Clinical Investigation and Reports

Randomized Trial of a Distal Embolic Protection Device During Percutaneous Intervention of Saphenous Vein Aorto-Coronary Bypass Grafts

Donald S. Baim, MD; Dennis Wahr, MD; Barry George, MD; Martin B. Leon, MD; Joel Greenberg, MD; Donald E. Cutlip, MD; Unsal Kaya, MS; Jeffrey J. Popma, MD; Kalon K.L. Ho, MD, MSc; Richard E. Kuntz, MD, MSc; on behalf of the Saphenous vein graft Angioplasty Free of Emboli Randomized (SAFER) Trial Investigators

Background—Stents provide effective treatment for stenotic saphenous venous aorto-coronary bypass grafts, but their placement carries a 20% incidence of procedure-related complications, which potentially are related to the distal embolization of atherosclerotic debris. We report the first multicenter randomized trial to evaluate use of a distal embolic protection device during stenting of such lesions.

Methods and Results—Of 801 eligible patients, 406 were randomly assigned to stent placement over the shaft of the distal protection device, and 395 were assigned to stent placement over a conventional 0.014-inch angioplasty guidewire (control group). The primary end point—a composite of death, myocardial infarction, emergency bypass, or target lesion revascularization by 30 days—was observed in 65 patients (16.5%) assigned to the control group and 39 patients (9.6%) assigned to the embolic protection device (P=0.004). This 42% relative reduction in major adverse cardiac events was driven by myocardial infarction (8.6% versus 14.7%, P=0.008) and “no-reflow” phenomenon (3% versus 9%, P=0.02). Clinical benefit was seen even when platelet glycoprotein IIb/IIIa receptor blockers were administered (61% of patients), with composite end points occurring in 10.7% of protection device patients versus 19.4% of control patients (P=0.008).

Conclusions—Use of this distal protection device during stenting of stenotic venous grafts was associated with a highly significant reduction in major adverse events compared with stenting over a conventional angioplasty guidewire. This demonstrates the importance of distal embolization in causing major adverse cardiac events and the value of embolic protection devices in preventing such complications. (Circulation. 2002;105:1285-1290.)

Key Words: embolism | grafting | stenosis | angioplasty | stents

Catheter-based intervention in saphenous venous aorto-coronary bypass grafts carries a significant (≈20%) risk of a major adverse clinical event (MACE) (predominantly myocardial infarction) or reduced antegrade flow (the no-reflow phenomenon).1 Several mechanisms have been offered, including spasm of the distal microcirculation, platelet clumping, and most recently, the distal embolization of pieces of friable lipid-rich plaque.2 Preliminary work with the PercuSurge GuardWire—a device for transient distal balloon occlusion during angioplasty or stent placement that allows recovery of any liberated plaque by aspiration before restoration of antegrade flow—has demonstrated consistent recovery of plaque constituents (cholesterol crystals, foam cells, fibrous plaque) that otherwise would have emboledized into the myocardial bed.3 This initial experience has also suggested a reduced incidence of myocardial infarction (<6%) compared with the 20% historical rate of infarction seen without such distal protection.4 The Saphenous vein graft Angioplasty Free of Emboli Randomized (SAFER) trial was an 801-patient US multicenter study in which patients undergoing saphenous vein graft intervention were randomized to undergo either stenting with a conventional guidewire or stenting with the GuardWire distal protection device. The SAFER trial was the pivotal trial that led to US Food and Drug Administration approval in August 2001.

Methods

The primary objective of Saphenous vein graft Angioplasty Free of Emboli Randomized (SAFER) trial was to compare the 30-day clinical outcome after saphenous vein graft stenting plus GuardWire...
distal protection versus that performed over a conventional guidewire (control arm). This randomized trial complied with the Declaration of Helsinki with regard to investigation in humans, was approved for Investigational Device Exemption by the US Food and Drug Administration, and was approved by the local hospital Institutional Review Boards at each of the investigational sites.

Eligibility Criteria
Patient candidates had a history of angina and signs of myocardial ischemia resulting from a target lesion >50% diameter stenosis (angiographic visual assessment) located in the mid-portion of a saphenous vein graft, with a reference diameter between 3 and 6 mm. In the first 142 patients, the lesion could not occupy more than one third of the graft length. In subsequent patients, no upper limit on lesion length was imposed. Major exclusion criteria included (1) recent myocardial infarction with baseline elevation of cardiac enzymes (creatine kinase-MB fraction), (2) significantly impaired left ventricular function (ejection fraction <25%), (3) baseline creatinine >2.5 mg/dL (unless on long-term hemodialysis), and (4) planned use of an atherectomy device.

Coronary Intervention
After informed consent, patients were premedicated with aspirin (325 mg orally) and brought to the interventional laboratory. During the procedure, intravenous heparin was administered to prolong the activated clotting time to >250 seconds. A platelet glycoprotein IIb/IIIa receptor blocker was used at the discretion of the operator. Subjects were randomized to undergo stenting performed over either a conventional 0.014-inch angioplasty guidewire or a 0.014-inch PercuSurge GuardWire balloon occlusion device, with randomization stratified by site and by whether the operator preselected IIb/IIIa receptor blockade.

The series of treatments for both arms of the study involved optional pre-stent dilatation of the lesion, deployment of ≥1 stent, and optional post-stent dilatation (at higher pressure or with a larger diameter balloon). In patients assigned to the GuardWire arm (Figure 1), the 0.014-inch hollow-core GuardWire was advanced across and beyond the target lesion and was attached to a proximal adaptor that allowed progressive inflation of the elastomeric balloon at its tip (range of inflated diameter, 3 to 6 mm) with dilute radiographic contrast until the antegrade flow of contrast within the graft was halted. The lumen of the GuardWire was then sealed, allowing removal of the adaptor and serial performance of the stent procedure (using the GuardWire shaft in lieu of a conventional guidewire). After satisfactory stent deployment, a 5F (1.7 mm) diameter aspiration catheter (Export) was advanced over the GuardWire until it lay just proximal to the occlusion balloon and was connected to an evacuated 20-cc syringe. Between 20 and 40 mL of blood was vigorously aspirated through this catheter and the distal occlusion balloon was deflated to restore antegrade blood flow.

After satisfactory stent deployment, final angiograms were obtained. Standard post-stent therapy (aspirin 325 mg/d, clopidogrel 300 mg oral load, followed by 75 mg/d for 2 to 4 weeks) was commenced. Serial 12-lead ECGs were performed after the procedure and daily until discharge, and blood samples for measurement...
of serum creatine kinase (CK) and its myocardial (MB) fraction were collected after the procedure and every 8 hours thereafter until discharge.

Data Collection and Core Laboratory Analysis
Detailed case report forms were completed by the clinical coordinators at each site, monitored by independent study monitors, and submitted to the data-coordinating center (Harvard Clinical Research Institute, Harvard Medical School, Boston, Mass). Angiograms obtained during the procedure were submitted to the angiographic core laboratory (Brigham and Women’s Angiographic Core Laboratory, Boston, Mass), where they were analyzed with a computer-based system (Medis; Leiden, the Netherlands). The diameter of the reference coronary and the minimum lumen diameter of the target lesion were determined before the procedure, immediately after the procedure, and at follow-up.

Study End Points and Statistical Methods
The primary end point of the study, MACE rate at 30 days, was defined as the composite of death, myocardial infarction, emergent bypass surgery, or target vessel revascularization within 30 days of the index procedure. Death was defined as the occurrence of death from any cause. Myocardial infarction was defined as the occurrence of an elevated CK-MB fraction >3× the upper limit of normal (standardized to each clinical site’s normal range) in at least 1 of 3 serial protocol-driven cardiac enzyme measurements performed during the first 18 to 24 hours after the index procedure or in any subsequent clinically driven measurement. Patients with enzymatic elevation were further divided into those with and without appearance of pathological Q waves on serial ECGs. A clinical events committee that was blinded to treatment assignment determined all clinical end points.

Technical success for patients assigned to the GuardWire arm was defined as delivery of GuardWire system to the intended target site, followed by successful inflation, aspiration, and deflation according to the Instructions for Use. Other prespecified secondary end points included acute thrombosis, postprocedure flow, and vessel injury (distal dissection or perforation).

The study was designed to reject the null hypothesis (ie, that there was no difference between the treatment groups) with a 2-tailed 5% level of significance and 80% power. On the basis of data from prior single-center vein graft intervention study, it was assumed that the 30-day primary end point rate would be 16% in the control arm and ≤11% in the embolic protection arm. A group sequential analysis that allowed for 2 interim analyses and 1 final analysis was incorporated using the group sequential spending algorithm of Geller and Pocock. Applying these assumptions and allowing for a 5% test-to-follow-up rate, it was determined that 800 patients would be randomized, with interim analyses at 350 and 550 patients. The nominal probability value assigned for the 3 group sequential analyses was 0.014 for 350 subjects, 0.021 for 550 subjects, and 0.030 for 800 subjects.

All primary comparisons used the intent-to-treat principle. Continuous variables were compared using Student’s t test if normally distributed and Wilcoxon rank-sum if not. Binary variables were compared using χ² with normal approximation or Fisher’s exact test when appropriate. A 2-tailed P value of 0.05 was considered significant. All statistical analyses were performed using the SAS, version 6.12 (SAS Institute, Cary, NC).

Results
Between June 1999 and August 2000, 801 patients were enrolled into the SAFER trial at 47 sites. After 492 patients were enrolled, the hospital discharge end point was compared. Because the difference between the 2 arms of the study did not reach the statistical threshold P value of 0.014, the trial was continued. At the time of the second interim Data and Safety Monitoring Committee review (after enrollment of 692 patients), the required adjusted 2-sided P value (P=0.024) for GuardWire superiority over conventional treatment was met, and the committee recommended early termination of the trial on the basis of finding a significant benefit for the active arm. An additional 109 patients had been enrolled before this could be communicated to all investigators, and the present study analysis includes all 801 randomized patients.

Baseline Demographics
The baseline demographics are shown in Table 1, reflecting the advanced age, severe angina, and multiple risk factors common in trials of saphenous aorto-coronary vein graft intervention.

Angiographic Findings
The baseline and postprocedural angiographic data are shown in Table 2. They are noteworthy for large graft diameter (mean, 3.4 mm), long lesion length (mean, 16 mm; maximum, 79 mm), and the common presence of lesion-associated thrombus (39%).

Procedural Details
Stenting was performed in 848 of 875 (96.9%) lesions, using either balloon-expandable or self-expanding (9.6% for GuardWire-assigned patients and 20.4% for control patients) designs. The mean number of stents per lesion was 1.35 and 1.38 in the GuardWire and control groups, respectively. Most involved “primary” stenting—that is, placement of the stent without predilatation (79.4% in the GuardWire group and 67.7% in the control group). Postdilatation after stent deployment was performed in 27.3% of GuardWire patients and 40% of the control patients, using a mean balloon size of

| TABLE 1. Baseline Clinical Characteristics of 801 Patients With Saphenous Vein Graft Lesions Treated by Stenting Assigned to Receive GuardWire Embolic Protection or Conventional Guidewire |
|----------------------------------|----------------|----------------|
| Patient Characteristic          | GuardWire     | Control        |
| Age, y                          | 68±10         | 69±9           |
| Male sex                        | 332 (82)      | 331 (84)       |
| Diabetes mellitus               | 134 (33)      | 133 (34)       |
| Prior myocardial infarction     | 240 (61)      | 248 (64)       |
| Prior CVA/TIA                   | 46 (11)       | 50 (13)        |
| Left ventricular ejection fraction | 47.6±12.0    | 47.0±12.1      |
| CCS class III or IV             | 303 (75)      | 299 (76)       |
| Worsening exertional angina     | 166 (41)      | 156 (40)       |
| Rest angina                     | 156 (39)      | 156 (40)       |
| No. of diseased native coronaries |            |                |
| Single                          | 22 (6)        | 19 (5)         |
| Double                          | 82 (20)       | 63 (16)        |
| Triple                          | 298 (74)      | 311 (79)       |
| Vein graft age, y (median [25th, 75th percentile]) | 10.4 (6.5, 13.1) | 10.9 (7.2, 14.6) |

Values are mean±SD or n (%) unless otherwise indicated. CVA indicates cardiovascular accident; TIA, transient ischemic attack; and CCS, Canadian Cardiovascular Society.
388 seconds (25th and 75th percentiles, 265 and 640 seconds). The median GuardWire occlusion time was 90.1% of cases (henceforth designated as the per-protocol cohort). Technical failures included inability to deliver the GuardWire to the intended location (5.4%), inability to achieve or sustain occlusion of antegrade flow (3.2%), and inability to perform at least 20 mL of aspiration before deflation (1.2%). The median GuardWire occlusion time was 388 seconds (25th and 75th percentiles, 265 and 640 seconds).

### End Point Results

There was a 6.9% absolute (42% relative) reduction in the 30-day primary end point (9.6% for GuardWire patients versus 16.5% for control patients; \( P = 0.004 \)) (Figure 2 and Table 4). This predominantly reflects a reduction in myocardial infarctions of all magnitudes (Figure 3). In addition, rates of TIMI grade 3 flow were higher for the GuardWire arm (98%) compared with the control arm (95%; \( P = 0.04 \); Table 3), and the incidence of clinically evident no-reflow was reduced (3% versus 9%; \( P = 0.001 \)). There was no significant increase in subacute closure of the treated graft (1.7% for GuardWire versus 0.5% for conventional treatment; \( P = 0.18 \)) and a lower rate of perforation for the GuardWire arm (0.2% versus 1.5%; \( P = 0.05 \)) (Table 3).

### Discussion

On the basis of perfusion models of rabbit hind-limb and intraoperative human coronary arteries, the process of balloon...
angioplasty was known to involve radial vessel expansion and fracturing of intimal plaque, with only rare distal embolization of plaque constituents. Evidence for more routine distal embolization during angioplasty and stent placement, however, has now emerged from 2 sources: (1) recording of echogenic material by middle cerebral artery transcranial Doppler during carotid stent placement and (2) recovery of atherosclerotic plaque debris when angioplasty is performed using one of the distal protection devices now in clinical testing. Those devices include various filters mounted near the end of conventional guidewires, as well as the occlusion/aspiration system used in the present study. It remains unclear whether these distal emboli are linked causally to adverse procedural events or whether their recovery would reduce the frequency of such events without producing other complications (ie, thrombosis, distal vessel injury, etc).

The model of saphenous vein graft intervention is particularly apt for testing these issues. By 7 to 10 years after bypass surgery, more than half of such grafts develop significant narrowing or occlusion. These narrowed grafts are commonly approached with catheter-based techniques (especially stenting) in an effort to avoid a repeat bypass surgery. Although high degrees of short-term success and low rates of in-stent restenosis have been achieved, the soft and friable nature of the lipid-rich plaque in such grafts contributes to the high occurrence of adverse clinical events (reduced flow despite a patent vessel, or periprocedural myocardial infarction), which are associated with increased 30-day and 1-year mortality in this population. Given the frequent presence of platelet thrombi in such grafts, serotonin released by such platelets might cause distal microvascular (arteriolar) spasm, which is consistent with the observation that selective arteriolar vasodilators (calcium channel blockers, adenosine, nitroprusside) frequently improve or normalize episodes of reduced flow during vein graft intervention. A second proposed mechanism is that platelet aggregation itself might cause or amplify distal embolization. No consistent benefit, however, has been seen with the use of potent antiplatelet agents during saphenous vein graft intervention. The focus on causation thus has shifted to distal embolization of atherosclerotic debris itself. Webb and colleagues described use of the GuardWire distal protection system in saphenous vein grafts, finding almost universal recovery of

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**TABLE 4. Clinical Outcomes of 801 Patients With Saphenous Vein Graft Lesions Treated by Stenting Assigned to Receive GuardWire Embolic Protection or Conventional Guidewire**

<table>
<thead>
<tr>
<th>Clinical End Point</th>
<th>GuardWire (n=406)</th>
<th>Control (n=395)</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>Primary end point (30 day)</td>
<td>39 (9.6)</td>
<td>65 (16.5)</td>
<td>0.004</td>
</tr>
<tr>
<td>Myocardial infarction (30 day)</td>
<td>35 (8.6)</td>
<td>58 (14.7)</td>
<td>0.008</td>
</tr>
<tr>
<td>Q-wave MI</td>
<td>5 (1.2)</td>
<td>5 (1.3)</td>
<td></td>
</tr>
<tr>
<td>Non-Q-wave MI (&gt;3 times normal)</td>
<td>30 (7.4)</td>
<td>54 (13.7)</td>
<td></td>
</tr>
<tr>
<td>CK-MB fraction 3–8 times upper limit normal</td>
<td>19 (4.7)</td>
<td>31 (7.8)</td>
<td></td>
</tr>
<tr>
<td>CK-MB fraction &gt;8 times upper limit normal</td>
<td>12 (3.0)</td>
<td>19 (4.8)</td>
<td></td>
</tr>
<tr>
<td>Any CK-MB elevation above upper limit of normal</td>
<td>66 (16.3)</td>
<td>95 (24.1)</td>
<td>0.006</td>
</tr>
<tr>
<td>Death (30 day)</td>
<td>4 (1.0)</td>
<td>9 (2.3)</td>
<td>0.17</td>
</tr>
<tr>
<td>Emergent bypass surgery (30 day)</td>
<td>0</td>
<td>2 (0.5)</td>
<td>0.24</td>
</tr>
</tbody>
</table>

Subgroup analyses

- In patients with intent to use lib/llla antagonist | 25/232 (10.8) | 42/232 (18.1) | 0.03 |
- In patients with intent not to use lib/llla antagonist | 14/174 (8.0) | 23/163 (14.1) | 0.08 |
- Actual use of a lib/llla antagonist (n=244) | 26/244 (10.7) | 48/247 (19.4) | 0.008 |
- No actual use of a lib/llla antagonist (n=162) | 13/162 (8.0) | 17/148 (11.5) | 0.34 |

Values are n (%) or n/total subset (%). MI indicates myocardial infarction. Some patients had >1 event.
atheroembolic particles and a fewer adverse events (MACE of 4%, versus 17% for historical controls).

The present study now completes this hypothesis by showing not only that embolic particles are recovered, but that their recovery is associated with a major reduction in adverse clinical events compared with placement of stents without distal protection. Some residual MACE are still seen in the GuardWire arm, suggesting ongoing technical challenges in obtaining complete distal protection. Importantly, there was no offsetting increase in the incidence of complications (distal dissection, perforation, or abrupt closure) because of use of the low-pressure elastomeric occlusion balloon in the distal graft. Although the SAFER trial was not powered to show a significant reduction in mortality, it did show a mortality trend (1.0% versus 2.3%; P=0.17) that parallels the significant reduction in the primary end point.

Finally, the addition of distal protection offered similar benefit against MACE whether or not the operator had decided to pretreat with a platelet glycoprotein IIb/IIIa receptor blocker.

The SAFER study makes clear the importance of distal atheroembolization and the benefit of devices that prevent it during catheter-based intervention in saphenous vein grafts and potentially in other territories (eg, native coronary, carotid, renal arteries) where distal embolization causes significant end-organ damage.

Appendix

In addition to the authors, the following institutions and investigators participated in the SAFER trial:

**Clinical Events Committee:** L. Garcia, J. Kannam, J. Markis, J.P. Oettgen

Coronary Angiographic Core Laboratory (Brigham and Women’s Hospital, Boston, Mass): M. Fitzpatrick, S. Giri

Data Coordinating and Statistical Center (Harvard Clinical Research Institute, Boston, Mass): A. Lanoue, D. Rockafellow, D. Vovcsko

Data and Safety Monitoring Committee: R. Piana (Chairman), J. Aroesty, F. Ling, J. Orav (Statistician)

ECG Core Laboratory (Harvard Clinical Research Institute, Boston, Mass): G. Foley, S. Ho, P. Zimetbaum

**Study Sites:** Allegheny General Hospital, Pittsburgh, Pa; Arizona Heart Institute, Phoenix, Ariz; Arkansas Heart Hospital, Little Rock, Ark; Baylor University Medical Center, Dallas, Tex; Beth Israel Deaconess Medical Center, Boston, Mass; Beth Israel Medical Center, New York, NY; Brigham and Women’s Hospital, Boston, Mass; Christ Hospital, Cincinnati, Ohio; Duke University Medical Center, Durham, NC; Emory University Hospital, Atlanta, Ga; Fletcher Allen Medical Center, Burlington, Vt; Florida Hospital, Orlando, Fla; Good Samaritan Hospital, Phoenix, Ariz; Good Samaritan of Los Angeles, Los Angeles, Calif; Hahnemann Hospital, Philadelphia, Pa; Iowa Heart Center, Des Moines, Iowa; Lenox Hill Hospital, New York, NY; Maine Medical Center, Portland, Me; Massachusetts General Hospital, Boston, Mass; Mayo Clinic, Rochester, Minn; Mercy Heart Institute, Sacramento, Calif; Miami Heart Institute, Miami Beach, Fl; Mid Carolina Cardiology, Charlotte, NC; Mid-West Heart Research Foundation, Lombard, Ill; Morton Plant Hospital, Safety Harbor, Fl; Mt Sinai Medical Center, New York, NY; Munroe Regional Medical Center, Ocala, Fla; North Shore University Hospital, Manhasset, NY; Northwestern Hospital, Chicago, Ill; Orlando Heart Center, Orlando, Fla; Ochsner Clinic, New Orleans, La; Riverside Hospital, Columbus, Ohio; Sarasota Memorial Hospital, Sarasota, Fla; Scripps Clinic and Research Foundation, LaJolla, Calif; Sequoia Hospital, Redwood City, Calif; St John’s Hospital, Springfield, Ill; St Joseph’s Health Hospital, Syracuse, NY; St Joseph Mercy Hospital, Ann Arbor, Mich; St Luke’s Medical Center, Kansas City, Mo; St Luke’s Medical Center, Phoenix, Ariz; St Thomas Medical Center, Nashville, Tenn; St Vincent’s Hospital, Indianapolis, Ind; Swedish Medical Center, Seattle, Wash; University of Arkansas, Little Rock, Ark; University of Chicago, Chicago, Ill; Valley Hospital, Ridgewood, NJ; Washington Hospital Center, Washington, DC; Western Baptist Hospital, Paducah, Ky; William Beaumont Medical Center, Royal Oak, Mich.

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**References**

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