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EXPEDITED REVIEW

Distal Filter Protection During Saphenous Vein Graft Stenting: Technical and Clinical Correlates of Efficacy

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OBJECTIVES The aim of this study was to evaluate the clinical, angiographic, and technical factors related to successful stenting of diseased saphenous vein grafts (SVGs) using a novel filter-based distal protection device.

BACKGROUND Protection of the distal microvasculature with a balloon occlusion and aspiration system has been shown to reduce atherothrombotic embolization and peri-procedural myocardial infarction (MI) after percutaneous coronary intervention (PCI) in SVGs. The safety, efficacy, and technical factors relating to procedural success with filter-based distal protection devices are unknown.

METHODS Percutaneous coronary intervention was performed in 60 lesions in 48 patients undergoing SVG intervention with the FilterWire EX distal protection system in a phase I experience at six sites. A larger phase II study was then performed in 248 lesions in 230 SVGs at 65 U.S. centers.

RESULTS Cumulative adverse events to 30 days occurred in 21.3% of patients in phase I, including a 19.1% rate of MI. Numerous anatomic, device-specific, and operator-related contributors to these adverse events were identified, resulting in significant changes to the protocol and instructions for use. Subsequently, despite similar clinical and angiographic characteristics to the phase I patients, the 30-day adverse event rate in phase II was reduced to 11.3% ($p = 0.09$), due primarily to a lower incidence of peri-procedural Q-wave and non–Q-wave MI.

CONCLUSIONS Distal protection during SVG PCI with the FilterWire EX is associated with a low rate of peri-procedural adverse events compared to historical controls. A unique set of anatomic, technical, and operator-related issues exist with distal filters which, if ignored, may reduce their effectiveness. (J Am Coll Cardiol 2002;40:1882–8i) © 2002 by the American College of Cardiology Foundation

Embolization of atherothrombotic debris after percutaneous coronary intervention (PCI) in diseased saphenous vein grafts (SVGs) results in peri-procedural myocardial infarction (MI) in as many as one-third of patients (1–4). Of numerous investigated approaches (5–11), only protection of the distal microcirculation by a balloon occlusion and aspiration system (the PercuSurge GuardWire) has been clearly demonstrated to enhance the safety of contemporary SVG intervention (12).

Catheter-based filters as an adjunct to SVG intervention have recently entered clinical investigation (13–15). Characterized by their relative ease of use and maintenance of perfusion, distal filters may at first seem inherently preferable to balloon occlusion and aspiration systems. However, the safety and efficacy of distal filters have not yet been demonstrated. Therefore, we performed two consecutive prospective, multicenter registries with a new distal protection device, the FilterWire EX (Embolic Protection Inc., Boston Scientific Corp., Natick, Massachusetts), to examine its effectiveness during PCI of SVGs, and to uncover technical and device related factors impacting procedural success.

METHODS

Before initiation of the pivotal U.S. randomized trial for device approval, the FilterWire EX was evaluated in a phase I study at six sites. After review of the phase I 30-day data, the multicenter pivotal phase II study commenced with a lead-in stage at 65 centers enrolling up to five patients per site. Both studies were performed under a Food and Drug Administration (FDA) investigational device exemption. The studies were approved by the investigational review board at each participating institution, and all patients signed written, informed consent before study entry.

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Abbreviations and Acronyms

GP = glycoprotein
LVEF = left ventricular ejection fraction
MACE = major adverse cardiac events
MI = myocardial infarction
PCI = percutaneous coronary intervention
SVG = saphenous vein graft
TIMI = Thrombolysis In Myocardial Infarction
TLR = target lesion revascularization

Study device. The FilterWire EX consists of a distal polyurethane filter with 80 to 110 μm diameter pores mounted on a 0.014-inch steerable guidewire via a "spinner tube" which permits independent 360° wire rotation and steering (Fig. 1). The filter is attached to a self-expandable radiopaque nitinol loop which is elliptical in shape, affording maximal surface area for particle capture and compatibility with vessels 3.5 to 5.5 mm in diameter with the same device. The collapsed filter (3.9F crossing profile) is passed distal to the lesion and deployed by retracting the delivery sheath. The filter is then closed with the delivery/retrieval sheath after PCI and withdrawn.

Phase I study—Patient entry criteria. Consecutive patients with ≥1 eligible SVG lesions meeting the following inclusion criteria were enrolled: age ≥21 years; lesion length <40 mm, reference vessel diameter 3.5 to 5.5 mm, diameter stenosis <100% and Thrombolysis In Myocardial Infarction (TIMI) flow grade ≥2; and presence of ≥2 cm of straight segment in the SVG distal to the lesion. Major exclusion criteria included: MI within 24 h or CK-MB >2× normal; contrast or study medication contraindication; treatment required in non-qualifying vessels; left ventricular ejection fraction <30%; and planned treatment with atherectomy, thrombectomy, laser or other distal protection devices.

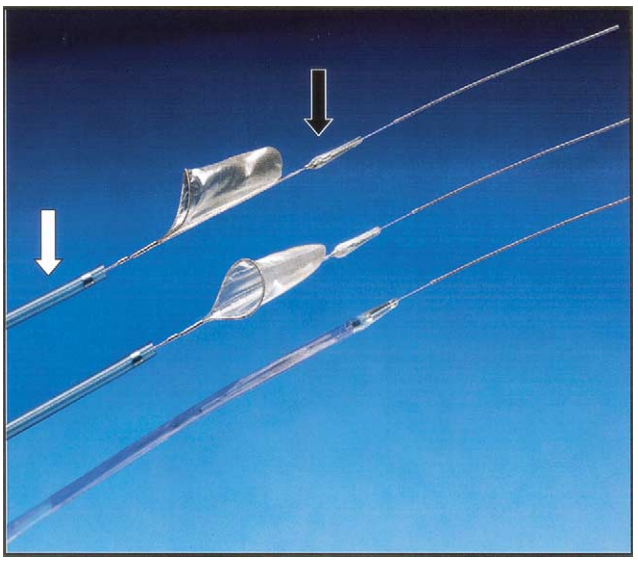

Figure 1. The FilterWire EX, consisting of a 0.014-inch steerable guidewire on which a freely rotating distal polyurethane filter is mounted, shown in its deployed configuration **(top and middle)** and retracted position **(bottom)** after being withdrawn into the delivery/retrieval sheath **(white arrow)**. A distal nosecone **(black arrow)** prevents passage of the sheath beyond the wire tip

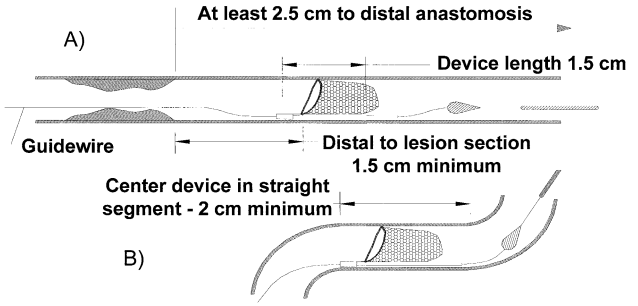

Figure 2. Diagrammatic representation of the FilterWire across a vein graft lesion, with the minimal distances pre-specified in the phase II protocol for optimal performance.

Phase I study—Study procedures. All patients received aspirin before the procedure and indefinitely thereafter. Clopidogrel (or ticlopidine) was recommended before the procedure and continued for 30 days after stent placement. An activated clotting time of >300 s was achieved before PCI, or 200 to 300 s if glycoprotein (GP) IIb/IIIa inhibitors were administered (per investigator discretion). Percutaneous coronary intervention was then performed with FilterWire distal protection. CK-MB levels were measured at baseline and every 8 h ×3 post procedure. Clinical follow-up occurred at 30 days.

Phase I failure analysis. Given a higher than expected adverse event rate in phase I, a detailed failure analysis was performed, including procedural technique and angiographic review. As described in the Results, four correctable technical errors were identified that appeared causally related to major adverse cardiac events (MACE). These technical issues were addressed in the phase II protocol and received repeated emphasis at a series of investigator meetings and study conferences.

Phase II study protocol and procedures. Compared with phase I, the phase II entry criteria allowed inclusion of *more complex* lesions, including vessels with TIMI-1 flow, and lesions of any length. Otherwise the phase I and II enrollment criteria were similar. The phase II protocol incorporated five important changes in technique and operator instructions: 1) a ≥2.5-cm gap before the distal anastomosis was required for placement of the filter apparatus distal to the lesion; 2) the FilterWire loop was required to be placed in the mid portion of a ≥2-cm straight section of the SVG to avoid deformation of the device (Fig. 2); 3) orthogonal views were mandated to document appropriate filter apposition before dilation; 4) specific instructions were provided *not* to retract the entire debris-laden filter into the sheath; and 5) the importance of established distal protection during all SVG dilations was emphasized.

End points and definitions. Study end points and definitions were identical for both registries. The primary end point was the incidence of MACE at 30 days, defined as

Table 1. Baseline Clinical and Angiographic Characteristics of Patients Enrolled in the Phase I and Phase II Registry Studies

	Phase I	Phase II	p Value
Clinical features			
N patients	48	230	—
Age (yrs)	69.9 ± 9.2	69.5 ± 9.7	0.79
Gender (male)	78.7%	82.7%	0.53
Hypertension	93.6%	77.0%	0.01
Hyperlipidemia	78.7%	88.3%	0.10
Diabetes mellitus	44.7%	35.0%	0.24
Cigarette smoking within past year	4.3%	16.1%	0.04
Prior stroke or transient ischemic attack	10.6%	18.3%	0.28
Prior MI	66.7%	62.0%	0.61
Angina class			
1	6.7%	4.3%	0.45
2	6.7%	19.6%	0.06
3	44.4%	35.9%	0.31
4	42.2%	40.2%	0.87
Graft age (yrs)	10.4 ± 5.8	11.0 ± 5.3	0.40
Target vessel			
SVG to LAD	26.3%	19.6%	0.27
SVG to LCX	33.3%	40.2%	0.44
SVG to RCA	40.4%	40.2%	0.99
LVEF	47% ± 11%	49% ± 12%	0.03
Quantitative coronary angiography (core lab)			
N lesions	60	248	
Thrombus present	64.9%	65.3%	0.98
Eccentricity	42.1%	55.3%	0.10
Ulceration	24.6%	20.1%	0.47
Calcification	8.8%	8.5%	0.96
Angulation (>45°)	0%	3.5%	0.39
Type B_2/C lesions	89.5%	81.4%	0.44
Reference vessel diameter pre (mm)	3.55 ± 0.6	3.46 ± 0.7	0.38
Minimal luminal diameter pre (mm)	1.22 ± 0.6	1.26 ± 0.5	0.61
Diameter stenosis pre (%)	66 ± 13	63 ± 14	0.20
Lesion length pre (mm)	15.5 ± 10.2	13.9 ± 9.1	0.24
TIMI flow pre			
0/1	7.0%	2.5%	0.36
2	7.0%	14.1%	0.18
3	86.0%	83.4%	0.84

LAD = left anterior descending artery; LCX = left circumflex artery; LVEF = left ventricular ejection fraction; MI = myocardial infarction; RCA = right coronary artery; SVG = saphenous vein graft; TIMI flow = Thrombolysis In Myocardial Infarction flow grade.

death, MI, or target lesion revascularization. Myocardial infarction was defined as any postprocedural CK-MB >3× normal.

Data collection, quality assurance, and statistical analysis. Data were independently monitored on-site for accuracy, and double-key entered into a computerized database by an independent research organization. An independent Clinical Events Committee adjudicated all adverse outcomes. Quality control measures included use of independent angiographic and electrocardiographic core laboratories. These processes and the organizations employed were identical for both studies.

Categorical variables were compared by chi-squared analysis or Fisher exact test. Continuous variables are presented as mean ± standard deviation and were compared by unpaired Student *t* test. All p values are two-tailed. Significance was determined at the p = 0.05 level. The independent determinants of 30-day MACE in the phase II cohort were determined by entering all variables predictive of adverse outcomes by univariate analysis with a p value <0.10 into a multivariate logistic regression model.

RESULTS

Phase I and phase II patient populations. Between October 2000 and April 2001, 48 consecutive patients underwent intervention of 60 SVG lesions with FilterWire distal protection in the phase I study. Subsequently, between May 2001 and April 2002, 230 consecutive patients underwent intervention of 248 SVG lesions with FilterWire distal protection during the roll-in period of the phase II study. The baseline demographic and lesion characteristics of the two study cohorts were similar, except hypertension was more common in phase I, patients in phase II were more

Table 2. 30-Day Adverse Cardiac Events in 48 Patients Undergoing SVG Intervention of 60 Lesions With FilterWire Distal Protection in the Phase I Registry

Death	2.1%
MI	19.2%
Q-wave MI	2.1%
non–Q-wave MI	17.1%
TLR	0%
Any major adverse cardiac event	21.3%

MI = myocardial infarction; SVG = saphenous vein grafts; TLR = target lesion revascularization.

likely to be active smokers, and left ventricular function was slightly better in phase II (Table 1).

Results of phase I. The FilterWire was successfully delivered and deployed in 95.7% of cases. Postprocedural TIMI-3 flow was present in 94.7% of grafts, TIMI-2 flow in 3.5%, and TIMI-0/1 flow in 1.8%. In-hospital MACE occurred in 18.8% of patients prior to hospital discharge, and in 21.3% of patients by 30 days. As shown in Table 2, most events consisted of peri-procedural MI.

Failure analysis. Detailed procedural and angiographic analysis of the 10 cases in which MACE occurred revealed the following possible causative factors (several of which were present in some patients): wire bias or geometric factors resulting in filter loop malapposition (Fig. 3), n = 3; excessively distal lesion location such that the filter could not open properly or was placed in a native coronary vessel, leaving proximal branches unprotected (Fig. 4), n = 4; balloon dilations and/or stent implantations performed without distal protection (excluding pre-dilation), n = 4; SVG diameter 7 mm with resultant filter malapposition, n = 1; filter placed in a single distal limb of a bifurcating Y graft, such that the other limb was unprotected, n = 1; and heavily loaded filter completely retracted into the delivery sheath, resulting in atheromatous extrusion and embolization, n = 1.

Results of phase II. The FilterWire was successfully delivered and deployed in 96.5% of cases. Stent use, implantation parameters, and procedural outcomes were similar to phase I, except that GP IIb/IIIa inhibitors were used more frequently (Table 3). Angiographic complications, as determined by the core laboratory, were less frequent in phase II compared with phase I, with fewer episodes of no reflow and distal thromboemboli noted. Moreover, 30-day cumulative MACE occurred in fewer patients in phase II than in phase I, predominantly because of a lower rate of peri-procedural MI (Fig. 5). From 18 baseline variables, the only univariate correlates of 30-day MACE in patients undergoing SVG intervention with FilterWire distal protection were longer lesion length, greater diameter stenosis, and the presence of thrombus (Table 4); by multivariate analysis, only long lesion length was independently predictive of MACE (odds ratio = 3.69, p = 0.015).

DISCUSSION

The present report details a large multicenter experience with FilterWire distal protection as an adjunct to PCI in 308 lesions in 278 SVGs. Use of this device resulted in 30-day rates of MACE below that expected from historical controls. Moreover, during the course of this sequential two-phase investigation, a unique set of anatomic, technical, and operator-related issues were uncovered which, if ignored, may reduce the effectiveness of the FilterWire.

Phase I results and failure analysis. A disturbingly high 21.3% 30-day event rate occurred in the first 60 lesions in

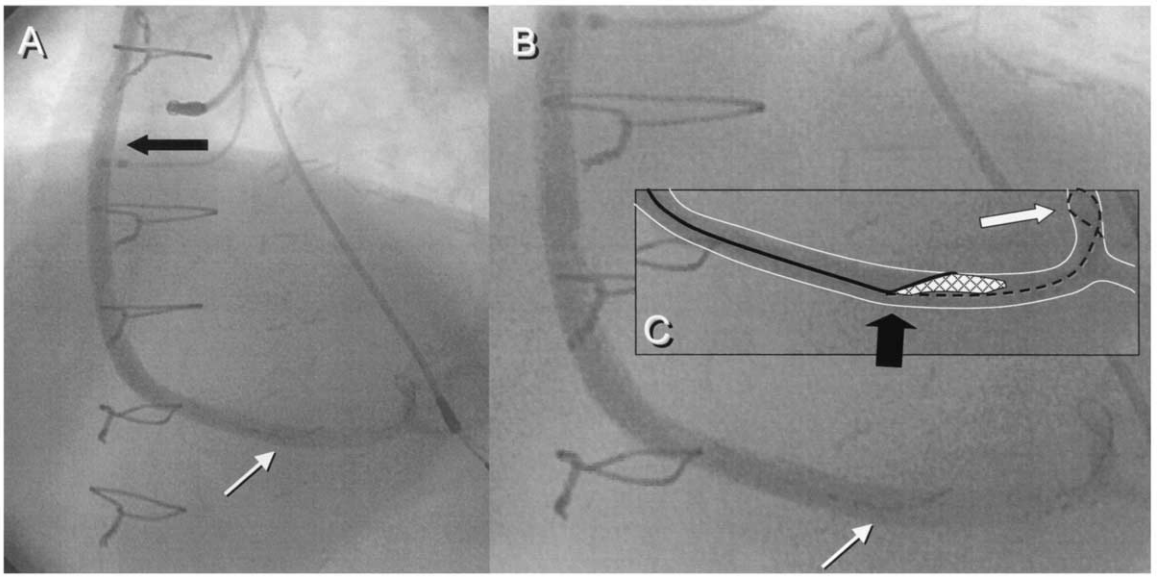

Figure 3. Potential failure mode—lack of filter apposition against the vessel wall. **(A)** Post-stenting of the mid shaft of the saphenous vein graft to the right coronary artery **(black arrow)** with the FilterWire in place **(white arrow)**. **(B)** Magnification of **panel A**—the nitinol loop of the FilterWire may be seen. **(C)** Further magnification and enhancement of the FilterWire, showing that the nitinol loop **(black arrow)** and collection filter **(cross hatched net)** are clearly lifted off the inferior wall of the vein graft, likely due to geometric wire bias resulting from placement of the distal wire tip in the posterolateral branch **(white arrow)**. Relocating the guidewire tip into the more inferior posterior descending artery may have apposed the filter loop against the vein graft wall.

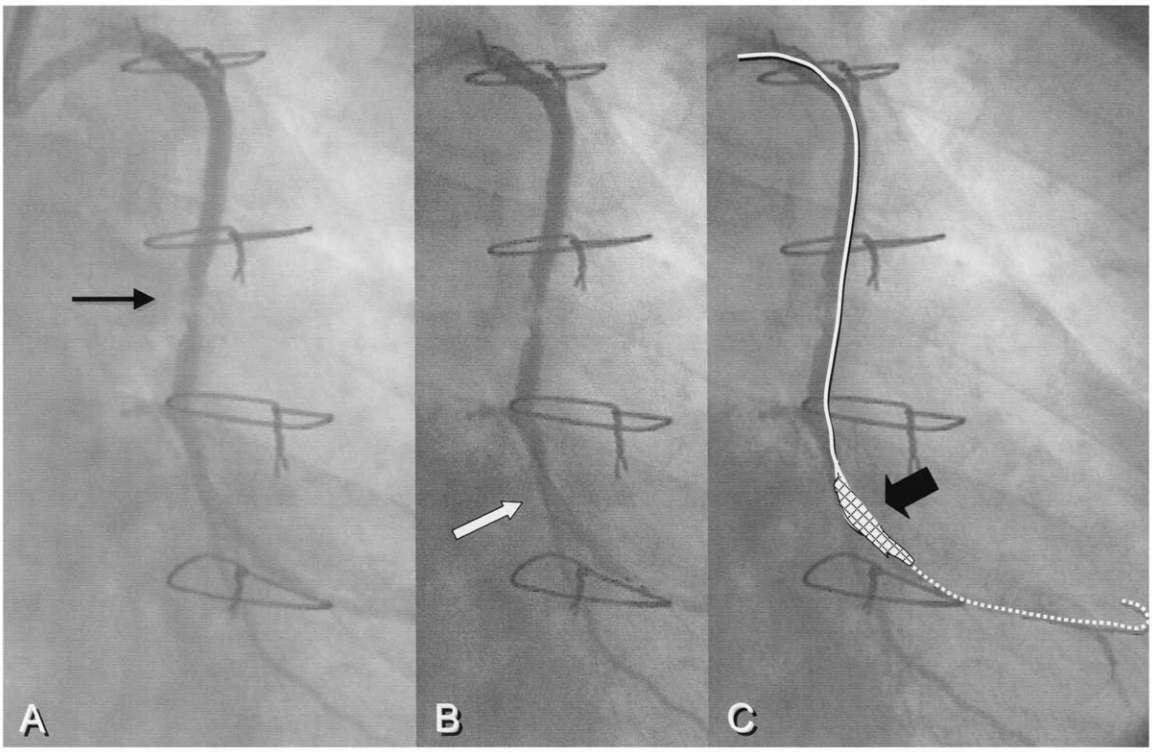

Figure 4. Potential failure mode—excessively distal lesion resulting in incomplete filter opening or unprotected native side branches. **(A)** Ulcerated lesion **(arrow)** in the distal shaft of the saphenous vein graft to the obtuse marginal branch of the left circumflex artery. **(B)** FilterWire deployed, with the distal nitinol loop protruding into the upper branch of the bifurcating obtuse marginal **(arrow)**. **(C)** As a result, the polyurethane collection filter **(arrow and cross hatched net)** cannot open fully and is compressed in the undersized branch (<3.0 cm), impairing particulate recovery both in the partially protected superior branch and unprotected inferior branch.

48 SVGs, similar to that expected from historical controls. A detailed failure analysis revealed several correctable conditions that may have contributed to adverse events. Several of these issues were intuitive (performance of dilation without protection in place), whereas others were clearly operator- or device-specific.

First, several cases of distal embolization were temporally related to balloon dilation without the protection device in place. Typically the device had been removed after an apparently successful result, following which residual disease or dissection were noted requiring further intervention, which was performed without protection either because of

Table 3. Procedural Results, Comparing Patients Enrolled in Phase I and Phase II

	Phase I	Phase II	p Value
N patients	48	230	—
N lesions	60	248	—
Lesions stented	96.7%	96.6%	0.99
N stents per patient	1.24 ± 0.4	1.16 ± 0.4	0.25
Total stent length (mm)	25.2 ± 13.1	22.2 ± 12.0	0.09
Maximum stent diameter (mm)	4.03 ± 1.3	4.13 ± 0.6	0.44
Maximum implantation pressure (atm)	13.8 ± 1.9	14.7 ± 4.1	0.11
Glycoprotein IIb/IIIa inhibitor use	29.8%	52.2%	0.01
No reflow	12.3%	5.0%	0.07
Visible distal thromboemboli	10.5%	3.0%	0.03
Abrupt closure	5.3%	2.5%	0.38
Quantitative coronary angiography (core lab)			
Reference vessel diameter post (mm)	3.60 ± 0.6	3.48 ± 0.7	0.24
In-lesion minimal luminal diameter post (mm)	3.07 ± 0.7	3.00 ± 0.7	0.51
In-lesion diameter stenosis post (%)	15% ± 15%	13% ± 12%	0.47
TIMI flow post			
0/1	1.7%	2.0%	0.97
2	3.4%	3.5%	0.99
3	94.9%	94.5%	0.93

TIMI flow = Thrombolysis In Myocardial Infarction flow grade.

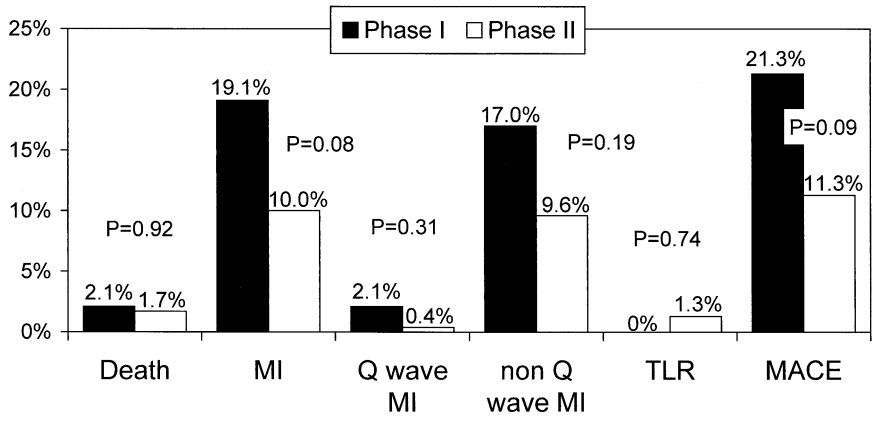

Figure 5. Cumulative 30-day major adverse cardiac event (MACE) rates in 48 patients in the phase I study compared to 230 patients in the phase II study. MI = myocardial infarction; TLR = target lesion revascularization.

difficulty in recrossing the treated zone or perceived low embolic potential. These cases reinforce the difficulty in predicting embolic risk during SVG intervention and emphasize the need for distal protection during all phases of the procedure. Similarly, placing the filter distal to a side-to-side Y-graft anastomosis will clearly allow emboli in the unprotected proximal branch.

A second and unexpected correlate of peri-procedural MI was the lack of optimal filter apposition against the SVG wall. Because even a freshly placed filter offers a modest flow barrier, blood perfusate containing embolic particles will take the path of least resistance, selectively shunting debris around the filter when possible. The most common cause of lack of filter apposition was lifting of the nitinol wire frame off the vessel wall due to wire bias from anatomic and geometric factors. Notably, this condition may be hidden when the filter is viewed *en face*, only to be revealed by observing the filter loop on edge in an orthogonal projection. This condition may at times be corrected by moving the filter apparatus to a straighter portion of the vessel, or redirecting the distal guidewire into another branch (Fig. 3). Moreover, as the unrestrained diameter of the nitinol loop is ~6 mm, positioning the distal apparatus in an oversized segment will by definition also result in malapposition.

A third cause of MACE was overestimation of the distance from the lesion to the distal anastomosis, resulting in the collection net being released in a native arterial branch, with either subsequent narrowing of the collection aperture or lack of protection of secondary branches.

Table 4. Variables Correlating With MACE Within 30 Days

Patient Characteristic	% MACE With Variable Present	% MACE With Variable Absent	p Value
Age > 70 yrs	10.3%	13.0%	0.68
Male gender	11.2%	12.8%	0.78
Hypertension	10.3%	15.4%	0.33
Diabetes	6.3%	14.3%	0.08
History of MI	12.4%	10.7%	0.83
Renal insufficiency	12.5%	11.3%	0.77
SVG age >10 yrs	11.7%	12.5%	0.91
LVEF > median	9.4%	12.2%	0.66
Reference vessel diameter > median	13.6%	10.8%	0.65
Minimal lumen diameter > median	11.2%	13.0%	0.82
Diameter stenosis > median	17.8%	6.6%	0.02
Lesion length > median	18.2%	5.7%	0.02
Baseline TIMI flow <3	18.8%	10.7%	0.23
Thrombus present	15.8%	4.9%	0.05
Eccentric lesion	12.5%	11.7%	0.95
Angulated lesion (>45°)	14.3%	12.1%	0.92
IIb/IIIa inhibitor used	13.3%	9.1%	0.31

LVEF = left ventricular ejection fraction; MACE = major adverse cardiac events; MI = myocardial infarction; SVG = saphenous vein graft; TIMI flow = Thrombolysis In Myocardial Infarction flow grade.

Phase II results. As a response to this analysis, the phase II protocol and Instructions for Use were modified, and an intense education campaign was initiated for all sites, consisting of investigator meetings, written communications, and teleconferences. Orthogonal views were mandated to detect filter loop malapposition; the distance required from the lesion to the distal anastomosis was increased; a straight section for the distal apparatus was required; instructions were given to retract the filter into the retrieval sheath just enough to close the nitinol loop; and the importance of established distal protection during all phases of the intervention was emphasized. In the large phase II experience consisting of SVG intervention in 248 lesions in 230 vessels at 65 sites, the MACE rate was reduced to 11.3%, approximately 50% lower than in phase I (despite nearly identical patient and vein graft characteristics), due largely to reductions in Q-wave and non–Q-wave MI. These improved results are especially notable given the greater number of sites with less experience in phase II, representing a real-world example of how early lessons learned may be effectively communicated to future operators.

An additional observation that deserves mention pertains to GP IIb/IIIa inhibitor use, which by operator choice was more common in phase II than phase I. Although

GP IIb/IIIa inhibitors have not been found to be beneficial as an adjunct to PCI in SVGs (6), it is conceivable that by reducing platelet-fibrin deposition on the filter surface, GP IIb/IIIa inhibitors might diminish the slow flow state that can occur when filters become overloaded, a phenomenon which has been related to MACE.

Other causes of MACE and device enhancements. Despite the improved outcomes in phase II, the fact that 10% of patients still developed peri-procedural MI in phase II suggests that other device- and operator-related variables may still result in MACE and highlights the need for future device enhancements. The MACE rates were increased approximately three-fold with long lesions, high-grade baseline stenoses, and in the presence of thrombus, emphasizing that particular care is warranted when intervening in SVGs with these characteristics, even with filter-based distal protection. Macroscopic or angiographically unapparent distal thromboemboli may be induced by guidewire or device crossing of high-grade friable lesions, suggesting that outcomes might be improved by more steerable, flexible, and lower profile catheters. Debris collection may be incomplete as smaller particles may pass through the filter pores, and an excessively burdened filter may pose challenges for loop closure and debris retrieval without material extrusion. Future FilterWire iterations will incorporate a self-centering mechanism to reduce the impact of geometric influences and a crossing profile below 3F.

Comparison with alternative methods for distal protection. The results of this investigation apply only to the FilterWire EX; other distal protection filter systems may have unique advantages or disadvantages which might result in a very different safety or efficacy profile. Similarly, the results of this study should not be used to support meaningful comparisons between the investigational FilterWire and balloon occlusion and aspiration with the FDA-approved PercuSurge GuardWire. However, on the basis of these phase II outcomes, a non-inferiority trial has been initiated in which 650 patients undergoing PCI in SVGs were randomized to distal protection with the FilterWire versus the GuardWire; the results of this study are expected in late 2002.

Clinical implications. The FilterWire, while currently investigational in the U.S., is widely used in many parts of the world, and thus the results of this investigation have immediate clinical implications for the operators using this device. Recognition of the unique set of anatomic, technical, and operator-related issues that exist with the FilterWire (and indeed with all distal protection devices), as described herein, may further improve the outcomes for high-risk patients undergoing PCI in degenerated SVGs with distal protection.

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APPENDIX

Phase I study organization: *Principal investigator (PI):* Gregg W. Stone. *Clinical sites and local PIs:* Lenox Hill Hospital, New York, NY, Gregg W. Stone (PI); Ochsner Clinic, New Orleans, LA, Steve Ramee (PI), Chris White; Brigham & Women's Hospital, Boston, MA, Campbell Rogers (PI); William Beaumont Hospital, Royal Oak, MI, Steve Almany (PI); Western Pennsylvania Hospital, Pittsburgh, PA, John George (PI); University of Texas San Antonio, San Antonio, TX, Steve Bailey (PI).

Phase II study organization: *Executive Committee:* Gregg W. Stone (PI), Campbell Rogers (Co-PI), Steve Ramee, Richard E. Kuntz, Milton McColl. *Clinical sites and local PIs:* Kaiser Permanente, Los Angeles, CA, Vicken Aharo-

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Common phase I and II study organization: *Data Management, Clinical Events Adjudication, and Biostatistical Analysis:* Harvard Clinical Research Institute, Cardiovascular Data Analysis Center, Boston, MA, Richard E. Kuntz (Director). *Data Monitoring:* Boston Scientific Corp, Natick, MA. *Core Angiographic Laboratory:* Brigham and Women's Hospital Core Angiographic Laboratory, Boston, MA, Jeffrey J. Popma (Director). *Electrocardiographic Core Laboratory:* Cardiovascular Data Analysis Center, Boston, MA, Peter Zimetbaum (Director).