Journal of the American College of Cardiology Vol. 46, No. 9, 2005

Published by Elsevier Inc.
ISSN 0735-1097/05/$30.00
doi:10.1016/j.jacc.2005.06.073

Randomized Evaluation of the TriActiv Balloon-Protection Flush and Extraction System for the Treatment of Saphenous Vein Graft Disease

Joseph P. Carrozza, JR, MD, FACC,* Michael Mumma, MD, FACC,†
Jeffrey A. Breall, MD, PHD, FACC,‡ Aland Fernandez, MD, FACC,§ Eugene Heyman, PHD,‖
Christopher Metzger, MD, FACC,¶ for the PRIDE Study Investigators

Boston, Massachusetts; Sarasota and Clearwater, Florida; Indianapolis, Indiana; Montgomery Village, Maryland; and Kingsport, Tennessee

OBJECTIVES The Protection During Saphenous Vein Graft Intervention to Prevent Distal Embolization (PRIDE) study compared outcomes with the TriActiv System (Kensey Nash Corp., Exton, Pennsylvania), a balloon-protection flush and extraction device, with an embolic protection group during treatment of saphenous venous grafts (SVGs).

BACKGROUND Treatment of SVGs with embolic protection reduces adverse cardiac events.

METHODS We conducted a prospective trial randomizing 631 patients with coronary ischemia and lesions in SVGs to embolic protection with the TriActiv System or control group (Guardwire System [Medtronic AVE, Santa Rosa, California] or Filterwire EX [Boston Scientific Corp., Maple Grove, Minnesota]).

RESULTS The incidence of major adverse cardiac events at 30 days was 11.2% for the TriActiv group and 10.1% for the control group (relative risk = 1.1%; 95% confidence interval 0.67 to 1.76; p = 0.65; p = 0.02 for non-inferiority). Safety and efficacy end points were similar between groups except that patients randomized to the TriActiv System had more hemorrhagic complications (10.9% vs. 5.4%; p = 0.01).

CONCLUSIONS The TriActiv System was not inferior to approved embolic protection devices for the treatment of diseased SVGs. (J Am Coll Cardiol 2005;46:1677–83) © 2005 by the American College of Cardiology Foundation

Percutaneous catheter intervention (PCI) for saphenous vein graft (SVG) disease is associated with significant myonecrosis, increasing the risk of late mortality (1). The pathophysiology of embolization is multifactorial, involving liberation of thrombus and atheromatous debris and soluble mediators of vasoconstriction (2,3). The Saphenous Vein Graft Angioplasty Free of Emboli, Randomized (SAFER) trial demonstrated that PCI performed with embolic protection was associated with a lower incidence of no-reflow, peri-procedural myocardial infarction and adverse events (4). The FilterWire EX Randomized Evaluation (FIRE) trial reported that use of the Filterwire EX (Boston Scientific Corp., Maple Grove, Minnesota) offered protection against distal embolization similar to the balloon-occlusion Guardwire System (Medtronic AVE, Santa Rosa, California) (5).

The SAFER and FIRE studies established that embolic protection with either balloon-occlusion or a filter was the first approach to improve outcome during SVG PCI. These devices were difficult to use, however, and did not prevent adverse events in 8% to 10% of patients. These limitations led to the development of a number of newer balloon-occlusion and filter devices. The multicenter, randomized Protection During Saphenous Vein Graft Intervention to Prevent Distal Embolization (PRIDE) study compared PCI of SVGs with a novel embolic protection system, TriActiv (Kensey Nash Corp., Exton, Pennsylvania), to the Guardwire (Medtronic AVE) and Filterwire EX (Boston Scientific Corp.) devices.

METHODS

TriActiv balloon protected flush extraction system. The components of the TriActiv System have been described previously (6). The lesion is crossed with the 0.014-inch Shieldwire temporary occlusion balloon guidewire and the balloon (expansion range 3 to 5 mm) inflated via CO_2-filled syringe. After intervention, the FlushCath catheter is attached side-to-side to the Shieldwire and advanced to the occlusion balloon. Saline is infused at 50 cc/min through the FlushCath catheter by a sterile unit (autostream flow control [n = 70]). This replaced a free standing, drive console used in the early part of the PRIDE study (n = 273). The effluent is extracted through the guiding catheter (200 cc/min through 8-F guiding catheters or 125 cc/min with 7-F guiding catheters). The balloon is deflated, and flow restored.

The PRIDE study. The PRIDE study was a "hybrid" investigation (Fig. 1). At the commencement of the study,

From the *Section of Interventional Cardiology-Beth Israel Deaconess Medical Center, Boston, Massachusetts; †Sarasota Memorial Hospital, Sarasota, Florida; ‡Krannert Institute of Cardiology, Indiana University of Medicine, Indianapolis, Indiana; §Morton Plant Hospital, Clearwater Cardiovascular & Interventional Consultants, Clearwater, Florida; ‖Montgomery Village, Maryland; and the ¶Wellmont Holston Valley Medical Center, Kingsport, Tennessee. Drs. Carrozza, Mumma, and Metzger served as members of the Scientific Advisory Board for the Kensey Nash Corp., the sponsor of this study.

Manuscript received February 28, 2005; revised manuscript received June 17, 2005, accepted June 21, 2005.

Abbreviations and Acronyms

FIRE = FilterWire EX Randomized Evaluation
MACE = major adverse cardiac events
MI = myocardial infarction
PCI = percutaneous coronary intervention
PRIDE = Protection During Saphenous Vein Graft Intervention to Prevent Distal Embolization trial
SAFER = Saphenous Vein Graft Angioplasty Free of Emboli, Randomized study
SVG = saphenous vein/venous graft
TIMI = Thrombolysis In Myocardial Infarction
TLR = target lesion revascularization
TVR = target vessel revascularization

one embolic protection device was approved in the U.S. Investigators randomized patients to protection with the TriActiv System versus PCI without embolic protection ("Cohort I"), to demonstrate superiority of the TriActiv System compared with an "unprotected" group. To demonstrate non-inferiority of the TriActiv System compared with a "protected" control group, investigators randomized patients to protection with TriActiv or another protection system approved for use in SVGs ("Cohort II"). Once a site enrolled a patient in Cohort II, future enrollment was limited to Cohort II. Each site enrolled a minimum of two to six "roll-in" patients. The PRIDE study was approved by the institutional review board at each site; all patients provided written informed consent to participate.

Entry criteria. Criteria for inclusion were age ≥21 years, angina or objective evidence of ischemia, lesion in a SVG (≥3.0 mm and ≤5.0 mm), Thrombolysis In Myocardial Infarction (TIMI) flow grade ≥0, and ability to provide informed consent. Patients were excluded if any of the following were present: pregnancy, lesion in a native artery or internal mammary graft, distal shoulder of the lesion within 2.0 cm of the distal anastomosis, left ventricular ejection fraction <25%, sequential grafts unless the lesion was >2 cm proximal to the branch point, myocardial infarction (creatine kinase [CK] and CK-MB more than twice the upper limit of normal within 24 h), allergy to aspirin or both clopidogrel and ticlopidine, treatment of ≥2 SVGs, and co-morbidities limiting life-expectancy to ≤6 months.

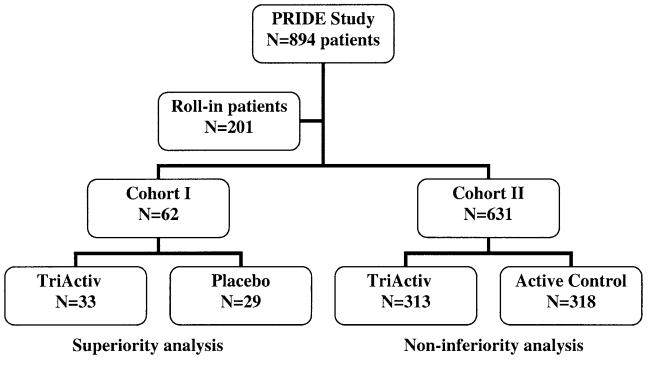

Figure 1. Enrollment in the PRIDE study.

Table 1. Baseline Demographics

	Cohort II		
	TriActiv (n = 313)	Active Control (n = 318)	p Value*
Female gender, n (%)	51 (16.3)	64 (20.1)	0.21
Age (yrs), mean ± SD	68.5 ± 9.9	68.5 ± 10.3	0.98
Range	39–99	41–93	
Hypertension, n (%)	269 (85.9)	264 (83.0)	0.31
Diabetes mellitus, n (%)	129 (41.2)	133 (41.8)	0.88
Dyslipidemia†, n (%)	266 (85.0)	278 (87.4)	0.37
Cigarette smoking, n (%)	54 (17.3)	54 (17.0)	0.93
Family history of CAD, n (%)	92 (29.4)	107 (33.7)	0.25
Prior MI, n (%)	201 (64.2)	200 (62.9)	0.73
Peripheral vascular disease, n (%)	81 (25.9)	82 (25.8)	0.98
Stroke or TIA, n (%)	44 (14.1)	37 (11.6)	0.36
Canadian cardiovascular class			
I	38 (12.2)	45 (14.3)	0.39
II	75 (24.1)	84 (26.8)	
III	98 (31.5)	87 (27.7)	
IV	100 (32.2)	99 (31.5)	
LVEF (%), mean ± SD	48.7 ± 11.5	48.7 ± 11.9	0.97
Range	25–75	25–88	

*TriActiv Cohort II versus Active Control. †Requiring treatment.
CAD = coronary artery disease; LVEF = left ventricular ejection fraction; MI = myocardial infarction; TIA = transient ischemic attack.

Randomization was stratified by intention to administer a glycoprotein IIb/IIIa receptor antagonist before intervention. Patients received aspirin before the procedure and either heparin or bivalirudin during the procedure. After the procedure, aspirin and either clopidogrel or ticlopidine were administered for a minimum of one month. Cardiac enzymes were assessed every 8 h for 24 h. Patients were assessed clinically at 30 days.

Prespecified study end points. Device success was defined as delivery of the device to the target location with successful operation and removal of the device. Lesion success was defined as the attainment of <50% residual stenosis at the end of the procedure. Procedure success was defined as device success without a major adverse cardiac event (MACE). The primary end point was MACE (either cardiac death, myocardial infarction [any post-procedure CK-MB level ≥3 × the upper limit of normal], or target lesion revascularization) at 30 days. Pre-specified efficacy and safety end points were device success and final TIMI flow grade, myocardial infarction, in-hospital MACE, stroke at 30 days, and major vascular complications (perforation, hematoma at access site >5 cm, false aneurysm, arteriovenous fistula, retroperitoneal hemorrhage, peripheral ischemia/nerve injury, vascular repair, ultrasound compression, and transfusion).

Study organization (Appendix). Electrocardiograms and angiograms were analyzed by core laboratories blinded to treatment assignment. A blinded events committee adjudicated all events. The overall performance of the study was reviewed by the Data Safety Monitoring Board.

Table 2. Procedural Data

	Cohort II		
	TriActiv (n = 313)	Active Control (n = 318)	p Value*
Number of lesions treated, mean	1.3	1.2	0.63
Range	1–4	1–4	
Number of SVGs treated, n (%)			
1	297 (94.9)	299 (94.0)	0.86
2	16 (5.1)	19 (6.0)	
Age of SVG (yrs), mean ± SD	11.9 ± 5.8	12.0 ± 6.0	0.87
Range	0.6–29.1	0.5–33.0	
Highest ACT (s), mean ± SD	305 ± 112	326 ± 438	0.44
Range	0–1,500	0–7,350	
Occlusion time† (min), mean ± SD	4.5 ± 2.1	5.0 ± 2.6	0.026
Range	1.0–16.6	1.5–22.1	
Procedure time (min), median	58 ± 108.2	52 ± 50.1	0.01
Pre-procedure clopidogrel or ticlopidine, n (%)	276 (88.2)	271 (85.2)	0.28
GP IIb/IIIa planned, n (%)	167 (53.4)	167 (52.5)	0.83
GP IIb/IIIa used, n (%)	169 (54.0)	174 (54.7)	0.86
Sheath size, n (%)			
5–F	1 (0.3)	0 (0)	<0.001‡
6–F	5 (1.6)	35 (11.3)	
7–F	149 (47.9)	149 (47.9)	
8–F	157 (50.3)	127 (40.8)	

*TriActiv Cohort II versus Active Control. †Occlusion time per each intervention. Occlusion time for Active Control is for GuardWire only. ‡Comparison of ≤7-F used in Cohort II.
ACT = activated clotting time; GP = glycoprotein; SVG = saphenous vein graft.

Table 3. Baseline Lesion Angiography

	Cohort II		
	TriActiv (n = 323)	Active Control (n = 322)	p Value*
Lesion location, n (%)			
Ostial	48 (15.0)	69 (21.6)	0.01
Proximal	123 (38.3)	86 (26.9)	
Mid	118 (36.8)	134 (41.9)	
Distal	32 (10.0)	31 (9.7)	
Lesion length, (mm) mean ± SD	14.2 ± 10.5	13.0 ± 8.8	0.11
Range	3.1–80.2	1.6–57.7	
Tortuosity, n (%)	19 (5.9)	9 (2.8)	0.05
SVG degeneration, n (%)			
0%–25%	153 (47.5)	174 (54.0)	
25%–50%	105 (32.6)	90 (28.0)	
50%–75%	43 (13.4)	39 (12.1)	0.21
>75%	21 (6.5)	19 (5.9)	
SVG degeneration score (%), mean ± SD	35.9 ± 23.1	33.0 ± 22.4	0.12
Range	0–100	0–100	
Plaque volume (mm^3), mean ± SD	337 ± 298	316 ± 267	0.35
Range	34–2,015	23–1,490	
Thrombus present, n (%)	187 (58.3)	186 (57.6)	0.78
Reference vessel diameter (mm), mean ± SD	3.2 ± 0.6	3.3 ± 0.6	0.42
Range	1.8–5.5	1.9–5.1	
MLD (mm), mean ± SD	1.1 ± 0.5	1.2 ± 0.6	0.24
Range	0–4.1	0–2.8	
Diameter stenosis (%), mean ± SD	65.7 ± 14.8	64.8 ± 15.0	0.45
Range	16.3–100	22.0–100	
TIMI flow grade, n (%)			
0	5 (1.6)	4 (1.3)	
1	6 (1.9)	5 (1.6)	
2	25 (7.8)	26 (8.1)	0.77
3	286 (88.8)	285 (89.1)	

*TriActiv Cohort II versus Active Control.
MLD = minimum lumen diameter; SVG = saphenous vein graft; TIMI = Thrombolysis In Myocardial Infarction.

Statistical methods. All analyses comparing patients in TriActiv Cohort II with those in the control group were made on the basis of intention-to-treat. With an assumed MACE rate of 10%, a sample size of 618 patients would provide 80% power to reject the null hypothesis of inferiority with a δ of 6% at the 5% level of significance. Continuous variables were compared with *t* tests and dichotomous variables by Pearson's chi-square or Fisher exact test if the expected number in any cell was <5. Ordinal variables (e.g., baseline CCS class, sheath size, TIMI flow grade) were tested by the Cochran-Mantel-Haenszel procedure, applying uniform scores to the ordered categories. All analyses were performed using SAS Version 8.2 (SAS Institute, Cary, North Carolina).

RESULTS

Baseline and procedural characteristics. From December 2001 through March 2004, 68 sites in the U.S. and 10 sites in Europe enrolled 894 patients in the PRIDE study, with 201 non-randomized "roll-in" patients and 62 patients randomized in Cohort I. Given the small number of patients in Cohort I, meaningful conclusions regarding the superiority of TriActiv to SVG intervention without embolic protection could not be made. This analysis describes the outcomes of patients in Cohort II. Demographic and procedural data were well-matched between TriActiv and the active control patients in Cohort II (Tables 1 and 2). No differences in baseline characteristics were observed within the control group of the GuardWire or FilterWire EX.

Angiography. Lesions randomized to the TriActiv System group had greater tortuosity and were less likely to be ostial (Tables 3 and 4). Device success was 94.5% in lesions treated with TriActiv and 94.7% in active control (p = 0.92). Lesion success was 99.0% with TriActiv and 99.4% in the control group (p = 0.68). After treatment, a TIMI flow grade of 3 was observed in 99.1% of lesions in the TriActiv group and in 97.8% in the active control cohort.

Clinical outcomes. One patient in Cohort II (in the TriActiv group) was lost to follow-up. Procedural success was similar in both groups (89.4% [TriActiv] versus 90.5% [control]; p = 0.64). In Cohort I, there were five in-hospital MACE (18.2%) in the TriActiv group and three (10.3%) in the placebo group. By 30 days, there were six in-hospital MACE (15%) in the TriActiv group and three (10.3%) in the placebo group. Given the small number of patients in each group, there was insignificant power to make statistical comparisons. For Cohort II, the incidence of MACE at 30 days was 11.2% for TriActiv and 10.1% for the control group (relative risk = 1.1%; 95%

Table 4. Post-Treatment Angiography

	Cohort II		
	TriActiv (n = 323)	Active Control (n = 322)	p Value*
MLD (mm), mean ± SD	2.8 ± 0.6	2.8 ± 0.6	0.59
Range	1.2–4.9	0–4.4	
Diameter stenosis (%), mean ± SD	14.5 ± 10.0	14.3 ± 11.5	0.85
Range	−10.2–96.7	−38.7–100	
Maximum stent diameter (mm), mean ± SD	3.7 ± 0.6	3.8 ± 0.6	0.09
Range	2.5–6.0	2.5–5.0	
Direct stenting (%)	167/201 (83.1%)	258/318 (81.1%)	0.40
Stent length (mm), mean ± SD	20.9 ± 7.8	20.7 ± 7.8	0.76
Range	2–38	8–38	
Maximum inflation pressure (atm), mean ± SD	14.8 ± 3.2	14.9 ± 3.3	0.51
Range	0–24	4–25	
Residual thrombus present, n (%)	37 (11.5)	30 (9.3)	0.53
Distal embolization, n (%)	5 (1.6)	2 (0.6)	0.45
Perforation, n (%)	1 (0.3)	4 (1.3)	0.22
TIMI flow grade, n (%)			
0	1 (0.3)	2 (0.6)	0.20
1	0 (0)	2 (0.6)	
2	2 (0.6)	3 (0.9)	
3	317 (99.1)	313 (97.8)	
TIMI frame count, mean ± SD	20.2 ± 9.7	20.2 ± 11.9	0.94
Range	0–60	0–99	
Dissection at site of protection balloon†, n (%)			
None	292 (96.7)	—	—
A	6 (2.0)	—	—
B	2 (0.7)	—	—
C	0 (0)	—	—
D	0 (0)	—	—
E	0 (0)	—	—
F	1 (0.3)	—	—

*TriActiv Cohort II versus Active Control. †Assessed only for TriActiv cases.
MLD = minimum lumen diameter; TIMI = Thrombolysis In Myocardial Infarction.

Table 5. Clinical Events—In-Hospital

	Cohort II			
	TriActiv (n = 313)	Active Control (n = 318)	p Value*	RR (95% CI)
Death, n (%)	3 (1.0)	1 (0.3)	0.37	3.05 (0.32–29.1)
Cardiac, n (%)	3 (1.0)	1 (0.3)	0.37	3.05 (0.32–29.1)
Non-cardiac, n (%)	0 (0)	0 (0)	1.0	—
Myocardial infarction, n (%)	28 (9.0)	27 (8.5)	0.84†	1.05 (0.64–1.75)
Q-wave, n (%)	3 (1.0)	1 (0.3)	0.37	3.05 (0.32–29.1)
Non–Q-wave, n (%)	25 (8.0)	26 (8.2)	0.93	0.98 (0.58–1.65)
TVR, n (%)	4 (1.3)	2 (0.6)	0.45	2.03 (0.37–11.0)
PCI, n (%)	3 (1.0)	2 (0.6)	0.68	1.52 (0.26–9.06)
CABG, n (%)	1 (0.3)	0 (0)	0.50	—
TLR	3 (1.0)	2 (0.6)	0.68	1.52 (0.26–9.06)
PCI, n (%)	2 (0.6)	2 (0.6)	1.0	1.02 (0.14–7.17)
CABG, n (%)	1 (0.3)	0 (0)	0.50	—
MACE, n (%)	31 (9.9)	29 (9.1)	0.74†	1.09 (0.67–1.76)
Vascular complications, n (%)	34 (10.9)	17 (5.4)	0.01†	2.03 (1.16–3.56)
Transfusion, n (%)	24 (7.7)	11 (3.5)	0.02†	2.22 (1.10–4.45)
Hematoma >5 cm, n (%)	9 (2.9)	2 (0.6)	0.03	4.57 (1.00–20.99)
Retroperitoneal bleed, n (%)	1 (0.3)	1 (0.3)	1.0	1.02 (0.06–16.17)
Pseudoaneurysm, n (%)	3 (1.0)	2 (0.6)	0.68	1.52 (0.26–9.06)
Arteriovenous fistula, n (%)	1 (0.3)	0 (0)	0.50	—
Vascular repair, n (%)	2 (0.6)	1 (0.3)	0.37	3.05 (0.32–29.1)
Peripheral ischemia/ nerve injury, n (%)	2 (0.6)	1 (0.3)	0.62	2.03 (0.19–22.3)
Stroke, n (%)	1 (0.3)	1 (0.3)	1.0	1.02 (0.06–16.2)

*TriActiv Cohort II versus Active Control. All p values calculated using Fisher exact test, except where indicated by †, where chi-square test was used.

CABG = coronary artery bypass graft; CI = confidence interval; MACE = major adverse cardiac events; PCI = percutaneous coronary intervention; RR = relative risk; TVR = target vessel revascularization; TLR = target lesion revascularization.

confidence intervals = 0.67 to 1.76; p = 0.65; p = 0.02 for non-inferiority) (Tables 5 and 6). Within the active control group, the incidence of MACE at 30 days was 10.6% for the Guardwire and 7.2% for the FilterWire. Procedure-related MACE were 10.1% and 10.2% for the active control group and TriActiv System, respectively. More than 16% of patients treated with TriActiv, GuardWire, and FilterWire EX exhibited some degree of myonecrosis (Fig. 2). Patients in the TriActiv group were more likely to require blood transfusion. The overall vascular complication rate was 10.9% for TriActiv versus 5.4% for Active Control (Table 5). Sub-group analysis indicated that the higher rate of transfusion in the TriActiv Cohort was associated with an early design of the hemostatic valve in combination with 8-F guiding catheters (Fig. 3).

Table 6. Clinical Events Through 30 Days

	Cohort II			
	TriActiv (n = 313)	Active Control (n = 318)	p Value*	RR (95% CI)
Death, n (%)	4 (1.3)	2 (0.6)	0.45	2.0 (0.37–11.01)
Cardiac, n (%)	4 (1.3)	2 (0.6)	0.45	2.0 (0.37–11.01)
Non-cardiac, n (%)	0 (0)	0 (0)	1.0	—
Myocardial infarction, n (%)	31 (9.9)	28 (8.8)	0.64†	1.12 (0.69–1.83)
Q-wave, n (%)	4 (1.3)	1 (0.3)	0.21	4.06 (0.46–36.2)
Non–Q-wave, n (%)	27 (8.6)	27 (8.5)	0.95†	1.02 (0.61–1.69)
TVR, n (%)	5 (1.6)	4 (1.3)	0.75	1.27 (0.34–4.69)
PCI, n (%)	3 (1.0)	4 (1.3)	0.68	0.76 (0.17–3.38)
CABG, n (%)	2 (0.6)	0 (0)	0.25	—
TLR	4 (1.3)	4 (1.3)	1.0	1.02 (0.26–4.03)
PCI, n (%)	2 (0.6)	4 (1.3)	0.69	0.51 (0.09–2.75)
CABG, n (%)	2 (0.6)	0 (0)	0.50	—
MACE, n (%)	35 (11.2)	32 (10.1)	0.65†‡	1.11 (0.71–1.75)
Stroke, n (%)	1 (0.3)	1 (0.3)	1.0	1.02 (0.06–16.2)

*TriActiv Cohort II versus Active Control. All p values calculated using Fisher exact test except where indicated by †, where chi-squared test was used. ‡Relative risk = 1.11 (one-sided 95% confidence interval [CI] on the difference = 5.2%; p value of 0.02 indicates non-inferiority of the TriActiv System to Active Control.

Abbreviations as in Table 5.

JACC Vol. 46, No. 9, 2005
November 1, 2005:1677–83

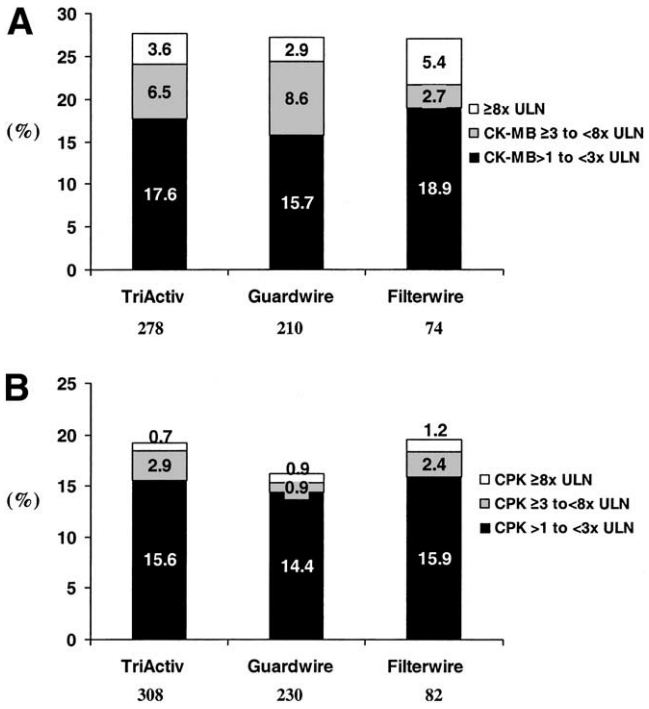

Figure 2. (A) Post-treatment creatine kinase (CK)-MB and **(B)** total creatine phosphokinase (CPK) elevation according to embolic protection system used. ULN = upper limit of normal.

DISCUSSION

Both the TriActiv and GuardWire require transient occlusion of the SVG during PCI. As observed in this study, the gas-filled balloon of the TriActiv System allows for more rapid inflation and deflation times. Using an active flush and extraction mechanism, the TriActiv System offers the potential for greater efficiency of particle removal. The FilterWire captures liberated particles in a retrieval basket. Unlike balloon occlusion systems, filter protection devices allow flow maintenance, avoiding potential ischemic complications; however, small particles and soluble vasoconstrictors are not always captured.

The PRIDE trial was designed to test two hypotheses: embolic protection with TriActiv is superior to an unprotected control group, and outcomes with TriActiv are not inferior to those with approved distal protection systems. Initially, investigators preferred to enroll in Cohort I. With emerging data demonstrating superiority of embolic protection with the GuardWire System and FilterWire EX, most investigators chose to randomize patients in Cohort II. The limited enrollment in Cohort I underpowered the superiority comparison, precluding any ability to exclude the null hypothesis.

The PRIDE study demonstrated that embolic protection during SVG intervention with the TriActiv System was not inferior to protection with the active control group of either the balloon-occlusion Guardwire System or the Filterwire EX device. The non-inferiority design of Cohort II precludes conclusions regarding the superiority of TriActiv to either the Filterwire EX or Guardwire devices for the prevention of adverse events, although the addition of flush and extraction to balloon occlusion did not appear to confirm additional clinical benefit. Vessels randomized to either TriActiv or the control group had post-treatment rates of TIMI flow grade 3 in excess of 97%, confirming a high degree of efficacy for all three embolic protection devices; however, patients randomized to the TriActiv System were more likely to suffer a hemorrhagic complication, but were not at higher risk of suffering a non-hemorrhagic vascular complication. When stratified according to guiding catheter size, this higher rate of transfusion was observed only in patients randomized to TriActiv and in whom large guiding catheters were used. This finding is best explained by the greater rate of aspiration with larger guiding catheters (200 cc/min with 8-F guiding catheters compared with 125 cc/min with 7-F guiding catheters).

The relatively high incidence of peri-procedural myonecrosis observed in patients treated with any of the three protection devices probably reflects both the complex nature of lesions in the PRIDE trial, and the reality that all three devices have limitations. One of the limitations of the TriActiv System was the longer mean procedure time compared with the active control group. It is possible that the extended time might have contributed to adverse events. To address this problem, the next generation TriActiv FX System, will incorporate a monorail flush catheter, a more precise balloon inflation mechanism, and a guidewire sealing mechanism allowing exchange over the back end of the guidewire. These improvements are expected to reduce total occlusion and procedure times.

Saphenous vein graft degeneration and pretreatment thrombus burden are independent predictors of MACE during SVG intervention (7). The pre-procedure SVG degeneration score was greater in the PRIDE trial than it was in the FIRE trial and lesions in the PRIDE trial also had greater pre-procedural thrombus. Despite greater graft degeneration and thrombus burden, the PRIDE study demonstrated non-inferiority of the TriActiv System compared with approved embolic protection devices. Advances

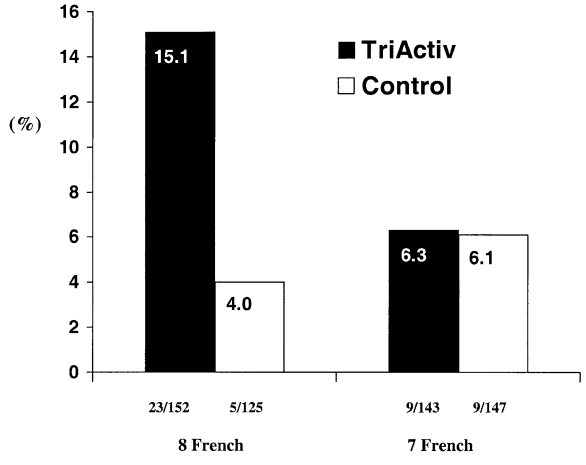

Figure 3. Vascular/hemorrhagic complications according to treatment assignment and catheter size.

in balloon occlusion systems and filters (e.g., the FilterWire EZ) presumably will improve outcomes with both systems.

Study limitations. This study has several limitations. Its findings are not generalizable to patients who do not meet entry criteria. The non-inferiority analysis precludes any conclusions of superiority of one group over another. With a pre-specified δ of 6%, statistical non-inferiority was achieved; however, this does not establish equivalence in terms of safety or efficacy, because the upper boundary of the 95% confidence interval allows for a relatively large difference within the bounds of non-inferiority. TriActiv could be as much as 29% better or 75% worse than the control device in preventing 30-day MACE. Unlike the SAFER trial, the PRIDE trial allowed enrollment of patients with aorto-ostial lesions and total occlusions. Thus, the outcomes for patients treated with the Guardwire in both trials are not directly comparable. No conclusions can be drawn concerning the comparison of TriActiv System to PCI without protection, because this arm of the trial enrolled too few patients to justify statistical comparisons. Finally, because the choice of Guardwire or FilterWire was left to operator discretion, potential selection bias precludes comparison of either FilterWire to Guardwire, or of either alone to TriActiv.

Reprint requests and correspondence: Dr. Joseph P. Carrozza, Jr., Section of Interventional Cardiology, Beth Israel Deaconess Medical Center, 330 Brookline Avenue, Boston, Massachusetts 02215. E-mail: jcarrozz@bidmc.harvard.edu.

REFERENCES

1. Hong MK, Mehran R, Dangas G, et al. Creatine kinase-MB enzyme elevation following successful saphenous vein graft intervention is associated with late mortality. Circulation 1999;100:2400–5.
2. Webb JG, Carere RG, Virmani R, et al. Retrieval and analysis of particulate debris after saphenous vein graft intervention. J Am Coll Cardiol 1999;34:468–75.
3. Golino P, Piscione F, Benedict CR, et al. Local effect of serotonin released during coronary angioplasty. N Engl J Med 1994;330:523–8.
4. Baim DS, Wahr D, George B, et al. Randomized trial of a distal embolic protection device during percutaneous intervention of saphenous vein aorto-coronary bypass grafts. Circulation 2002;105:1285–90.
5. Stone GW, Rogers C, Hermiller J, et al. Randomized comparison of distal protection with a filter-based catheter and a balloon occlusion and aspiration system during percutaneous intervention of diseased saphenous vein aorto-coronary bypass grafts. Circulation 2003;108:548–53.
6. Carrozza JP Jr., Braden G, Braun P, et al., for the TriActiv Pilot Study Investigators. Embolic protection during saphenous vein graft intervention using a second-generation balloon protection device- results from the combined U.S. and European pilot study of the TriActiv Balloon Protected Flush Extraction System. Am Heart J 2005;149:1136.
7. Giugliano GR, Kuntz RE, Popma JJ, Cutlip DE, Baim DS. Determinants of 30-day adverse events following saphenous vein graft intervention with and without a distal occlusion embolic protection device. Am J Cardiol 2005;95:173–7.

APPENDIX

STUDY ORGANIZATION

Sponsor: Kensey Nash Corp., Exton, Pennsylvania.

Principal Investigator: Joseph P. Carrozza, Jr., MD, Beth Israel Deaconess Medical Center, Boston, Massachusetts.

Angiographic Core Laboratory: Jeffrey J. Popma, MD, Brigham and Women's Hospital, Boston, Massachusetts.

ECG Core Laboratory: Alexandra Lansky, Cardiovascular Research Foundation, New York, New York.

Clinical Events Committee: Clifford J. Berger, MD (Chairman), Boston University Medical Center, Boston, Massachusetts.

Data Safety Monitoring Board: Frederick S. Ling, MD (Chairman), University of Rochester, Rochester, New York.

Statistical Analysis: Eugene R. Heyman, PhD, Montgomery Village, Maryland.

Data Management and Analysis: PPD Medical Device, Minneapolis, Minnesota.

Study Monitor: Bailer Research, San Ramon, California.