Published in final edited form as:

Vasc Endovascular Surg. 2005 ; 39(1): 15–23.

Design and Rationale of the PREVENT III Clinical Trial: Edifoligide for the Prevention of Infrainguinal Vein Graft Failure

Michael S. Conte, MD^{*}, Todd J. Lorenz, MD[†], Dennis F. Bandyk, MD[‡], Alexander W. Clowes, MD[§], Gregory L. Moneta, MD[#], and B. Lynn Seely, MD[‡]

Boston MA; South San Francisco CA; Tampa, FL; Seattle, WA; and Portland OR

Abstract

Surgical bypass of peripheral arterial occlusive disease with autologous vein grafts provides an effective means of restoring blood flow to the lower extremity, and has been a standard therapy for patients with disabling claudication or critical limb ischemia (CLI). However, failure rates may run as high as 50% within 5 years.

These graft failures occur as a result of neointimal hyperplasia, a ubiquitous biologic response of blood vessel walls to injury, which is characterized by the migration and proliferation of smooth muscle cells (SMC). The E2F family of transcription factors regulates the expression of genes controlling SMC proliferation. Edifoligide (E2F Decoy) is a novel therapy that inhibits E2F function, thus attenuating neointimal hyperplasia. Its use in conjunction with a patented drug delivery pressurization chamber is under investigation. Using this system, edifoligide is administered to vein grafts in a single, ex vivo treatment following vein harvest and before implantation, resulting in minimal systemic drug exposure and excellent patient compliance.

This Phase 3, randomized, double-blind, multicenter clinical trial is designed to evaluate the safety and efficacy of edifoligide in a population of approximately 1400 patients with CLI undergoing infrainguinal bypass for peripheral arterial disease (PAD). The primary outcome measure will be the time to occurrence of non-technical graft failure resulting in either graft revision or major amputation at 12 months after enrollment. A governing Clinical Events Classification committee (CEC) will adjudicate each graft failure to determine its etiology.

The PREVENT III trial is the largest multicenter trial ever performed in patients receiving autologous vein bypass grafts for CLI. This landmark study will determine if edifoligide is safe and effective at preventing vein graft failure in patients undergoing lower extremity bypass, but it also provides a unique opportunity to observe current treatment practices in vascular surgery.

Introduction

Surgical bypass of peripheral arterial occlusive disease with autologous vein grafts provides an effective means of restoring blood flow to the lower extremity, and has been a standard therapy for patients with disabling claudication or critical limb ischemia (CLI). More than 105,000 lower extremity bypass procedures were performed in the United States in 2001. The utility of this procedure is limited, however, by failure rates that may reach as high as 50%

Correspondence: Michael S. Conte, MD, Division of Vascular Surgery, Brigham and Women's Hospital, 75 Francis Street, Boston, MA 02115, E-mail: mconte@partners.org..

^{*}From the Brigham and Women's Hospital, Boston, MA;

[†]Corgentech Inc., South San Francisco, CA;

[‡]University of South Florida, Tampa, FL;

[§]University of Washington, Seattle, WA;

[#]Oregon Health Sciences University, Portland, OR

This study is sponsored by Corgentech Inc. and Bristol-Myers Squibb

within 5 years.¹ While 5% to 10% of vein grafts fail shortly after implantation due to technical factors, mid-term failure (3 to 24 months) may occur in another 20% to 30% of cases and has been the primary focus of ultrasound surveillance and prophylactic reintervention.²⁻⁴ Although both open and endovascular reinterventions for failing grafts are effective, they incur patient discomfort, morbidity, and mortality, as well as significant resource utilization. In addition, not all grafts can be salvaged, even with intensive monitoring and an aggressive surgical posture. The consequences of vein graft occlusion are often severe for the patient, including recurrent ischemic symptoms, difficult reoperative surgery, and potential limb loss. To date, pharmacotherapies have had modest impact on reducing vein graft failure.

Neointimal hyperplasia is a predictable biologic response of blood vessels to injury, and it develops to varying degrees in all vein grafts following implantation in the arterial circulation.⁵ When excessive, neointimal hyperplasia can lead to lumen compromise, blood flow reduction, and subsequent graft failure. The development of neointimal hyperplasia requires the migration and proliferation of smooth muscle cells (SMC), which form a chaotically organized, pro-inflammatory neointimal layer. Thus, the regulation of SMC proliferation has been a central interest in efforts to control neointimal hyperplasia, and the elucidation of growth control mechanisms at the cell cycle level has yielded novel targets for potential molecular therapies. The E2F family of transcription factors mediates the expression of several cell cycle genes that are necessary for SMC proliferation. Inhibition of E2F function is expected to prevent SMC proliferation and attenuate neointimal hyperplasia, potentially yielding a graft that is also relatively resistant to accelerated atherosclerosis.⁶

Edifoligide (E2F Decoy) is a short piece of double-stranded DNA that mimics the consensus binding sequence for E2F. When introduced into cells under hyperbaric conditions, edifoligide traverses the plasma membrane and localizes in the nucleus, where it acts as a competitive inhibitor of E2F, binding the transcription factor and thereby reducing E2F-mediated activation of cell cycle genes⁷ (Figure 1). Studies in a rabbit carotid-jugular interposition graft model⁸ have demonstrated that edifoligide treatment of the vein at implantation reduces target gene (proliferating cell nuclear antigen and c-myc) expression and SMC proliferation, and significantly reduces neointimal hyperplasia in the grafts as compared to controls. Importantly, studies utilizing human saphenous veins demonstrate that administration of edifoligide using a non-distending pressure device results in drug delivery to approximately 90% of the cells in the vein wall.⁷ These preclinical studies formed the basis for further examination of edifoligide in humans.

Edifoligide has been studied in two clinical trials to date. The PREVENT I study enrolled 46 patients who received vein grafts for peripheral arterial disease. This pilot study demonstrated that edifoligide could inhibit E2F-mediated cell cycle gene expression and smooth muscle cell proliferation in human vein tissues. The PREVENT II study enrolled 200 patients who received coronary bypass vein grafts and demonstrated a significant decrease in the incidence of critical vein graft stenosis (defined as $\geq 75\%$ blockage) on angiography at 12 months after enrollment.⁹ No increase in adverse events was seen in the patients treated with edifoligide versus placebo in either study. Together, these studies established the safety and feasibility of this approach.

The PREVENT III trial will be the third clinical trial to address the effect of intraoperative treatment of vein grafts with edifoligide. It has been initiated to provide definitive evidence that edifoligide decreases the risk of vein graft failure in patients undergoing lower extremity vein bypass procedures. A companion Phase 3 trial, PREVENT IV, has also been initiated to evaluate the effect of edifoligide in 3000 patients undergoing coronary artery bypass graft surgery. In this manuscript, we describe the design and rationale of the PREVENT III trial, which is certain to be a landmark clinical study in the specialty of vascular surgery.

Study Plan

This prospective, randomized, double-blind, multicenter trial is designed to evaluate the safety and efficacy of edifoligide, administered to vein grafts using a hyperbaric device following harvest and prior to implantation in patients requiring surgical bypass to treat CLI (Figure 2).

Primary and Secondary Endpoints

The primary outcome measure was chosen to demonstrate the clinical benefit likely to accrue from the prevention of neointimal hyperplasia within the graft. Specifically, the primary endpoint will be the time to occurrence of non-technical graft failure resulting in either graft revision or major amputation (i.e., transtibial or above) at 12 months after enrollment.

Technical graft failures (i.e., those associated with a complicated or a suboptimal surgical result) will not be included in the primary endpoint, because they are not caused by neointimal disease. A Clinical Events Classification committee (CEC) (Appendix A), comprised of board-certified vascular surgeons, will review each case of graft failure to determine whether it is due to a technical or non-technical etiology according to prespecified criteria. Graft stenoses or occlusions that are not treated with thrombolysis, revision, or amputation will be censored in the primary endpoint analysis.

Secondary endpoints of the trial will include

- Time to loss of non-technical graft primary patency within 12 months after enrollment (loss of patency will include non-technical revision or occlusion of the index graft)
- Freedom from clinically significant stenosis of the index graft (as defined by a severe stenosis in the graft by either angiography or duplex ultrasonography, or index graft occlusion on either angiogram or duplex ultrasound) OR index graft revision or major amputation performed as a result of graft failure, whichever comes first, within 12 months of enrollment
- Time to occurrence of any graft revision or major amputation due to index graft failure, (i.e., due to either non-technical or technical graft failure, at 12 months after enrollment)
- Amputation and index graft failure-free survival
- Quality of life assessment (VascuQoL questionnaire) at 3 and 12 months

Patient Population

The patient population will consist of approximately 1400 patients with CLI undergoing infrainguinal bypass with autologous vein enrolled at approximately 80 sites in the United States and Canada.

Inclusion and Exclusion Criteria

Patients must be scheduled to undergo an infrainguinal bypass procedure for peripheral arterial disease using an autologous vein conduit for treatment of CLI and be at least 18 years old. For the purpose of this study, CLI is defined as arterial insufficiency with gangrene, a non-healing ischemic ulcer, or rest pain. Patients presenting with rest pain as their sole presenting symptom must have the diagnosis 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 PO₂ of less than 30 mm Hg, or a severely ischemic or flat line transtarsal pulse volume recording. Hemodynamic criteria are not required for patients with either gangrene or non-healing ischemic ulcers to avoid inappropriate

exclusion of the subset of patients that have non-compressible ankle arteries (especially those with diabetes and renal failure) and because the clinical diagnosis of limb threat is obvious.

Exclusion criteria are listed in Table I. Patients undergoing lower extremity vein bypass for intermittent claudication will be excluded, as will patients receiving an in-situ saphenous vein bypass configuration (precluding the graft from ex vivo treatment in the pressurized drug-delivery device). Patients will also be excluded from the trial if they have an intended vein graft that is to be attached to a non-autologous infrainguinal graft below the femoral bifurcation, have an intended revision of an existing infrainguinal graft, or will require any non-autologous or synthetic infrainguinal conduit as part of the reconstruction. Permissible reconstructions include re-do vein grafts, vein grafts that arise from a prosthetic patch on the inflow artery, those that arise from a prosthetic inflow graft at or above the femoral bifurcation, spliced vein grafts, and infrainguinal bypass in the setting of simultaneous inflow (catheter-based or surgical) reconstructions.

Study Drug Administration

Study drug (edifoligide, 40 μ M or placebo) will be administered to the vein graft as a single dose in the operating room following vein harvest and before implantation. After harvest, the vein will be placed in the drug delivery pressurization chamber and study drug infused through the lumen to fill the vein and the pressurization chamber (Figure 3). With drug both inside and outside of the vein, 6 pounds per square inch (psi) of non-distending pressure will be applied for 10 minutes. The pressure will then be released, the vein graft rinsed and flushed in the surgeon's standard vein bath solution, and the graft implanted. Participating surgeons and operating room assistants will be trained on the proper use of the device using on-site training sessions, a training video, and explicit directions for use.

Study Procedures and Follow-up

The early success of the surgical procedure will be assessed by intraoperative imaging with angiography or duplex ultrasound immediately following completion of the case or with duplex ultrasound before discharge. The index graft will then be observed with intensive graft surveillance for 12 months. This includes duplex ultrasound at 1, 3, 6, and 12 months. A duplex ultrasound will also be obtained at 9 months if a flow abnormality is observed at 6 months. Ultrasounds will be interpreted and recorded locally; a central imaging laboratory will not be used to better reflect community practice. Physical examination for vascular status, including ABI, will be conducted at baseline, at day 2, and at months 1, 3, 6, 9, and 12. Angiography (contrast or magnetic resonance) is mandated before elective graft revision, unless contraindicated. Any episode of graft occlusion, revision, or amputation will be recorded through month 12 and submitted to the CEC for adjudication as described subsequently. A VasuQol quality of life questionnaire will be completed prior to surgery and at 3 and 12 months postoperatively.

Safety will be assessed by the collection of adverse events through the first 30 days following surgery, after which only deaths, rehospitalizations, and index limb-related events will be recorded. Clinical laboratories (chemistry, hematology and urinalysis) will be collected at baseline and 48 hours after enrollment.

Concomitant Medications

Investigators will be 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 does, however, discourage (but not proscribe) the use of postoperative warfarin, heparin, and low-molecular-weight heparin for the prevention of bypass graft occlusion, because the effectiveness of these modalities remains controversial.¹² The use of specific concomitant

medications will be collected at baseline, at discharge from the hospital following the index graft surgery, and at 1, 3, 6, 9, and 12 months.

Graft Revision

The protocol specifies guidance as to when a graft revision may be contemplated (Table II). Specifically, this would occur when an angiographic stenosis of greater than 70% is identified, when recurrent symptomatic critical limb ischemia is confirmed by an angiographic stenosis of greater than 50%, and in the presence of hemodynamic compromise (ABI <0.4 or a toe pressure <30 mm Hg). It might likewise occur if duplex ultrasonography indicates a severe graft stenosis (peak systolic velocity [PSV] ratio of > 3.0 or PSV > 300 cm/sec). It is recognized, however, that individual patients may require more aggressive approaches that cannot be anticipated in advance; surgical judgment will always supercede the study protocol.

Endpoint Adjudication

A CEC will be used to adjudicate all cases of graft revision, graft occlusion, and major amputation due to index graft failure as to whether they are technical or non-technical in etiology. This will be accomplished by identification of suspected events from the patient's Case Report Form. Source documents including hospital admission and discharge notes, operative notes, and reports of all index graft imaging studies and procedural notes for each suspected event will be requested by the CEC and will be reviewed and adjudicated by two CEC members in Phase I of the adjudication process. If the two CEC adjudicators disagree on event classification, the case will be referred to Phase II of the adjudication process, wherein a third vascular surgeon will review all source documentation and both reviewers' comments, and will render a final decision.

Graft failures will be classified as technical if they can be assigned to one of four categories: inadequate inflow, inadequate outflow, extrinsic lesions, and intrinsic lesions. The criteria developed by the CEC for each category are briefly summarized here. Inadequate inflow may be caused by failure of a previous inflow reconstruction or thrombosis due to a low cardiac output state (e.g., cardiogenic shock). Inadequate outflow is suspected whenever there is no change in foot perfusion after graft placement and is confirmed by hemodynamic or radiographic criteria. Extrinsic causes include cases where tunneling errors or graft compression is recognized, or a hypercoagulable state is diagnosed. Intrinsic vein graft defects include a poor caliber or sclerotic graft segment, a retained valve or valvulotome injury, and anastomotic problems. The CEC will adopt a conservative approach in the adjudication process, considering all failures to be non-technical in nature unless they clearly fit the prespecified detailed criteria developed for each of these categories.

CEC activities will be coordinated by the Duke Clinical Research Institute, Durham, NC. Endpoint adjudication will be determined by board-certified vascular surgeons who will remain blinded as to treatment assignment.

Data Analyses

Sample Size Justification

Sample size determination for the PREVENT III study presents two major challenges. First, the primary endpoint of the study is the expected incidence of non-technical graft revision and/or major amputation due to graft failure as determined by the CEC. The use of a CEC to categorize infrainguinal vein graft failure in a clinical trial is novel and the exact incidence of non-technical failure has not previously been determined. Therefore, we decided to power the study based on the secondary endpoint of all graft revisions and/or major amputation due to graft failure. This should actually provide greater statistical power for the primary endpoint,

since technical revisions are expected to occur in roughly equal proportions in both treatment arms and would thus represent statistical “noise” in the analysis.

Second, and perhaps most important, there is no pre-existing multi-center study of an intent-to-treat: population of patients with CLI undergoing lower extremity vein bypass. While numerous retrospective series have reported experiences that provide ample context for this study, this will be the first study to scrutinize results in this population in a prospective, multicenter fashion. The Division of Vascular Surgery at the Brigham and Women’s Hospital in Boston, MA, maintains a prospectively captured database to analyze outcomes of its surgical patients. The 12-month incidence of vein graft failure in CLI patients ($n = 1219$) was 29% during a two-decade experience at the Brigham and Women’s Hospital.⁴

Accordingly, the planned sample size of 1400 patients was calculated to provide 90% power to detect a 28% decrease in the expected 29% incidence of the secondary endpoint of any graft revision and/or major amputation due to graft failure.

Method of Analyses

Patients were considered randomized when the treated vein was implanted. The time to event primary endpoint analysis was performed on an intent-to-treat basis using the log rank test. Patients who died during the follow-up period were censored from the primary analysis at the time of last observation, as were patients who experienced a technical revision or a major amputation not due to graft failure.

Study Organization

Steering Committee

The Steering Committee for PREVENT III will be composed of four members of the academic vascular surgery community and a representative of the sponsor (Appendix A). The Steering Committee will meet monthly by telephone or in person to monitor the progress of the trial and to provide scientific oversight.

Data and Safety Monitoring Board

An independent data and safety monitoring board (DSMB) will be composed of three members: a board-certified vascular surgeon not otherwise involved in the trial, an experienced clinical trialist, and a statistician (Appendix A). All members of the DSMB will be drawn from the academic community. The DSMB will meet at least twice during the study to monitor the safety of patients enrolled in the trial.

Clinical Events Classification Committee

A clinical events classification (CEC) committee, blinded as to study treatment assignment, will adjudicate all episodes of graft revision or occlusion as to whether the cause was technical or non-technical. They will also adjudicate each major amputation to determine whether it was due to graft failure. If so, those amputations will be adjudicated as technical or non-technical. The CEC is composed of board certified vascular surgeons (Appendix A). A detailed process document will be developed to provide guidelines for the CEC adjudicators and to ensure a uniform approach. An underlying philosophy of the CEC approach will be conservative regarding technical graft failure (i.e., failure will be considered non-technical in all cases in which the pre-specified criteria for technical failure are not clearly met). It is expected that the novel nature of this CEC approach will merit separate publication of the process and results obtained using this adjudication scheme.

Publications and Presentations Committee

A publications and presentations committee (PPC) will be formed to address all issues regarding the dissemination of scientific information emanating from the PREVENT III trial. The PPC will consist of the surgical members of the Steering Committee, complemented by an additional group of selected principal investigators from centers involved in the study (Appendix A). This group will prioritize scientific queries for the database, with collaborative input and statistical resources provided by the trial sponsors.

Discussion

The PREVENT III study will be the largest multi-center trial ever performed in patients who receive autologous vein bypass grafts for advanced lower limb peripheral arterial disease. Although the primary objective of the trial is to evaluate the safety and efficacy of edifoligide therapy in these patients, the study will also be of sufficient size to provide a unique opportunity to observe current treatment practices in vascular surgery and to correlate baseline factors with clinical outcomes.

Rationale for Study Design

The PREVENT III study will be a double-blinded, randomized, multicenter, placebo-controlled clinical trial. This design is the most rigorous approach to evaluate a new therapy and will provide a high level of confidence in the study results. It will provide Level I evidence for guiding subsequent clinical practice in relation to edifoligide in lower extremity vein bypass.

Choice of Study Population

The PREVENT III study design limits enrollment to patients who present with CLI. This will be done for two reasons. First, the literature indicates that the incidence of graft failure in patients with claudication alone is less than in patients with chronic CLI,¹¹ and so including these patients would have required a larger sample size. In the Brigham and Women's Hospital registry, the failure rate for all autologous vein grafts (patients with claudication or CLI) was 25% at 1 year, in comparison to 29% for the CLI population alone over the same interval (unpublished data). Second, the CLI population, which is at risk for immediate limb loss, theoretically has more to gain from edifoligide therapy than do patients with claudication, and it is appropriate to restrict study of a novel therapy to a higher risk population. Finally, the clinical implications of graft failure are much greater in CLI patients, and the associated high frequency of additional surgical procedures to treat failing or failed grafts (inclusive of amputation) provides a more meaningful target for edifoligide therapy.

Study Drug Administration

The unique mechanism of action of edifoligide and the acute time course of the initiation of neointimal hyperplasia allow for a single administration of study drug in this trial. Importantly, this drug is administered to the vein graft ex vivo in the operating room, resulting in minimal systemic drug exposure to the patient and excellent study drug compliance in the trial.

Choice of Study Endpoint

The primary endpoint for the PREVENT III study will be the occurrence of revision for non-technical graft failure or major amputation due to graft failure. This endpoint is the most appropriate to assess the impact of a drug therapy such as edifoligide, because its hypothesized mechanism of action—the prevention of neointimal hyperplasia—would have no anticipated effect on technical causes of vein graft failure. A salient feature of the PREVENT III study is

that it is well powered to examine the effects of edifoligide on both non-technical graft failure and on all graft failures.

The secondary endpoints include non-technical primary patency, which is defined as time to loss of primary patency due to non-technical index graft revision or occlusion, and freedom from clinically-significant stenosis (>70% diameter reduction) of the index graft detected by duplex ultrasound surveillance or angiography. Serial duplex ultrasound evaluation of the vein bypass should permit detection of difference in the development, progression, and extent of myointimal hyperplasia between the two treatment groups. Other endpoints usually reported in the vascular surgery literature—including primary assisted patency, secondary patency, and limb salvage—are not listed as protocol-specified endpoints of the trial for two reasons: (1) because the trial is not powered to show a difference in these endpoints, and (2) because these endpoints more strongly reflect the surgical decision-making regarding the need and appropriateness of reintervention of the surgeon rather than the effect of the drug. Data for these endpoints will, however, be collected and reported.

Endpoint Adjudication

The concept of using a CEC to adjudicate endpoint events has been used extensively in clinical trials,^{12–14} although the current study marks its initial use in a multicenter study of patients undergoing bypass for peripheral arterial disease. Use of the CEC concept in the PREVENT III study is critical to allow a consistent, unbiased adjudication of events across all investigational sites. It is important to acknowledge, however, that the algorithms used by the CEC are to some degree subjective, and subsequent clinical trials may choose to modify the definitions of technical graft failure which are used in this study.

Conclusion

The large, 1400 patient PREVENT III trial is designed to evaluate the potential superiority of edifoligide over placebo in the prevention of non-technical graft revision and/or major amputation due to graft failure according to the most rigorous principles of clinical science. In addition, this trial will provide an unprecedented opportunity to examine the practice and outcomes of vein bypass surgery in patients with advanced limb ischemia.

References

1. Whittemore AD, Belkin M: Infrainguinal bypass. In: Vascular Surgery, vol. 1, ed. by Rutherford R. Philadelphia: WB Saunders, 1995, pp 794–814.
2. Bandyk DF, Schmitt DD, Seabrook GR, et al. Monitoring functional patency of in situ saphenous vein bypasses: The impact of a surveillance protocol and elective revision. *J Vase Surg* 1989;9:286–296.
3. Taylor LM, Porter JM. Clinical and anatomic considerations for surgery in femoropopliteal disease and the results of surgery. *Circulation* 1991;83(2 suppl):I63–I69. [PubMed: 1991402]
4. Conte MS, Belkin M, Upchurch GR, et al. Impact of increasing comorbidity on infrainguinal reconstruction: A 20-year perspective. *Ann Surg* 2001;233:445–452. [PubMed: 11224635]
5. Cox JL, Chiasson DA, Gotlieb AI. Stranger in a strange land: The pathogenesis of saphenous vein graft stenosis with emphasis on structural and functional differences between veins and arteries. *Progr Cardiovasc Dis* July–Aug;1991 XXXIV:45–68.
6. Mann MJ, Dzau VJ. Therapeutic applications of transcription factor decoy oligonucleotides. *J Clin Invest* 2000;106:1071–1075. [PubMed: 11067859]
7. Ehsan A, Mann MJ, Dell'Acqua G, et al. Long-term stabilization of vein graft wall architecture and prolonged resistance to experimental atherosclerosis after E2F decoy oligonucleotide gene therapy. *J Thorac Cardiovasc Surg* 2001;121:714–722. [PubMed: 11279413]

8. Mann MJ, Whittemore AD, Donaldson MC, et al. Ex-vivo gene therapy of human vascular bypass grafts with E2F decoy: The PREVENT single-centre, randomized, controlled trial. *Lancet* 1999;354:1493–1498. [PubMed: 10551494]
9. Grube E, Felderhoff T, Fitzgerald PJ, et al: Genetic manipulation of human coronary artery bypass grafts with E2F decoy (cgt003) reduces clinical graft failure—results of the randomized, controlled PREVENT II trial (abstract). Late Breaking Clinical Trials, American Heart Association, Nov. 2001.
10. Jackson MR, Clagett GP. Antithrombotic therapy in peripheral arterial occlusive disease. *Chest* 1998;114:666S–682S. [PubMed: 9822070]
11. Belkin M, Conte MS, Donaldson MC, et al. The impact of gender on the results of arterial bypass with in situ greater saphenous vein. *Am J Surg* 1995;170:97–102. [PubMed: 7631942]
12. The SYNERGY Executive Committee. The SYNERGY trial. Study design and rationale. Superior yield of the new strategy of enoxaparin, revascularization, and glycoprotein IIb/IIIa inhibitors. *Am Heart J* 2003;143:952–960.
13. Dhainaut JF, Laterre PF, LaRosa SP, et al. The clinical evaluation committee in a large multi-center Phase 3 trial of drotrecogin alfa (activated) in patients with severe sepsis (PROWESS): Role, methodology, and results. *Crit Care Med* 2003;31:2291–2301. [PubMed: 14501959]
14. Higashida RT, Furlan AJ. Trial design and reporting standards for intra-arterial cerebral thrombolysis for acute ischemic stroke. *Stroke* 2003;34:e109–e137. [PubMed: 12869717]

APPENDIX A

PREVENT III Central Committees

Steering Committee

Michael Conte, MD, Chair (Boston, MA)

Dennis Bandyk, MD (Tampa, FL)

Alexander Clowes, MD (Seattle, WA)

Gregory Moneta, MD (Portland, OR)

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, MA)

Dennis Bandyk, MD (Tampa, FL)

Scott Berceci, MD (Gainesville, FL)

David Chew, MD (Boston, MA)

Alexander Clowes, MD (Seattle, WA)

Michael Conte MD (Boston, MA)

Edwin Gravereaux, MD (Boston, MA)
 Matthew Menard, MD (Boston, MA)
 Gregory L. Moneta, MD (Portland, OR)
 Publications and Presentations Committee
 Gregory Moneta, MD, Chair (Portland, OR)
 Dennis Bandyk, MD (Tampa, FL)
 Michael Belkin MD, Chair (Boston, MA)
 Scott Berceli, MD (Gainesville, FL)
 Scott Berman, MD (Tucson, AZ)
 Alexander Clowes, MD (Seattle, WA)
 Michael Conte, MD (Boston, MA)
 Richard DeMasi, MD (Norfolk, VA)
 Alan Hamdan, MD (Boston, MA)
 Sean Roddy, MD (Albany, NY)
 Russell Samson, MD (Sarasota, FL)

Figure 1.

Edifoligide, an E2F transcription factor decoy, crosses the cell membrane where it binds to the activated transcription factor, E2F, thereby “turning off” the function of the target gene.

Figure 2.
PREVENT III study design.

Figure 3.

Vein grafts are treated with edifoligide in the operating room after harvest and before implantation. The vein is placed in the pressurization chamber and drug solution is infused up through the lumen to fill the chamber, thereby surrounding the vein both on the inside and outside with drug. Non-distending pressure, 6 psi, is then applied for 10 minutes.

Table I

Major exclusion criteria for PREVENT III.

-
- Claudication (or any non-CLI indication) as the indication for bypass
 - Intended in situ vein graft approach
 - Documented hypercoagulable state
 - Revision (i.e., jump, interposition) of a preexisting infrainguinal graft
 - The infrainguinal reconstruction involves the use of non-autologous or synthetic material^{*}
-

^{*} Patch angioplasty of inflow artery is permissible, as is origin of the index graft from a non-autologous inflow reconstruction at or above the femoral bifurcation.

Table II

Criteria for graft revision in PREVENT III.

-
- Stenosis >70% by angiography
 - Recurrent CLI symptoms with evidence of hemodynamic compromise (ankle-brachial index <0.4, toe pressure <30 mm Hg) and an angiogram demonstrating stenosis > 50%
 - Duplex ultrasound indicating severe graft stenosis (peak systolic velocity [PSV] > 300 cm/sec and/or PSV ratio > 3.0) and an angiogram demonstrating stenosis > 50%
-