Efficacy and Safety of Edifoligide, an E2F Transcription Factor Decoy, for Prevention of Vein Graft Failure Following Coronary Artery Bypass Graft Surgery
PREVENT IV: A Randomized Controlled Trial

PREVENT IV Investigators*

CORONARY ARTERY BYPASS GRAFT (CABG) surgery is one of the most common surgical procedures performed in the United States. In appropriately selected patients, CABG surgery results in improved survival, relief of angina, and improved quality of life. Despite frequent use of internal thoracic artery (ITA) grafts, autologous saphenous vein remains the most frequently used conduit. The long-term patency of vein grafts is limited and graft failure has consequences similar to those of native coronary artery disease: recurrent angina, myocardial infarction (MI), additional revascularization procedures, and premature death.

Neointimal hyperplasia leading to accelerated atherosclerosis and thrombosis is one proposed mechanism of vein graft failure. Neointimal hyperplasia begins as an adaptive response to the increased pressure and shear forces of arterial circulation. Hyperplasia results from proliferation and migration of vascular smooth muscle cells, which release cytokines that degrade the surrounding matrix and contribute to an inflammatory and highly atherogenic environment. The E2F transcription factors have been implicated in the up-regulation of several genes believed to play a key role in the initiation of neointimal hyperplasia.

A novel approach to inhibiting neointimal hyperplasia involves the double-stranded oligonucleotide decoy to E2F, edifoligide (Corgentech Inc, South San Francisco, Calif). Edifoligide is an oligonucleotide that binds to and inhibits E2F transcription factors and thus may prevent neointimal hyperplasia and vein graft failure.

Context Coronary artery bypass graft (CABG) surgery with autologous vein grafting is commonly performed. Progressive neointimal hyperplasia, however, contributes to considerable vein graft failure. Edifoligide is an oligonucleotide decoy that binds to and inhibits E2F transcription factors and thus may prevent neointimal hyperplasia and vein graft failure.

Objective To assess the efficacy and safety of pretreating vein grafts with edifoligide for patients undergoing CABG surgery.

Design, Setting, and Participants A phase 3 randomized, double-blind, placebo-controlled trial of 3014 patients undergoing primary CABG surgery with at least 2 planned saphenous vein grafts and without concomitant valve surgery, who were enrolled between August 2002 and October 2003 at 107 US sites.

Intervention Vein grafts were treated ex vivo with either edifoligide or placebo in a pressure-mediated delivery system. The first 2400 patients enrolled were scheduled for 12- to 18-month follow-up angiography.

Main Outcome Measures The primary efficacy end point was angiographic vein graft failure (>=75% vein graft stenosis) occurring 12 to 18 months after CABG surgery. Other end points included other angiographic variables, adverse events through 30 days, and major adverse cardiac events.

Results A total of 1920 patients (80%) either died (n=91) or underwent follow-up angiography (n=1829). Edifoligide had no effect on the primary end point of per patient vein graft failure (436 [45.2%] of 965 patients in the edifoligide group vs 442 [46.3%] of 955 patients in the placebo group; odds ratio, 0.96 [95% confidence interval (CI), 0.80-1.14]; P=.66), on any secondary angiographic end point, or on the incidence of major adverse cardiac events at 1 year (101 [6.7%] of 1508 patients in the edifoligide group vs 121 [8.1%] of 1506 patients in the placebo group; hazard ratio, 0.83 [95% CI, 0.64-1.08]; P=.16).

Conclusions Failure of at least 1 vein graft is quite common within 12 to 18 months after CABG surgery. Edifoligide is no more effective than placebo in preventing these events. Longer-term follow-up and additional research are needed to determine whether edifoligide has delayed beneficial effects, to understand the mechanisms and clinical consequences of vein graft failure, and to improve the durability of CABG surgery.

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When administered ex vivo, edifoligide inhibited neointimal hyperplasia in a rabbit bypass model. Edifoligide treatment results were favorable in preventing vein graft neointimal hyperplasia in 2 small trials of patients undergoing peripheral arterial bypass surgery (Project of Ex-vivo Vein Graft Engineering via Transfection [PREVENT] I; N = 41) and CABG surgery (PREVENT II; N = 200).

The objectives of the PREVENT IV trial were to assess (1) the efficacy of edifoligide in preventing angiographic vein graft failure 12 to 18 months after CABG surgery; (2) the safety of edifoligide; and (3) the effect of edifoligide on the occurrence of major adverse cardiac events following CABG surgery.

**METHODS**

**Design**

The PREVENT IV trial, the design of which has been described in detail, was a phase 3, multicenter, randomized, double-blind, placebo-controlled trial in which autologous vein grafts were treated ex vivo with edifoligide for patients undergoing primary CABG surgery. PREVENT IV was designed and led by an academic steering committee, which included representatives of the Society of Thoracic Surgeons, and was coordinated by the Duke Clinical Research Institute (Durham, NC).

**Patient Population**

A total of 3014 patients were enrolled between August 2002 and October 2003 at 107 centers across the United States. The majority of sites were identified from those participating in the Society of Thoracic Surgeons’ National Cardiac Database. Patients aged 18 to 80 years, undergoing a first, isolated CABG surgery for atherosclerotic coronary artery disease with at least 2 planned vein grafts, were eligible. For the purpose of eligibility, grafts with multiple distal anastomoses were counted as single grafts. The first 2400 patients enrolled were assigned to an angiographic cohort and scheduled to return for angiography 12 to 18 months after surgery.

Major exclusion criteria included prior cardiac surgery or planned concomitant valve surgery (because of the increased early mortality associated with these procedures), vasculitis or another nonatherosclerotic cause of coronary artery disease, hypercoagulable state, involvement in another investigational drug or device study within 30 days, or a comorbid illness that would make 5-year survival unlikely. Institutional review board approval was obtained at all sites and all patients gave written informed consent prior to participation.

**Study Drug Administration**

Sites used blinded drug kits in a randomized, predetermined numerical order using an onsite kit administration log. Randomization was stratified by site with a block size of 4. Patients were considered randomized only after a treated segment of vein graft was implanted. Those who did not have a treated segment of vein graft implanted were not included in the trial. Randomized patients were registered through a central interactive voice response system as soon as possible following surgery.

Each patient’s harvested vein was treated ex vivo with either edifoligide, formulated as double-stranded oligonucleotide at a concentration of 0.38 mg/mL (40 µmol/L), or identical appearing buffered normal saline placebo. Patients who required a supplemental drug kit were assigned the kit through an interactive voice response system to ensure that it matched the patient’s initial kit. Study drug was administered using a pressure-mediated delivery system (Corgentech Inc, South San Francisco, Calif), which was a trough inserted in a fluorinated ethylene polypropylene tube attached to a pressure syringe. Each vein was harvested in the usual manner, placed on the trough, and inserted into the tube, which was then filled with either edifoligide or placebo solution. Six pounds per square inch of nondistending pressure was applied to the tube for 10 minutes. Each treated vein was then removed from the device, divided into appropriate lengths for grafting, and grafted into the patient using standard surgical techniques. Other than administration of study drug, all graft handling, surgical, and medical interventions were left to the discretion of the operating surgeon.

**Outcome Measures**

The primary end point was death or vein graft stenosis of ≥75% or greater in at least 1 vein graft as assessed by quantitative coronary angiography 12 to 18 months following surgery. Patients in the angiographic cohort who underwent angiography for clinical reasons prior to 12 months and who met the primary end point were not required to return for additional protocol angiography.

Secondary angiographic end points included (1) per patient incidence of vein graft occlusion, (2) per graft incidence of vein graft failure (≥75% stenosis) and vein graft occlusion, (3) per graft incidence of vein graft occlusion, and (4) mean vein graft lumen diameter (a continuous measure of vein graft disease). All angiograms were interpreted at the PERFUSE Angiographic Core Laboratory (Boston, Mass), using standard quantitative coronary angiographic techniques.

Adverse events were recorded through day 30. Secondary end points included major adverse cardiac events and the composite of death, MI, or repeat revascularization with vein graft failure. Perioperative MI was not included in the end point of major adverse cardiac events. Patients were contacted via mail or telephone at 6 and 9 months and at 1 year following CABG surgery. Annual follow-up is ongoing and planned at 2, 3, 4, and 5 years after CABG surgery. For those who reported a possible MI or revascularization procedure, additional medical records were obtained from their hospitals.

All suspected MIs and revascularization procedures were adjudicated by a blinded, independent clinical events committee using prespecified criteria. Perioperative MI was defined as a creatine kinase-MB (CK-MB) fraction of greater than 10 times the upper limit of normal (ULN) or greater than 5 times
Figure 1. PREVENT IV Trial Design and Patient Disposition

3014 Patients Randomized

1508 Assigned to Edifoligide (E2F Transcription Factor Decoy) Group
1197 Assigned to Angiographic Cohort*
311 Assigned to Nonangiographic Cohort
222 Excluded
157 Refused Angiography
14 Renal Insufficiency
61 Other
965 in Efficacy Population
30 Early Angiography With End Point
895 Protocol Angiography
42 Died <18 mo Without Angiography

1506 Assigned to Placebo Group
1203 Assigned to Angiographic Cohort*
903 Assigned to Nonangiographic Cohort
248 Excluded
166 Refused Angiography
21 Renal Insufficiency
61 Other
905 in Efficacy Population
35 Early Angiography With End Point
871 Protocol Angiography
49 Died <18 mo Without Angiography

1523 Had Follow-up for Major Adverse Cardiac Events at 1 y
2 Withdrew Consent
3 Lost to Follow-up

1494 Had Follow-up for Major Adverse Cardiac Events at 1 y
3 Withdrew Consent
9 Lost to Follow-up

Asterisk indicates that these patients were among the first 2400 enrolled patients. PREVENT indicates Project of Ex-vivo Vein Graft Engineering via Transfection.

The ULN with new Q waves longer than 30 ms in 2 contiguous leads or, if postoperative CK-MB samples were not available, new Q waves longer than 30 ms in 2 contiguous leads. Perioperative MI was diagnosed if CK-MB was elevated within 24 hours of surgery when there was not an interval clinical event and when the elevation was not attributable to a preoperative MI.

Postoperative MI was defined as either spontaneous (CK-MB > 2 times the ULN or new Q waves > 30 ms in 2 contiguous leads), after percutaneous coronary intervention (CK-MB > 3 times the ULN or new Q waves > 30 ms in 2 contiguous leads), or after CABG surgery (CK-MB > 10 times the ULN or > 5 times the ULN with new Q waves > 30 ms in 2 contiguous leads). For patients for whom CK-MB samples and electrocardiograms were not available, MI could be defined by the presence of “myocardial infarction,” “heart attack,” or similar term in the medical record documenting that an MI had occurred after the initial CABG procedure. Revascularization with vein graft failure was defined as any percutaneous or surgical revascularization procedure and vein graft stenosis of 75% or greater in at least 1 vein graft.

Sample Size and Analysis
We estimated that failure of 1 or more vein grafts would occur in 25% of patients in the placebo group by 12 to 18 months after enrollment.6,7 A total sample size of 1920 (960 patients per treatment group) had 91% power to detect a 25% reduction in vein graft failure using a 2-sided χ² test with an α level of .05. Enrollment of 2400 patients allowed for 20% of the cohort assigned to 12- to 18-month follow-up angiography to be lost to follow-up.

A sample size of 3000 patients was selected for the end point of major adverse cardiac events. The 5-year composite rate of major adverse cardiac events was assumed to be 28% in the placebo group.28 Assuming that no patients were lost to follow-up, a total sample size of 3000 patients would have 91% power to detect a 19% reduction in the 5-year event rate. This sample size is based on a 2-sided log-rank test with an α level of .05 assuming a constant hazard.

All analyses were performed independently by the Duke Clinical Research Institute. The primary and secondary end points of occlusion in at least 1 treated vein graft were assessed using the Cochran-Mantel-Haenszel χ² test, stratified on the number of treated vein grafts implanted.29 Because patients were randomized at the time of vein graft implantation, patients were analyzed as initially treated. Patients (n = 3) who received a supplemental kit of a type different from their initial kit were analyzed as initially treated. For the secondary end points of vein graft stenosis of 75% or greater and occlusion on a per graft basis, graft failure rates were adjusted for intrapatient correlation using general estimating equation techniques.30-32 Mean graft lumen diameter was assessed using a t test for the differences in treatment of least-squares means from a mixed-linear model.

Clinical end points at 1 year were assessed with the log-rank test.33,34 Cumulative event rates were calculated by the Kaplan-Meier method, with time to the first event as the outcome variable.35 Clinical characteristics were summarized in terms of frequencies and percentages for categorical variables and by median and 25th and 75th percentiles for continuous variables. Race was collected in 6 predefined categories (white [caucasian], Asian, Native American, black, Hispanic, or other) as recorded in the patient’s medical record. Treatment group differences were assessed using the χ² test for categorical variables and the Wilcoxon rank sum test for continuous variables. All tests of significance were 2-tailed; a P value of less than .05 was considered significant. Analyses were performed using SAS software version 8.2 (SAS Institute Inc, Cary, NC).

RESULTS
Baseline Characteristics
A total of 3014 patients were enrolled between August 2002 and October 2003 at 107 centers across the United States (Figure 1). Of 113 sites that received study drug kits, more than 95% enrolled 1 or more patients. Baseline characteristics of patients enrolled in

PREVENTION OF VEIN GRAFT FAILURE FOLLOWING CABG SURGERY
PREVENT IV appear in Table 1. The median age was 64 years (interquartile range [IQR], 56-71 years), 2385 (79%) were male, 1137 (38%) had diabetes, and the median left ventricular ejection fraction was 50% (IQR, 40-60%). There were no significant differences in baseline characteristics between patients assigned to edifoligide and to placebo.

Among the 2400 patients enrolled in the angiography cohort, those who survived and underwent follow-up angiography were generally less sick than those who survived and did not undergo angiographic follow-up. The primary reason patients did not return for angiographic follow-up was patient refusal (Figure 1). Compared with patients who did not undergo angiographic follow-up, patients who underwent angiographic follow-up were younger (63 years vs 66 years; \(P<.001\)); more likely to be male (1434/1764 [81%] vs 345/480 [70%]; \(P<.001\)); weighed more (89 kg vs 85 kg; \(P=.001\)); more had hypercholesterolemia (1360/1764 [77%] vs 334/480 [70%]; \(P=.001\)); and less had hypertension (1288/1764 [73%] vs 379/480 [79%]; \(P=.008\)), chronic lung disease (238/1764 [14%] vs 90/480 [19%]; \(P=.004\)), renal failure (22/1764 [1%] vs 19/480 [4%]; \(P<.001\)), congestive heart failure (119/1764 [7%] vs 73/480 [15%]; \(P<.001\)), peripheral vascular disease (195/1764 [11%] vs 75/480 [16%]; \(P=.006\)), and cerebrovascular disease (170/1764 [10%] vs 85/480 [18%]; \(P<.001\)).

### Surgery and Hospital Care

Surgical and in-hospital care data appear in Table 2. More than 58% of patients had endoscopic vein graft harvesting and there were a median of 2 (IQR, 2-3) vein grafts placed per patient; approximately 92% of patients had left ITA grafts, slightly more among those who were assigned to placebo; and 21% of patients had surgery without the support of cardiopulmonary bypass. The median duration of surgery was 231 minutes, with a median duration of 100 minutes for cardiopulmonary bypass. Postoperatively, patients were ventilated for 7.5 hours, remained in the intensive care unit for 26 hours, and had a postoperative hospital length of stay of 6 days. More than 90% of patients were taking aspirin at discharge, with more than 20% also taking a thienopyridine. In addition to differences in baseline characteristics, patients in the angiographic cohort were ventilated postoperatively for less time (7 hours vs 9 hours; \(P<.001\)) and had a shorter postoperative length of stay (6 days vs 7 days; \(P<.001\)) than patients who were not in the angiographic cohort.

### Angiographic Results

Of the 2400 patients in the angiography cohort, primary end point data were available for 1920 (80.0%) (Figure 1). Of these patients, 65 (3.4%) had early, clinically driven angiography with a result that met the primary end point; 1764 (91.9%) had protocol angiography; and 91 (4.7%) died prior to the 18-month angiographic follow-up. The majority of angiographic follow-up was performed between 12 and 14 months after surgery (Figure 2).

Angiographic results are summarized in Table 3. The primary end point occurred in 436 (45.2%) of 965 patients assigned to edifoligide and 442 (46.3%) of 955 patients assigned to placebo (odds ratio, 0.96; 95% confidence interval, 0.80-1.14; \(P=.66\)). The majority of graft failure was due to graft failure.
occlusion, which occurred among a similar proportion of patients (41.8% of edifoligide group vs 41.7% of placebo group; \( P = .97 \)). On a per graft basis, the rates of vein graft failure (28.5% vs 29.7%; \( P = .44 \)) and vein graft occlusion (26.1% vs 26.5%; \( P = .83 \)) were also similar among patients assigned to edifoligide and placebo, respectively. Finally, the continuous measure of mean vein graft diameter in nonoccluded grafts was similar among patients assigned to edifoligide and placebo (2.92 mm vs 2.97 mm; \( P = .17 \)). At 1 year, among the 1593 patients who had thoracic artery angiography, ITA grafts had a lower failure rate than vein grafts (8% vs 29%). Although higher event rates were seen among women, patients who were not White, patients with diabetes, patients not taking aspirin or statins at 30 days, and those taking thienopyridine at 30 days, there was no meaningful difference in the effect of edifoligide on vein graft failure among any subgroup (FIGURE 3).

**Clinical Events**

Clinical follow-up for major adverse cardiac events is complete through 1 year and available for 99.4% of patients (FIGURE 1). Clinical events are summarized in TABLE 4. Mortality was similar among patients assigned to edifoligide and placebo at 30 days (1.3% vs 1.1%) and at 1 year (3.5% vs 2.9%). The composite of death, MI, or revascularization with vein graft failure occurred in 101 (6.7%) of patients assigned to edifoligide and 121 (8.1%) of patients assigned to placebo (\( P = .16 \)). From the first few weeks after CABG surgery, the risk of a major adverse cardiac events event was approximately constant through 1 year (FIGURE 4). With all revascularization procedures included, the total number of events increased from 222 to 251, with a proportional increase among patients assigned to edifoligide and placebo. Major adverse cardiac events were more frequent among patients subsequently found to have vein graft failure than among patients without vein graft failure (TABLE 5).
Edifoligide was well tolerated. Major adverse events appear in Table 6. There was no difference in the rate of adverse events among patients assigned to edifoligide or placebo. More than 25% of patients had postoperative atrial fibrillation, 9.8% had MI during CABG surgery, 3.3% had new or worsening renal failure, 2.5% had bleeding that required reoperation, and 1.5% of patients had a postoperative stroke. The rate of perioperative MI in CABG surgery was higher among patients with vein graft failure than among patients with vein graft failure (Table 5).

**COMMENT**

In PREVENT IV, treatment with edifoligide had no effect on the primary end point of vein graft failure 12 months after CABG surgery. There was also no effect seen on any secondary angiographic end point. Even mean lumen diameter by quantitative coronary angiography, a continuous and sensitive angiographic measure of graft neointimal hyperplasia, failed to demonstrate an effect of edifoligide. With the observed rate of vein graft failure, PREVENT IV was well powered to detect a beneficial effect of edifoligide on angiographic patency at 12 to 18 months. Although not measured directly in PREVENT IV, based on prior preclinical work, the treated vein should have had adequate uptake of edifoligide. These negative results are consistent with the main results of the PREVENT III trial, which also failed to demonstrate a beneficial effect of edifoligide on vein graft patency in peripheral arterial bypass surgery. Given negative results in 2 large, adequately powered phase 3 trials, the early promising results with edifoligide in PREVENT II were most likely due to its small sample size, less complete follow-up, and the play of chance.

Despite an absence of effect on angiographic outcomes, patients assigned to edifoligide did have numerically fewer major adverse cardiac events events at 1 year. Given the absence of an angiographic effect on vein graft patency, this finding, although intriguing, is most likely due to chance. Longer-term follow-up, however, is warranted to define whether treatment with edifoligide results in long-term clinical benefit despite an absence of effect on 12-month angiographic outcomes.
The rate of vein graft failure in PREVENT IV is generally higher than that reported by other studies in the literature.\textsuperscript{20,21,45} Comparison between published studies is challenging because of different patient populations with more or less aggressive revascularization; differing completeness, timing, and techniques of angiographic follow-up; variable reporting of both per graft and per patient graft failure rates; the retrospective observational nature of many published studies; and the increasing risk profile of patients undergoing CABG surgery with more extensive and diffuse anatomic disease.\textsuperscript{40} Alternatively, the pressure-mediated delivery system or other vein graft handling techniques that were used in both edifoligide- and placebo-treated patients could theoretically have contributed to higher rates of vein graft failure. Based on the similarity of baseline characteristics with an age-matched population from the Society of Thoracic Surgeons’ National Cardiac Database, however, it is most likely that PREVENT IV is representative of true, real-world contemporary rates of vein graft failure.\textsuperscript{23}

In PREVENT IV, there was an association between angiographic vein graft failure and clinically important major adverse cardiac events. Although vein graft failure was measured after the occurrence of these clinical events, this association suggests that a substantial proportion of vein graft failure may occur early in the perioperative period and that vein graft failure is clinically important, at least in some cases. This early vein graft failure may be due to technical or thrombotic factors, thus masking any potential effect of edifoligide. Interestingly, more than half of patients with vein graft failure did not have major adverse cardiac events. Some vein grafts may be clinically unimportant and supply either small areas of the myocardium, areas with significant competitive flow from native coronary arteries (almost 20% of patients in PREVENT IV had only 1 major epicardial artery with ≥75% stenosis), or areas with diffuse disease but extensive native collaterals. Alternatively, these graft failures may result in other clinically important consequences, such as angina or heart failure, that are not reflected in our end point of major adverse cardiac events. The ongoing follow-up of PREVENT IV patients will allow better definition of the long-term clinical consequences of angiographic vein graft failure.

As observed in PREVENT IV, the ITA grafts have better long-term patency than vein grafts. Use of ITA grafts also results in improved outcomes and is now a recognized quality indicator in CABG surgery.\textsuperscript{2} Because most patients undergoing CABG surgery require multiple grafts, however, saphenous vein is likely to remain the most common conduit in CABG surgery. Current therapies to prevent vein graft failure after CABG surgery are limited to antiplatelet therapy with aspirin, angiotensin-converting enzyme inhibitors, and lipid-lowering therapy.\textsuperscript{41,44} Although proven effective, these interventions are not used in all eligible patients following CABG surgery. Other promising, although yet unproven, antiproliferative interventions are in various early stages of development.\textsuperscript{20,21,45}

Although not effective in PREVENT IV, therapeutic inhibition of the E2F transcription factors may still be a promising approach to prevent vein graft fail-
PREVENTION OF VEIN GRAFT FAILURE FOLLOWING CABG SURGERY

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PREVENTION OF VEIN GRAFT FAILURE FOLLOWING CABG SURGERY

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26. Approval based on a surrogate endpoint or on an effect on a clinical endpoint other than survival or irreversible morbidity (1999), 21 CFR §314.510.