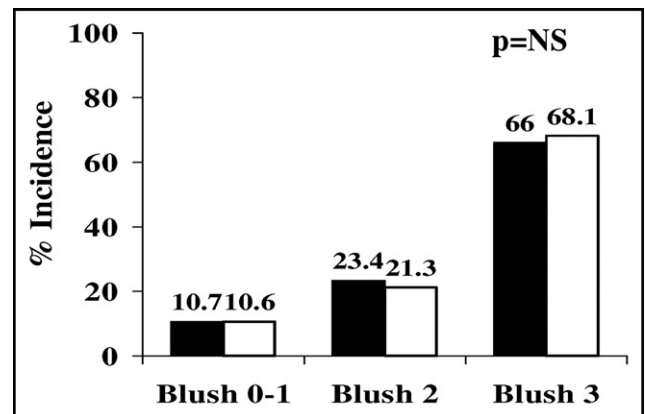


Figure 3. Final procedural myocardial blush score of the control group (n = 48) (black bars) and FilterWire group (n = 49) (white bars).

the 63 patients arriving <6 hours or 80 patients arriving <12 hours at emergency room admission from chest pain onset.

The 2 groups were similar regarding 60- and 90-minute percent ST-segment resolution, even in the 63 patients arriving <6 hours or 80 patients arriving <12 hours from chest pain onset to emergency room admission. Sixty-six percent of study participants had complete, 25% had partial, and 10% had no ST-segment resolution (Figure 4). Complete ST-segment resolution at 30 minutes from the last contrast injection was also the same in the 2 groups (Figure 5).

The FilterWire EZ was designed for optimal use in vessels ≥3 mm. In a subgroup analysis (n = 42), a blush score of 3 was achieved in 94% of patients in whom the filter’s landing zone was in a vessel >2.5 mm in diameter compared with only 55% in those with a smaller vessel diameter ($p = 0.04$). This corresponds to a better microscopic debris capture in filters located in large versus small vessels (58% vs 37%, $p = 0.08$).

During 30-day follow-up, 4 patients (4%) developed major adverse cardiac events. Two patients (4.5%) from the filter wire group and none from the control group died ($p =$

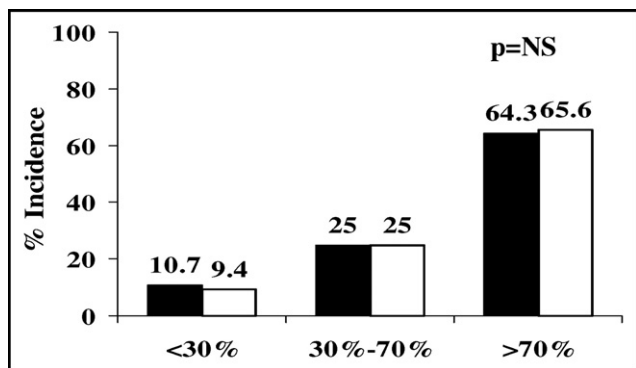


Figure 4. Percent ST-segment resolution at 60 minutes categorized as complete (>70%), partial (30% to 70%), or absent (<30%) ST-segment resolution using the Schroeder classification in the control (black bars) and FilterWire (white bars) groups.

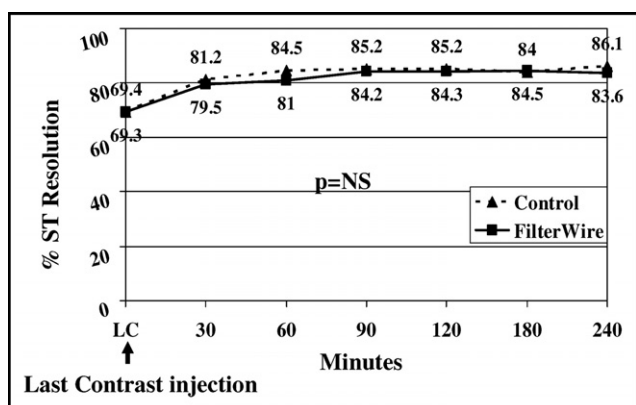


Figure 5. Mean percent ST-segment resolution from last contrast (LC) injection in the study cohort.

0.17); 1 developed a hemorrhagic stroke on day 1 and died within a week and the other patient died of septic shock on day 4. Recurrent myocardial infarction was observed in 1 patient (2.3%) in the control group and none in the FilterWire group (p = 0.33). Angina pectoris after myocardial infarction was observed in 1 patient (2.4%) in the filter group and none in the control group (p = 0.30). There was no incident of congestive heart failure during 30-day follow-up in any study participant.

Discussion

The use of the FilterWire EZ distal protection device in patients undergoing primary PCI for STEMI did not improve angiographic epicardial coronary blood flow or myocardial tissue reperfusion as assessed by ST-segment resolution and myocardial blush score.

The ability of the filter wire to capture thromboembolic debris has been described in previous studies and the safety and feasibility of the FilterWire EZ in patients with acute myocardial infarction previously suggested by Limbruno et al,¹ Giri et al,¹² and Henriques et al.¹³ In this study, angiographically visible distal embolization occurred in only 2% of patients with filter wire protection compared with 15% in a matched case-control group (p = 0.03), although captured debris was found in all microscopically examined filters.

Accordingly, compared with a matched case-control group, the filter wire significantly improved ST-segment resolution and corrected TIMI frame count. Our myocardial perfusion findings contradict those of Limbruno et al,¹ whose findings should be interpreted cautiously because their study was nonrandomized with a limited sample and a low rate of postinterventional TIMI grade 3 flow (85%) in the control group. The results of our present study are in concordance with 2 relatively large prospective randomized trials, the Enhanced Myocardial Efficacy and Recovery by Aspiration of Liberalized Debris (EMERALD)¹⁴ and the Protection Devices in PCI Treatment of Myocardial Infarction for Salvage of Endangered Myocardium (PROMISE)¹⁵ studies. The PROMISE study, which randomized 200 patients with non-STEMI and STEMI to distal protection, used the FilterWire EX (a previous prototype of the FilterWire EZ) or no protection during primary PCI and demonstrated that the filter wire was as effective in capturing embolic debris as in our UpFlow MI study. A possible explanation for the negative results of the PROMISE trial could be due to the inclusion criteria, which differed from those in our study: (1) patients with non-STEMI and STEMI were enrolled in the PROMISE trial compared with only patients with STEMI in our study; (2) the PROMISE study enrolled patients <48 hours from symptom onset compared with <24 hours in our study; and (3) 1 inclusion criterion in the PROMISE trial was increased myocardial markers. These discrepancies raise the possibility of a belated attempt to decrease myocardial damage in the PROMISE trial. However, this explanation is not supported by the negative results of our study. Another important limitation of the PROMISE study was the use of the FilterWire EX, which was replaced by the manufacturer with the EZ version to improve the centering of the device in the vessel to improve its capturing capabilities. However, the relatively lower crossing success of the EZ filter (84%), the need for balloon predilation in 16% of patients, and the 95% crossing success in PROMISE but with a 50% need for balloon predilation probably contributed to the failure of the 2 studies to effectively protect myocardial perfusion. In lieu of the PROMISE and our present study results, it appears more likely that distal embolization after primary PCI, which may be prevented by protection devices, exerts only minor effects compared with consequences of ischemic microvascular damage^{16,17} or spontaneous distal embolization arising from ruptured or eroded plaques during the natural course of acute myocardial infarction insult.^{18,19} Moreover, catheter device-induced myocardial damage may play a role in compromising the clinical benefit of distal protection. This theory is supported by the EMERALD study, which used a balloon occlusion system for distal protection.¹⁴

Although this was a randomized study, there was a 1-hour median time difference from chest pain onset to emergency room arrival between the 2 treatment arms. We cannot exclude the possibility that the longer lapse from chest pain to emergency room arrival impaired myocardial microcirculation before the procedure in the FilterWire group, thus limiting its efficacy, although improved preprocedural TIMI flow grades counteract this assumption. However, when analyzing those patients who arrived <6 or ≤12 hours from chest pain onset to hospital admission, there

were no significant differences between the 2 study groups with regard to their primary outcomes, including TIMI and blush scores before and after the procedure and 60- and 90-minute percent ST-segment resolutions. Because debris was noted in only 52% with use of the FilterWire EZ, a substantial amount of debris might have already embolized before the procedure or even with the FilterWire placement, thus decreasing its clinical efficacy. With longer time from pain onset, further irreversible myocardial damage at the time of reperfusion may be expected and additional thrombus material, which might have already been embolized distally, could affect the microvasculature. Due to technical problems we were able to perform complete analysis of ST-segment resolution in only 87% of patients and therefore unable to study the effectiveness of the FilterWire EZ on ST-segment resolution according to vessel size.

We conclude that this study does not provide a rationale for routine use of the FilterWire EZ as an adjunct to primary PCI in myocardial infarction.

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