Results of PREVENT III: A multicenter, randomized trial of edifoligide for the prevention of vein graft failure in lower extremity bypass surgery

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Objective: **The PREVENT III study was a prospective, randomized, double-blinded, multicenter phase III trial of a novel molecular therapy (edifoligide; E2F decoy) for the prevention of vein graft failure in patients undergoing infrainguinal revascularization for critical limb ischemia (CLI).**

Methods: **From November 2001 through October 2003, 1404 patients with CLI were randomized to a single intraoperative ex vivo vein graft treatment with edifoligide or placebo. After surgery, patients underwent graft surveillance by duplex ultrasonography and were followed up for index graft and limb end points to 1 year. A blinded Clinical Events Classification committee reviewed all index graft end points. The primary study end point was the time to nontechnical index graft reintervention or major amputation due to index graft failure. Secondary end points included all-cause graft failure, clinically significant graft stenosis (>70% by angiography or severe stenosis by ultrasonography), amputation/reintervention-free survival, and nontechnical primary graft patency. Event rates were based on Kaplan-Meier estimates. Time-to-event end points were compared by using the log-rank test.**

Results: **Demographics, comorbidities, and procedural details reflected a population with CLI and diffuse atherosclerosis. Tissue loss was the presenting symptom in 75% of patients. High-risk conduits were used in 24% of cases, including an alternative vein in 20% (15% spliced vein and 5% non–great saphenous vein) and 6% less than 3 mm in diameter; 14% of the cases were reoperative bypass grafts. Most (65%) grafts were placed to infrapopliteal targets. Perioperative (30-day) mortality occurred in 2.7% of patients. Major morbidity included myocardial infarction in 4.7% and early graft occlusion in 5.2% of patients. Ex vivo treatment with edifoligide was well tolerated. There was no significant difference between the treatment groups in the primary or secondary trial end points, primary graft patency, or limb salvage. A statistically significant improvement was observed in secondary graft patency (estimated Kaplan-Meier rates were 83% edifoligide and 78% placebo; $P = .016$) within 1 year. The reduction in secondary patency events was manifest within 30 days of surgery (the relative risk for a 30-day event for edifoligide was 0.45; 95% confidence interval, 0.27-0.76; $P = .005$). For the overall cohort at 1 year, the estimated Kaplan-Meier rate for survival was 84%, that for primary patency was 61%, that for primary assisted patency was 77%, that for secondary patency was 80%, and that for limb salvage was 88%.**

Conclusions: **In this prospective, randomized, placebo-controlled clinical trial, ex vivo treatment of lower extremity vein grafts with edifoligide did not confer protection from reintervention for graft failure. (J Vasc Surg 2006;43:742-51.)**

Autologous vein remains the best-performing conduit for small-caliber arterial reconstructions. However, the arterialized vein is subject to a spectrum of hemodynamic, inflammatory, and humoral mechanisms of injury that may induce pathologic changes.[1,2] Such changes are responsible for a significant incidence of vein graft stenosis or occlusion, which occur in approximately 30% to 50% of lower extremity bypasses within 3 to 5 years.[3-5] The remodeling response of vein grafts is incompletely understood but involves some requisite degree of wall thickening, which reduces wall tension. Invariably a hyperplastic neointima forms, which, when excessive, may lead to compromise of

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Competition of interest: Drs Conte, Bandyk, Clowes, Moneta, Belkin, and Berceli have each served as paid consultants to Corgentech Inc. Dr Conte has served as a paid consultant to Bristol-Myers Squibb. Dr Moneta owns stock in Bristol-Myers Squibb that predated the PREVENT III trial. Drs Seely, Lorenz, and Namini were employees of Corgentech Inc during the study and retain shares in the company.

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the lumen. Hence, neointima formation in the vein has been a primary target of experimental therapies designed to improve long-term bypass graft function.

Smooth muscle cell (SMC) proliferation is a key feature of neointimal lesions in veins and arteries, and much effort has focused on understanding SMC growth control at the molecular level. The transcription factor E2F plays a critical role in coordinating the expression of several genes that regulate cell-cycle progression, and, therefore, inhibition of E2F function is expected to block cellular proliferation.[6] Recently a new class of molecular therapeutics has been developed that consists of short double-stranded oligodeoxynucleotides (ODN) that bear a consensus binding site for a specific transcription factor. Once delivered into cells, these ODN can serve as a competitive inhibitor (decoy) to the transcription factor, thus blocking the activation of the downstream genes specific to that transcription factor.[7,8] A transcription factor decoy approach was developed to specifically target E2F and was found to be effective at inhibiting SMC proliferation and reducing neointimal hyperplasia in animal models of vascular injury.[9] Studies in a rabbit carotid-jugular interposition graft model demonstrated that edifoligide (E2F decoy) treatment of the vein at implantation reduced target gene (proliferating cell nuclear antigen and c-*myc*) expression and SMC proliferation and significantly reduced neointimal hyperplasia in the grafts as compared with controls.[10] Studies using human saphenous veins demonstrated that administration of edifoligide by using a nondistending pressure device resulted in drug delivery to approximately 90% of the cells in the vein wall.[11] The ability to effectively deliver this therapeutic agent to vein grafts with a brief (10-minute) ex vivo incubation protocol, in combination with a positive safety profile and a lack of other effective therapies to reduce vein graft disease, led to a series of clinical trials to test edifoligide in human subjects.

Phase I and II studies conducted in peripheral (PREVENT I; n = 46 patients)[11] and coronary (PREVENT II; n = 200 patients)[12] bypass graft settings suggested that edifoligide treatment of vein grafts was safe and feasible. These studies confirmed target gene inhibition in the graft wall and suggested a biological effect. The PREVENT III study was designed to test the hypothesis that edifoligide, administered ex vivo to the vein graft just before implantation, would reduce the incidence of vein graft failure in patients undergoing lower extremity bypass for the treatment of chronic limb ischemia.

METHODS

Study design. The Project or Ex-Vivo vein graft Engineering via Transfection III (PREVENT III) Study was a phase III multicenter, randomized, double-blinded, placebo-controlled trial of edifoligide for prevention of vein graft failure in patients undergoing lower extremity revascularization for critical limb ischemia (CLI). Details of the trial design are reported elsewhere[13] and are summarized here. The study was cosponsored by Corgentech Inc (South San Francisco, Calif) and Bristol-Myers Squibb (Princeton, NJ) and was conducted at 83 North American sites (Appendix I online). Enrollment was initiated in November 2001 and closed in October 2003.

The primary trial end point was the time to occurrence of nontechnical index graft failure resulting in either graft revision or major amputation (ie, transtibial or above) within 12 months of enrollment. A Clinical Events Classification (CEC) committee (Appendix II online) performed a blinded, independent review of each case of index graft failure to determine a technical or nontechnical etiology according to prespecified criteria.[13] In each case, the CEC reviewed primary source documents, including hospital admission and discharge notes, operative notes, and reports of all index graft imaging studies. For the purposes of this study, technical graft failure was predefined to exclude events that were clearly unrelated to the development of intrinsic vein graft or anastomotic disease (eg, intimal hyperplasia).

Technical failures were thus considered to be encompassed within one of four possible categories: inadequate inflow, inadequate outflow, extrinsic lesions, and intrinsic lesions. For each category, specific diagnostic criteria were detailed for the CEC in a governing process document and included factors such as the timing of the event in relation to the original surgery and the nature of findings reported by the operating surgeon/interventionalist or interpreting radiologist. The CEC was guided by a conservative philosophy in the adjudication process, considering failures to be nontechnical unless they clearly fit these prespecified detailed criteria.

Secondary end points of the study included all-cause graft failure (ie, technical or nontechnical), nontechnical primary patency, freedom from clinically significant index graft stenosis (defined as the first occurrence of any of the following: >70% stenosis by angiography, severe stenosis or occlusion by ultrasonography, index graft revision, or major amputation secondary to index graft failure), and amputation and index graft failure-free survival. In addition to these protocol-specified end points, traditional vascular surgery outcomes such as graft patency and limb salvage were calculated in accordance with suggested reporting standards.[14]

Inclusion and exclusion criteria. Patients were eligible for enrollment if they were at least 18 years of age and were scheduled to undergo an infrainguinal bypass procedure with an autologous vein conduit for the treatment of CLI (gangrene, nonhealing ischemic ulcer, or ischemic rest pain; Rutherford categories 4-6). In patients presenting with rest pain as their sole symptom, the diagnosis of CLI was corroborated by at least one of the following hemodynamic criteria: an ankle systolic pressure of 50 mm Hg or less, an ankle-brachial index (ABI) of 0.4 or less, a toe pressure of 30 mm Hg or less, a transcutaneous Po_2 of less than 30 mm Hg, or a severely ischemic or flat-line transtarsal pulse volume recording. Permissible reconstructions included reoperative vein grafts, spliced veins, vein grafts that arose from a prosthetic inflow graft at or above the femoral bifurcation, and infrainguinal bypass in the setting of simultaneous inflow (catheter-based or surgical) reconstructions.

Exclusion criteria included intermittent claudication as the indication for bypass, a planned in situ saphenous vein reconstruction (precluding the graft from ex vivo treatment in the pressurized drug-delivery device), or a documented history of a hypercoagulable condition. Revisions of preexisting infrainguinal bypass grafts, reconstructions that used any synthetic or nonautologous component, or vein grafts attached to a nonautologous graft below the femoral bifurcation were excluded.

Randomization and study drug administration. Randomization was performed at the time of operation by the investigational pharmacy at each participating site. A 1:1 randomization scheme was established by using numbered, blinded study drug kits that were supplied to each site along with a drug dispensation list. Study drug (edifoligide 40 μmol/L or placebo [buffered normal saline]) was administered ex vivo to the vein graft as a single dose in the operating room after vein harvest and before implantation. The vein was placed in a specially designed pressurization chamber (Corgentech pressure-mediated delivery system), and study drug was infused through the lumen to fill the chamber and immerse the graft. With drug both inside and outside of the vein, the chamber was pressurized to 6 pounds per square inch of nondistending pressure for 10 minutes. Subsequently the vein was removed, rinsed, and flushed in the surgeon's standard vein bath solution, and the graft was implanted. A prior clinical study had demonstrated efficient uptake of the decoy ODN by cells in the vein wall with this technique.[11] Participating surgeons and operating room assistants were trained on the proper use of the device by using on-site training sessions, a training video, and explicit directions for use.

Postoperative care and study assessments. Clinical laboratories (chemistries, hematology, and urinalysis) were collected at baseline and at 48 hours after surgery. All adverse events were recorded through the first 30 days after surgery, after which rehospitalizations, index limb-related events, and deaths were recorded through study termination at 12 months. An independent Data Safety Monitoring Board (Appendix II online) provided safety data at intervals during the study.

Early graft patency was to be documented either by intraoperative imaging (contrast angiography or duplex ultrasonography) or by duplex ultrasonography before discharge. The study protocol mandated intensive postoperative surveillance of the index graft, with duplex ultrasound imaging at 1, 3, 6, and 12 months after bypass surgery. A 9-month study was also obtained if a flow abnormality was observed at 6 months. Ultrasound studies were interpreted and recorded at the individual sites. Physical examination for vascular status, including an ABI, was conducted at baseline, on postoperative day 2, and at months 1, 3, 6, 9, and 12. A quality of life questionnaire (VascuQol[15]) was completed before surgery and at 3 and 12 months after surgery.

Investigators were allowed to use any and all appropriate concomitant medications, both before and after the procedure, as dictated by their usual clinical practice patterns. The protocol discouraged the use of postoperative anticoagulants (warfarin, heparin, or low-molecular-weight heparin) solely for the prevention of bypass graft occlusion. Concomitant medications were recorded at baseline and at all follow-up study visits.

The protocol specified an algorithm for determining the need for graft reintervention. The criteria included an angiographic stenosis of greater than 70%, recurrent symptomatic CLI and an angiographic stenosis of greater than 50%, severe hemodynamic compromise of the index limb (ABI of <0.4 or a toe pressure of <30 mm Hg), or a duplex ultrasound study indicating severe graft stenosis (a peak systolic velocity ratio of >3.0 or a peak systolic velocity of >300 cm/s). Angiography (contrast or magnetic resonance) was mandated before elective graft revision, unless contraindicated. All episodes of index graft occlusion, revision, or amputation were recorded through month 12 and submitted to the CEC committee for adjudication.

A pharmacokinetic (PK) substudy was also conducted at five sites. Thirty-one subjects were enrolled and underwent blood sampling at baseline (before the treated vein graft was implanted) and at 5, 10, 30, and 60 minutes and 2, 4, and 24 hours after flow was initiated through the index graft.

Statistical methods. The protocol-specified time-to-event end-point analyses were performed on an intent-to-treat basis by using the Kaplan-Meier method, and the treatment groups were compared by using the log rank test. Other analyses performed (Kaplan-Meier estimates) included primary, primary assisted, and secondary graft patency, as well as limb salvage, defined in accordance with published standards for outcomes reports in lower extremity revascularization.[14] All statistical tests were performed at a nominal significance level of .05. No statistical adjustment was considered for multiplicity of statistical testings.

RESULTS

Characteristics of the study cohort and index surgical procedures. A total of 1404 patients were randomized for the efficacy study at the 83 participating trial sites and make up the intention-to-treat population. Of these 1404 patients, 1138 (563 edifoligide and 575 placebo) completed the 12-month follow-up. A total of 18 (1.3%) patients (12 edifoligide and 6 placebo) were lost to follow-up, and 26 (1.9%) patients (17 edifoligide and 9 placebo) withdrew from the study. There were 222 deaths (15.8%; 115 edifoligide and 107 placebo) during the year after enrollment. An additional group of 16 patients were enrolled to complete the PK substudy after the intention-to-treat group was fully enrolled. The safety population for PREVENT III therefore included 1420 patients. As prespecified in the protocol, these additional 16 patients were followed up only for adverse events for 30 days and were not included in the efficacy analyses.

Characteristics of the study population (intention-to-treat) are summarized in Table I and are consistent with advanced atherosclerosis. Most patients were male (64%), with a mean (±SD) age of 69 ± 12 years. Prevalent comor-

Table I. Characteristics of the PREVENT III study population at baseline

Variable	*Edifoligide (n = 707)*	*Placebo (n = 697)*
Age (y)		
Mean ± SD	68.7 ± 11.68	68.3 ± 11.42
Median	70.0	69.0
Male	454 (64.2%)	443 (63.6%)
Ethnic origin		
White	526 (74.4%)	491 (70.4%)
Black	116 (16.4%)	133 (19.1%)
Asian	3 (0.4%)	7 (1.0%)
Hispanic	53 (7.5%)	54 (7.7%)
Other	9 (1.3%)	12 (1.7%)
CLI criterion (worst)		
Rest pain	184 (26.0%)	169 (24.2%)
Nonhealing ulcer	273 (38.6%)	280 (40.2%)
Gangrene	247 (34.9%)	246 (35.3%)
Ankle-brachial index		
Mean	0.5	0.5
Median	0.4	0.4
Comorbidities		
Hypertension	577 (81.6%)	569 (81.6%)
Diabetes	461 (65.2%)	439 (63.0%)
CAD	353 (49.9%)	324 (46.5%)
CVD	144 (20.4%)	140 (20.1%)
Smoking*	520 (73.5%)	513 (73.6%)
Dyslipidemia	393 (55.6%)	373 (53.5%)
Dialysis	84 (11.9%)	86 (12.3%)
Prior leg revascularization†		
Inflow	146 (20.7%)	147 (21.1%)
Infrainguinal (either limb)	190 (26.9%)	193 (27.7%)

CLI, Critical limb ischemia; *CAD,* coronary artery disease (prior myocardial infarction or surgical or percutaneous revascularization); *CVD,* cerebrovascular disease (prior stroke or transient ischemic attack).
Data are n (%) unless otherwise noted; *P* values for all are not significant.
*Smoking includes current or former as self-reported.
†Prior leg revascularization includes either surgical or percutaneous interventions.

Table II. Characteristics of procedures performed

Variable	*Edifoligide (n = 707)*	*Placebo (n = 697)*
Reoperative bypass	124 (17.5%)	106 (15.2%)
Conduit type		
Single segment GSV, reversed	371 (52%)	360 (52%)
Single segment GSV, nonreversed	207 (29%)	193 (28%)
Spliced vein	95 (13%)	110 (16%)
Single segment non-GSV	34 (5%)	34 (5%)
Vein diameter <3 mm	36 (5.1%)	49 (7.0%)
Total high-risk conduits*	158 (22%)	181 (26%)
Proximal anastomosis		
Common femoral	352 (50%)	335 (48%)
Superficial femoral	164 (23%)	184 (26%)
Deep femoral	39 (6%)	41 (6%)
Popliteal	129 (18%)	118 (17%)
Other	23 (3%)	19 (3%)
Distal anastomosis		
Popliteal, above knee	69 (10%)	76 (11%)
Popliteal, below knee	161 (23%)	151 (22%)
Anterior tibial	106 (15%)	113 (16%)
Posterior tibial	136 (19%)	154 (22%)
Peroneal	132 (19%)	107 (15%)
Pedal/plantar	80 (11%)	86 (12%)
Other	17 (2%)	10 (1%)

GSV, Great saphenous vein.
All data are n (%); *P* = not significant.

bidities included hypertension (82%), smoking (74%), diabetes (64%), and hyperlipidemia (55%). Forty-eight percent had a history of advanced coronary artery disease, including previous myocardial infarction in 30%, previous coronary artery bypass in 25%, and previous percutaneous coronary intervention in 17%. Twenty percent of patients had a history of stroke or transient ischemic attack (symptomatic cerebrovascular disease). Previous lower extremity bypass surgery had been performed in 27% of patients, and 17% were in the limb contralateral to the index graft. Dialysis-dependent renal failure was present in 12% of patients at study entry. The groups were well matched for all of the comorbidities and baseline demographics.

Seventy-five percent of patients presented with tissue loss (39% ulcer and 35% gangrene). Diabetic patients were significantly more likely to present with tissue loss (86% vs 56%; $P < .0001$). For 16% of patients, the index operation constituted a reoperative infrainguinal bypass in that limb. A single-segment vein graft was used in 85% of cases, and 15% required spliced vein grafts. Overall, 20% of cases required either a spliced or non–great saphenous venous conduit. These conduits, in addition to those having less than a 3-mm initial diameter (6%), were designated as high risk (24% overall).

Proximal anastomoses arose from the common femoral artery in 49%, the superficial femoral artery in 25%, and the popliteal artery in 18% of patients. Distal anastomoses were performed primarily to tibial vessels (53%); 33% were performed to popliteal and 12% to pedal targets. Procedural details are summarized in Table II. There were no significant differences between the study arms.

Review of relevant medications being taken by subjects at study entry revealed that 67% were receiving antiplatelet agents (including aspirin in 61% and thienopyridine drugs in 17%) and that 20% were taking anticoagulant medications. In total, 76% of patients were taking some antithrombotic drug at the time of entry into PREVENT III. Lipid-lowering drugs were taken by 46% of patients and β-blockers were taken by 48% at baseline. There were no significant differences in use of these medications between the edifoligide and placebo treatment arms. A detailed analysis of factors related to the use of cardioprotective medications in PREVENT III is reported elsewhere.[16]

Adherence to the protocol-specified ultrasound surveillance schedule was achieved in a high percentage of patients. Overall, 98% of eligible grafts were imaged at least once by duplex scan. Compliance at each of the individual study windows was 92% at 1 month, 83% at 3 months, 85% at 6 months, and 62% at 12 months.

Early (30-day) adverse postoperative events. Perioperative (30-day) mortality for the entire trial cohort was 38 patients (2.7%). Major complications (Table III)

Table III. Postoperative (30-day) complications

Variable	*Edifoligide*	*Placebo*	*Total*
Total major morbidity	123 (17.4%)	124 (17.8%)	247 (17.6%)
Cardiac or respiratory arrest	12 (1.7%)	9 (1.3%)	21 (1.5%)
DVT	6 (<1.0%)	8 (1.1%)	14 (<1.0%)
Death	20 (2.8%)	18 (2.6%)	38 (2.7%)
Graft occlusion	30 (4.2%)	43 (6.2%)	73 (5.2%)
Major amputation	13 (1.8%)	12 (1.7%)	25 (1.8%)
Myocardial infarction	33 (4.7%)	33 (4.7%)	66 (4.7%)
Pneumonia	10 (1.4%)	13 (1.9%)	23 (1.6%)
Pulmonary embolism	1 (<1.0%)	0 (0.0%)	1 (<1.0%)
Stroke/TIA	12 (1.7%)	8 (1.1%)	20 (1.4%)
Major wound complication	37 (5.2%)	30 (4.3%)	67 (4.8%)
Dehiscence	3 (<1.0%)	9 (1.3%)	12 (<1.0%)
Infection	24 (3.4%)	15 (2.2%)	39 (2.8%)
Necrosis	9 (1.3%)	6 (<1.0%)	15 (1.1%)
Unknown	1 (<1.0%)	0 (0.0%)	1 (<1.0%)
Graft Hemorrhage	3 (0.4%)	3 (0.4%)	6 (0.4%)

DVT, Deep venous thrombosis; *TIA,* transient ischemic attack.
All data are n (%); P = not significant.

included myocardial infarction in 66 patients (4.7%) and cerebrovascular event (stroke or transient ischemic attack) in 20 (1.4%). Early occlusion of the index graft occurred in 73 (5.2%) patients. There were no significant differences in early adverse postoperative events between the study treatment groups. The PK substudy demonstrated that serum levels of edifoligide were not detectable in most patients and that if they were detectable in the highly sensitive assay used, they were generally only slightly above the lower level of detection (2 ng/mL).

Protocol-specified study end points. The primary study end point, a Kaplan-Meier estimate of nontechnical index graft failure, was observed in 356 (25.4%) patients in the trial, with no significant difference noted between the edifoligide (25.2%) and placebo (25.5%) study arms (Fig 1, *A*). The other protocol-specified end points (Table IV and Fig 1), including Kaplan-Meier estimates at 12 months of all-cause clinical failure (34.8% vs 36%), freedom from clinically significant index graft stenosis (44.3% vs 46.1%), nontechnical primary index graft patency (70.7% vs 70.7%), and amputation/reintervention-free survival (50.1% vs 48.6%) also failed to demonstrate a significant treatment effect.

Graft patency, limb salvage, and patient survival. For the overall trial cohort, primary, primary assisted, and secondary graft patency rates (as conventionally defined[14]) were 61%, 77%, and 80%, respectively. Comparison between the study arms revealed no significant difference in primary or primary assisted graft patency (Table IV and Fig 2). However, a significant improvement in secondary graft patency was noted in the edifoligide group (83% vs 78%; $P = .016$). A significant difference in secondary patency was manifest within 30 days of surgery (relative risk of 30-day event for edifoligide group, 0.45; 95% confidence interval, 0.27-0.76; $P = .005$; Fig 2, *C*).

Several post hoc subgroup analyses were performed to evaluate for potential drug effects. Among high-risk grafts (defined as a diameter <3 mm, a spliced vein, or a non–great saphenous vein conduit), primary (42% vs 46%), primary assisted (63% vs 64%), and secondary (71% vs 67%) patency outcomes were not different between treatment groups. No significant treatment effects could be discerned when outcomes were evaluated separately in diabetic patients or for reoperative graft procedures or when the operations were stratified by mode of presentation, distal outflow target, or graft length. Patient survival (84%) and limb salvage (88%) were not significantly different between the two treatment groups (Table IV; Fig 2, *D* and *E*).

Nature of graft lesions and types of reinterventions performed. We attempted to evaluate the overall burden of vein graft disease by examining the nature of lesions that required reintervention and the types of procedures performed (Table V). Of grafts that underwent any reintervention during the study period, 70% had a single revision, 22% had two, and 8% had three or more; the proportions were nearly identical in both study arms. The first graft reintervention was a percutaneous angioplasty or open patch in 56%; a jump or interposition graft in 16%; and a thrombectomy, thrombolysis, or the creation of an entirely new graft in 28.5%. In this post hoc analysis, there were 73 patients in the placebo group who had thrombectomy, thrombolysis, or an entirely new graft placed as their first reintervention, in comparison to 51 in the edifoligide group ($P = .040$; χ^2). We also analyzed data from the ultrasonography preceding the first reintervention and compared the number of graft lesions identified. In 57% of cases, a single lesion had been identified, whereas in 20% there were two; no significant difference was found in the number of lesions according to treatment group.

DISCUSSION

The PREVENT III trial was well powered to test its primary hypothesis, with a randomized population of more than 1400 subjects; hence, the results of the study are unambiguous. The data clearly demonstrate that edifoligide treatment did not reduce the incidence of vein graft reintervention or the development of significant stenoses in a large cohort of patients undergoing infrainguinal reconstruction for CLI. However, although none of the protocol-specified study end points was met in the edifoligide arm, a significant improvement in graft secondary patency was observed. The risk reduction observed (5% absolute and 19% relative reduction in secondary patency events) seems to suggest some beneficial biological effect of the therapy that merits further inspection.

The improvement in secondary patency observed in the edifoligide group, in the absence of any observed effect on primary graft patency or the occurrence of clinically significant stenosis, was unexpected and raises important questions about the presumed biologic effects of the drug, as well as the relationship between the process presumably being targeted (intimal hyperplasia) and the clinical end points measured. Possible explanations for the observed

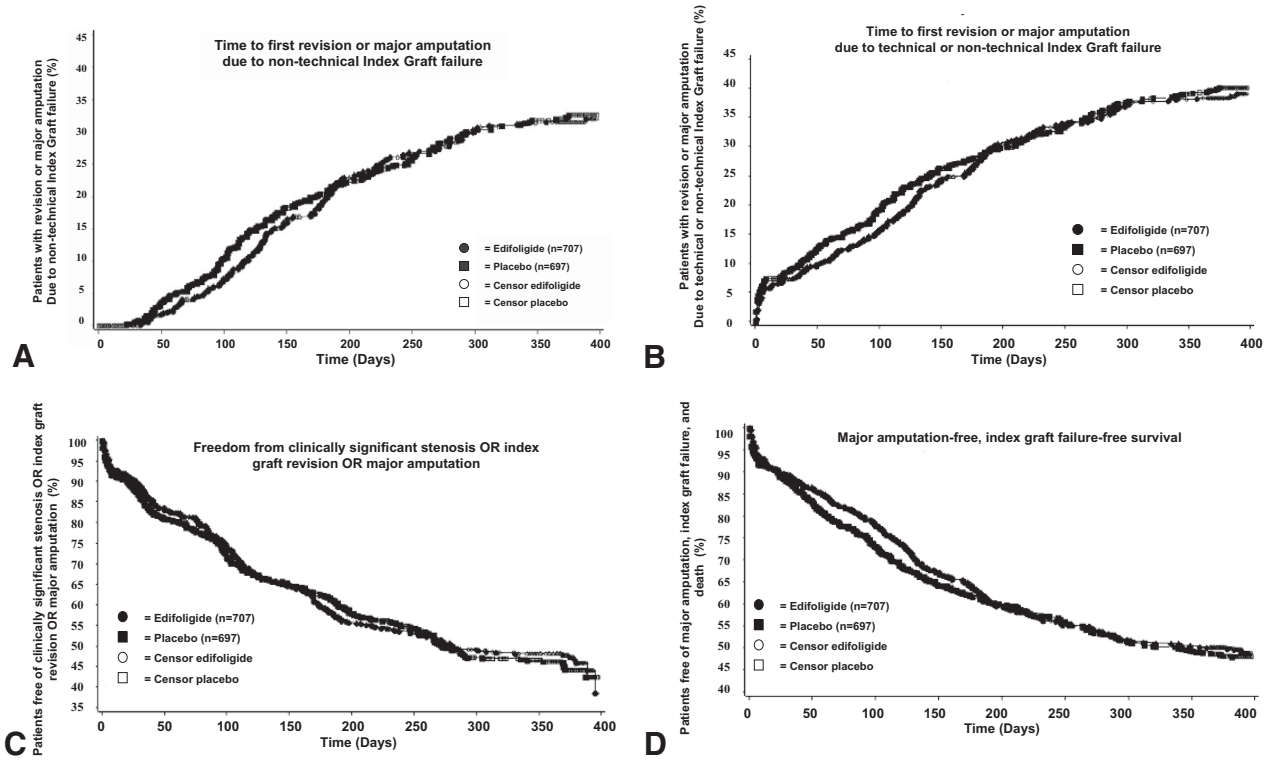

Fig 1. Analysis of protocol-specified end points by the Kaplan-Meier method (P = not significant for all). **A,** Primary study end point: nontechnical index graft failure. **B,** All-cause index graft failure. **C,** Freedom from clinically significant index graft stenosis. **D,** Event-free survival.

Table IV. Summary of outcomes at 1 year (all data reported as Kaplan-Meier estimated percentages)

Variable	*Edifoligide*	*Placebo*	P *value*
Protocol-specified end points			
Primary trial end point (nontechnical failure)	25.2	25.5	.69
All clinical failures	34.8	36	.51
Freedom from clinically significant stenosis	44.3	46.1	.62
Amputation/ reintervention-free survival	50.1	48.6	.47
Conventional end points			
Primary patency	61.5	59.5	.38
Primary assisted patency	78.6	74.7	.10
Secondary patency	82.6	77.5	.02
Limb salvage	87.7	89.2	.37
Survival	83.2	84.4	.55

effect include previously unknown antithrombotic or anti-inflammatory properties of the drug. It is also possible that the secondary patency benefit relates to a reduction in the virulence of the hyperplastic process, which in its most severe form could result in rapidly progressive or unheralded occlusions. The secondary patency benefit is also reflected in the nature of the first intervention, as presented in Table V. Of course, the possibility that this statistically significant finding occurred by chance alone and would not be replicated if the trial were repeated must also be considered.

Prevention of amputation or graft reintervention was rightfully selected as the primary study end point in PREVENT III, because it directly relates to patient morbidity. However, these end points very likely do not accurately reflect the overall burden of proliferative disease within the graft, because a very focal lesion treatable by patch angioplasty and a long severe stricture requiring extensive graft replacement were counted equally as end points. We examined the number of lesions observed by ultrasonography, the number of reinterventions performed, and the magnitude of the reinterventions performed as potential surrogates for graft disease burden; however, each of these measures has limitations. Intravascular ultrasonography has been used effectively for this purpose in coronary artery and vein graft disease and was used in PREVENT II; however, the technique is costly and invasive and adds real potential risk in the lower extremity setting. Lacking a better surrogate measure of graft intimal hyperplasia, we are ultimately unable to discriminate between an incorrect target (E2F specifically or SMC proliferation in general) or ineffectiveness of the therapy to block the target as an explanation for the failure of edifoligide to prevent vein graft failure in this large study.

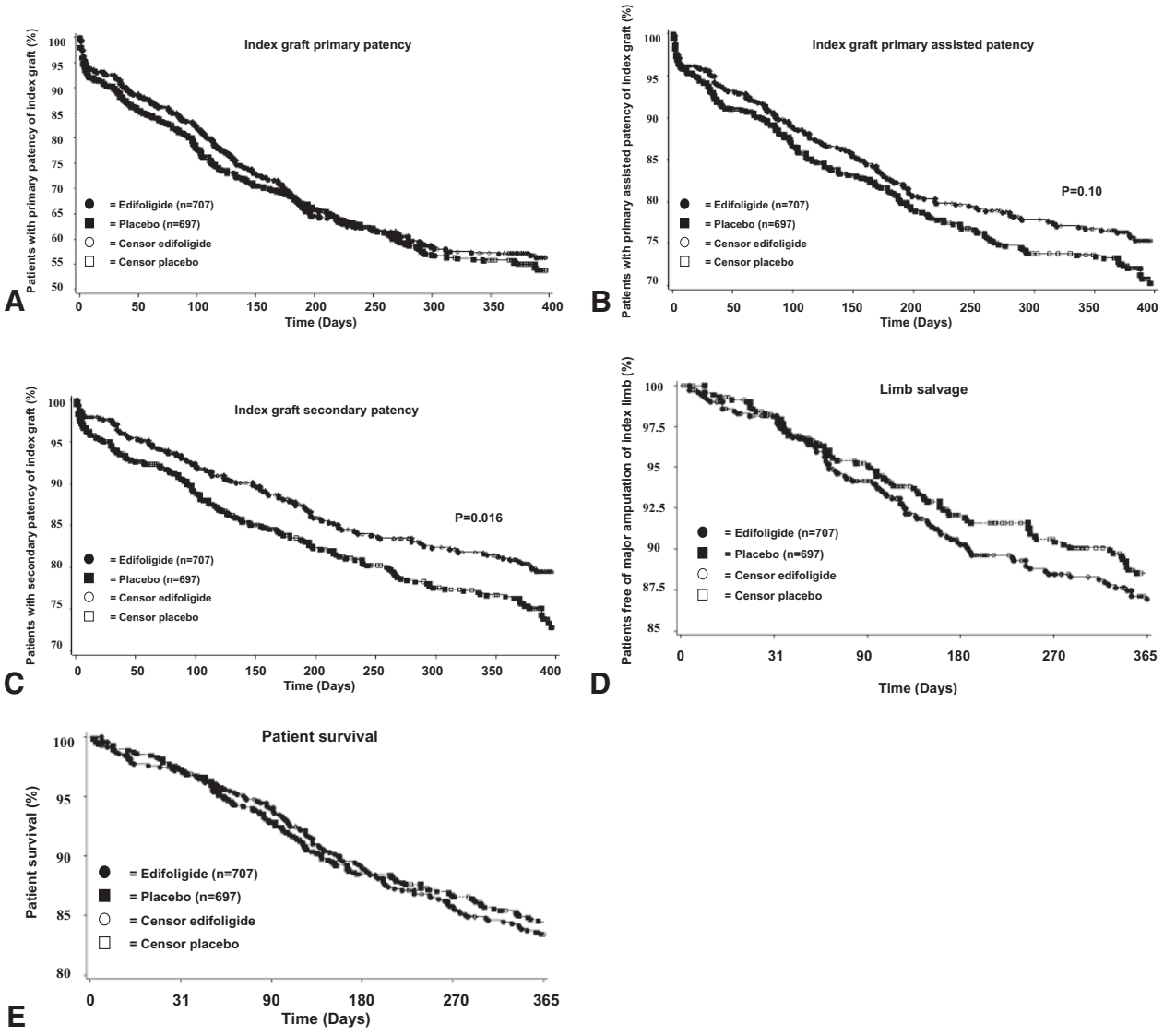

Fig 2. Outcomes at 1 year by the Kaplan-Meier method. **A,** Primary graft patency (P = not significant). **B,** Primary assisted graft patency (P = not significant). **C,** Secondary graft patency (P = .016; log-rank test). **D,** Limb salvage (P = not significant). **E,** Patient survival (P = not significant).

PREVENT III was a novel trial in multiple respects. It constitutes the largest prospective, randomized study of vein bypass for advanced lower extremity ischemia performed to date, and the overall surgical results will stand as a benchmark for current practice. The population studied was restricted to CLI specifically because traditionally reported failure rates have been higher than in claudicants and also because this population was believed to have the most potential gain from a beneficial therapy. In addition, study entry criteria were intentionally set to be broad, thus allowing the enrollment of patients requiring complex reoperative procedures as well as those with advanced comorbid conditions (eg, dialysis-dependent renal failure). The study population thus truly reflects the current practice of limb salvage surgery, with its inherent medical and surgical complexities, complications, and mortality. In this context, the perioperative mortality (2.7%) and graft occlusion (5.2%) rates observed in PREVENT III compare well to those of retrospective single-center series. This attests to the high standard of care provided by the participating investigators and centers. Furthermore, the 1-year outcomes of 84% survival, 80% secondary patency, and 88% limb salvage are well within the expected range for patients with CLI.

These data suggest that treatment of the vein ex vivo with edifoligide in the pressurized drug-delivery system was well tolerated. The drug-delivery parameters used (concentration, time, and pressure) were based on extensive pre-

Table V. Nature of treated graft lesions and reinterventions

Variable	*Edifoligide*	*Placebo*	*Total*
Total number of reinterventions per graft			
One	162 (70.7%)	160 (69.6%	322 (70.2%)
Two	52 (22.7%)	49 (21.3%)	101 (22.0%)
Three or more	15 (6.6%)	21 (9.1%)	36 (7.8%)
Nature of first reintervention*			
PTA or patch angioplasty	123 (57.2%)	118 (53.9%)	241 (55.6%)
Jump or interposition graft	41 (19.1%)	28 (12.8%)	69 (15.9%)
Thrombectomy/thrombolysis or new graft†	51 (23.7%)	73 (33.4%)	124 (28.5%)
Number of significant lesions via prior ultrasonography‡			
Zero	38 (16.2%)	41 (17.9%)	79 (17.0%)
One	130 (55.3%)	135 (59.0)%	265 (57.1%)
Two	54 (23.0%)	20 (17.5%)	94 (20.3%)
Three or more	13 (5.6%)	13 (1.3%)	26 (1.1%)

PTA, Percutaneous transluminal angioplasty.
All data are presented as the number (%) of patients, where the denominator consists soley of those that underwent an index graft reintervention or amputation.
*Excludes amputations.
†$P = .04$, χ^2; all other comparisons are not significant.
‡Ultrasound findings on the most recent study before the first graft reintervention.

clinical testing for optimization of ODN transfection into veins.[17] Device training was provided to all investigators in the study. Nonetheless, there remains a possibility that incorrect or inappropriate use of the device could have led either to inadequate drug delivery or to inadvertent damage to the vein. No vein graft samples were taken in this trial to verify that adequate drug was delivered or to examine the biological effects of drug treatment (eg, target gene inhibition or cell proliferation), as was done in the PREVENT I study.[11] Furthermore, in PREVENT III, grafts in the control arm were also treated with pressurization in the device, to ensure complete blinding as to study drug treatment. Prior phase I and II investigations had not demonstrated an apparent adverse effect of vein exposure to nondistending pressure of this nature; however, formal testing would have required a three-arm study to include standard intraoperative handling of the vein. Because there are no comparable large, multicenter, prospective studies in this population, we are unable to make a definitive comment on whether the handling of vein grafts in the placebo arm had any effects on outcome. However, early graft thrombosis/reintervention rates in PREVENT III were well within the range of prior retrospective reports, and the Data Safety Monitoring Board (which reviewed study data at three prespecified intervals) overseeing the trial confirmed a lack of safety concerns. The use of this system or similar systems to efficiently deliver small oligonucleotides (or other molecular agents) locally to veins ex vivo has great attractiveness for intraoperative therapies, and the feasibility of such an approach has been definitively established by PREVENT III.

In addition to the points already mentioned, there are some other relevant limitations to this study. Graft surveillance studies were performed and interpreted at the individual sites, in accordance with local vascular laboratory procedures. All study sites used fully accredited vascular laboratories. A central core laboratory was not used for review of imaging studies in PREVENT III. Because surveillance studies lead directly to reinterventions, variability in patient compliance or in the performance of these studies could have direct effects on study end points. Nonetheless, the study was executed in the fashion that most mirrors clinical practice, and randomization would be expected to balance any local variability in reintervention rates. Along similar lines, mandating a standardized approach to concomitant medical therapy would offer scientific advantages but would require major changes in the local and individual practice settings.

Recently reported results from PREVENT IV, the phase III trial of edifoligide vs placebo in 3000 patients undergoing coronary artery vein bypass graft procedures, also demonstrated the absence of a drug effect on any of the primary or secondary end points.[18] These two large phase III trials of edifoligide were based largely on data from two prior single-center phase I and II trials: one in the lower extremity and one in the coronary circulation. Because of the wide variability in surgical technique and in the geographic variability of surgical patient populations, it seems prudent to recommend that phase III surgical trials be based on multicenter phase II experience if at all possible.

In conclusion, this prospective, randomized clinical trial failed to demonstrate a reduction in vein graft failure in CLI patients treated with a single ex vivo administration of a novel molecular agent, edifoligide. Although the primary results are disappointing, PREVENT III has demonstrated that large multicenter trials of an intraoperative genetic intervention designed to modulate the vascular injury response can be executed safely and with high surgical and scientific quality. It is hoped that future investigations, informed by the design and outcomes of this study, will continue to explore targeted molecular therapies to improve outcomes for patients undergoing vascular reconstructions.

Bryan Selby, MS, and Rob Tatum (Corgentech Inc) provided data manipulation and biostatistical services for the PREVENT III study.[15]

AUTHOR CONTRIBUTIONS

Conception and design: MSC, DFB, AWC, GLM, TJL
Analysis and interpretation: MSC, DFB, AWC, GLM, LS, TJL, HN, MB
Data collection: MSC, DFB, AWC, GLM, LS, TJL, ADH, SPR, MB, SAB
Writing the article: MSC, LS
Critical revision of the article: MSC, DFB, AWC, GLM, LS, TJL, HN, MB
Final approval of the article: MSC, DFB, AWC, GLM, LS, TJL, ADH, SPR, HN, MB, SAB
Statistical analysis: HN
Obtained funding: TJL
Overall responsibility: MSC

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DISCUSSION

Dr Frank LoGerfo *(Boston, Mass)*. I think you can argue that this is the most accurate outcome study of lower extremity vein grafts, certainly in my career in vascular surgery, where we have such detailed duplex study outcomes in every patient, including the 1-month outcome. I wonder if this trial is really a failure in the sense that a 20% improvement in secondary patency is certainly, in the long run, what we are most concerned about. And I'm wondering, then, what about that first month where those are purely technical failures. If you take that out of the picture, how does it look? And finally, you have dozens of interesting risk factors here that you could relate to outcome. Are you prepared and capable of further analyzing these data, which are so extraordinarily valuable?

Dr Conte. Thank you, Dr LoGerfo. We certainly appreciate the support of your institution in this study as our leading enroller. As you point out, the secondary patency effect was significant. And, in fact, a prevention of secondary events in one out of five patients seems like a fairly good result. As you might expect, the primary difference between the groups was in the frequency of abandoned grafts. It turns out that the early difference in secondary patency is significant but is small. If you exclude the 30-day events, the secondary patency curves are still different. We're not sure what to ascribe this to. It's possible that this drug has some other effects that we don't know about, such as effects on thrombosis or inflammation, that might explain some of this. The subgroup analyses, as you know, have been ongoing, and we have looked at some things. What I can tell you, to date, is that there did not appear to be an enhancement of effect, for example, in high-risk grafts, diabetic patients, or any of the categories that we've looked at thus far. We have not boiled out a subgroup that really showed an enhanced drug effect. There is still a lot of work to be done in this database, and we hope to be able to do that over the next few months.

Dr Alan Dardik *(New Haven, Conn)*. Even though the results of the primary intervention were not dramatic, the importance of establishing that molecular therapy is safe, is important in our literature. Two questions. First, did you or any of the investigators have the opportunity to examine these grafts in follow up with IVUS [intravascular ultrasound] and, perhaps, examine the intima-media ratios of these grafts? I think that some of your preliminary reports indicated that changing the I-to-M [intima-media] ratios were an important benefit of this

drug. And second, I'm wondering, how does this result compare with some of the previous results of the cardiac trials? Do they imply anything for us?

Dr Conte. As you can see from the last bit of what I presented, we have been struggling with trying to get a measure, a surrogate measure, of intimal hyperplasia in the graft. I agree with you that one of the best ways that I could think of doing that would be IVUS. It was not done in this study, and I think it is actually considerably more difficult to accomplish in the lower extremity as compared to in the coronary circulation where you're not actually puncturing the graft. But I think it would have been quite valuable to have a measure of total graft wall thickening. Unfortunately, we don't have that type of data in this study. In regard to the cardiac trial results, all I can say about that is what's been said publicly in the press release, which is that PREVENT IV was also negative in terms of the primary study end points. They are also doing many other analyses in their database and will be presenting their data very shortly.

Dr Thomas Lindsay *(Toronto, Ontario, Canada)*. I wanted to ask, as an investigator, how do we know that we actually delivered the drug to the vein grafts equally across so many investigational sites? As you know, pressurizing the device was subject to a little bit of error, I would imagine, despite the fact that we'd all been trained. So how do we know that we actually delivered the drug appropriately?

Dr Conte. It's a terrific question and one that we continue to wonder about. And I can only give you a partial answer. What was recorded by study monitors were gross problems with drug delivery in the operating room if, for example, the device didn't function or there was some other mishap in drug handling. That turned out to be a very, very small number of cases. So, of course, we're left with several possibilities, including the possibility that the molecular target was wrong or the possibility that that target is right but was inadequately treated by the drug either because of the variability in delivery or perhaps the mode of a single delivery. We just don't know how to discriminate those at the present time. Having said that, all the centers had training with the device, as you know, including either on-site training or a video, and it's a fairly simple device to use.

APPENDIX I: PREVENT III TRIAL PRINCIPAL INVESTIGATOR LIST BY ENROLLMENT

Alan Hamdan, MD (Boston, Mass); 77 patients
Sean Roddy, MD (Albany, NY); 68 patients
Scott Berceli, MD (Gainesville, Fla); 67 patients
David Cossman, MD (Los Angeles, Calif); 64 patients
William H'Doubler, MD (Roanoke, Va); 60 patients
James McNeil, MD (Baton Rouge, La); 52 patients
Dennis Bandyk, MD (Tampa, Fla); 49 patients
Michael Conte, MD (Boston, Mass); 48 patients
Scott Berman, MD (Tucson, Ariz); 42 patients
John Eidt, MD (Little Rock, Ark); 40 patients
Gregory Moneta, MD (Portland, Ore); 36 patients
Russell Samson, MD (Sarasota, Fla); 36 patients
Silverio Cabellon, MD (Washington, DC); 35 patients
Richard DeMasi, MD (Norfolk, Va); 34 patients
Ralph Pfeiffer, MD (Mobile, Ala); 32 patients
Robert Hye, MD (San Diego, Calif); 27 patients
David Mozersky, MD (San Antonio, Tex); 27 patients
Victoria Teodorescu, MD (New York, NY); 26 patients
Roman Nowygrod, MD (New York, NY); 25 patients
Charles Shanley, MD (Royal Oak, Miss); 24 patients
Mark Davies, MD (Rochester, NY); 22 patients
Andrew Hill, MD (Ottawa, Ontario, Canada); 22 patients
William Bogey, MD (Greenville, NC); 20 patients
Edith Tzeng, MD (Pittsburgh, Pa); 20 patients
David Han, MD (Hershey, Pa); 19 patients
Kenneth Harris, MD (London, Ontario); 19 patients
Richard Powell, MD (Lebanon, NH); 19 patients
Jeffrey Martinez, MD (San Antonio, Tex); 18 patients
Michael Dalsing, MD (Indianapolis, Ind); 17 patients
Randy Guzman, MD (Winnipeg, Manitoba); 17 patients
Alan Lumsden, MD (Houston, Tex); 16 patients
Elliott Chaikof, MD (Atlanta, Ga); 14 patients
Paul Gagne, MD (New York, NY); 14 patients
Ronald Dalman, MD (Palo Alto, Calif); 12 patients
William Edwards, Jr, MD (Nashville, Tenn); 12 patients
Randolph Geary, MD (Winston-Salem, NC); 12 patients
Paul Petrasek, MD (Calgary, Alberta); 12 patients
Thomas Brothers, MD (Charleston, SC); 11 patients
Mark Eskandari, MD (Chicago, Ill); 11 patients
Sushil Gupta, MD (Sayre, Pa); 11 patients
Peter H'Doubler, MD (Atlanta, Ga); 11 patients
John Blebea, MD (Philadelphia, Pa); 10 patients
Eric Choi, MD (St. Louis, Mo); 10 patients
Ted Kohler, MD (Seattle, Wash); 10 patients
Edward Marcaccio, MD (Providence, RI); 10 patients
Frank Veith, MD (New York, NY); 10 patients
Cornelius Dyke, MD (Gastonia, NC); 9 patients
Joseph Mills, MD (Tucson, Ariz); 9 patients
Barry Rubin, MD (Toronto, Ontario); 9 patients
Mark Sarfati, MD (Salt Lake City, Utah); 9 patients
G. Melville Williams, MD (Baltimore, Md); 9 patients
Enrico Ascher, MD (New York, NY); 8 patients
Timothy Baxter, MD (Omaha, Neb); 8 patients
Robert Cambria, MD (Milwaukee, Wis); 8 patients
Anthony Comerota, MD (Toledo, Ohio); 8 patients
York Hsiang, MD (Vancouver, British Columbia, Canada); 8 patients
Timur Sarac, MD (Cleveland, Ohio); 8 patients
Mark Glickman, MD (Norfolk, Va); 7 patients
Gary Nackman, MD (New Brunswick, NJ); 7 patients
John Castronuovo, MD (Morristown, NJ); 6 patients
Jim Estes, MD (Boston, Mass); 6 patients
Michael Silva, MD (Lubbock, Tex); 6 patients
Jonathan Deitch, MD (Brooklyn, NY); 5 patients
Jens Eldrup-Jorgensen, MD (Portland, Me); 5 patients
Michael Freeman, MD (Knoxville, Tenn); 5 patients
Peter Pappas, MD (Newark, NJ); 5 patients
Thomas Rehring, MD (Denver, Colo); 5 patients
Jodi Spelay, MD (Saskatoon, Saskatchewan, Canada); 5 patients
Tina Desai, MD (Chicago, Ill); 4 patients
William Jordan, MD (Birmingham, Ala); 3 patients
Audra Noel, MD (Rochester, Minn); 3 patients
David Drezner, MD (Hartford, Conn); 2 patients
Michael Golden, MD (Philadelphia, Pa); 2 patients
Michael Lilly, MD (Baltimore, Md); 2 patients
Craig Kent, MD (New York, NY); 1 patient

APPENDIX II: PREVENT III TRIAL CENTRAL COMMITTEES

Steering Committee
Michael Conte, MD, Chair (Boston, Mass)
Dennis Bandyk, MD (Tampa, Fla)
Alexander Clowes, MD (Seattle, Wash)
Gregory Moneta, MD (Portland, Ore)
Lynn Seely, MD (Corgentech Inc)

Data Safety Monitoring Board
Robert Harrington, MD, Chair (Durham, NC)
Kerry Lee, PhD (Durham, NC)
John Ricotta, MD, (Stonybrook, NY)

Clinical Events Committee
Michael Belkin MD, Chair (Boston, Mass)
Dennis Bandyk, MD (Tampa, Fla)
Scott Berceli, MD (Gainesville, Fla)
David Chew, MD (Boston, Mass)
Alexander Clowes, MD (Seattle, Wash)
Michael Conte MD (Boston, Mass)
Edwin Gravereaux, MD (Boston, Mass)
Matthew Menard, MD (Boston, Mass)
Gregory L. Moneta, MD (Portland, Ore)

Publications and Presentations Committee
Gregory Moneta, MD, Chair (Portland, Ore)
Dennis Bandyk, MD (Tampa, Fla)
Michael Belkin, MD, Chair (Boston, Mass)
Scott Berceli, MD (Gainesville, Fla)
Scott Berman, MD (Tucson, Ariz)
Alexander Clowes, MD (Seattle, Wash)
Michael Conte, MD (Boston, Mass)
Richard DeMasi, MD (Norfolk, Va)
Alan Hamdan, MD (Boston, Mass)
Sean Roddy, MD (Albany, NY)
Russell Samson, MD (Sarasota, Fla)