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Edifoligide and Long-Term Outcomes After Coronary Artery Bypass Grafting: PREVENT IV 5-Year Results

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Abstract

Background—Edifoligide, an E2F transcription factor decoy, does not prevent vein graft failure or adverse clinical outcomes at 1-year in patients undergoing coronary artery bypass grafting (CABG). We compared the 5-year clinical outcomes of patients in PREVENT IV treated with edifoligide and placebo and to identify predictors of long-term clinical outcomes.

Methods—A total of 3014 patients undergoing CABG with at least 2 planned vein grafts were enrolled. Kaplan-Meier curves were generated to compare the long-term effects of edifoligide and placebo. A Cox proportional hazards model was constructed to identify factors associated with 5-year post-CABG outcomes. The main outcome measure was death, myocardial infarction (MI), repeat revascularization, and rehospitalization through 5 years.

Results—Five-year follow-up was complete in 2865 (95.1%) patients. At 5 years, patients randomized to edifoligide and placebo had similar rates of death (11.7% and 10.7%), MI (2.3% and 3.2%), revascularization (14.1% and 13.9%), and rehospitalization (61.6% and 62.5%). The 5-year composite outcome of death, MI, or revascularization occurred at similar frequency in patients assigned to edifoligide and placebo (26.3% and 25.5%; hazard ratio 1.03 [95% confidence interval 0.89–1.18]; $P=0.721$). Factors associated with death, MI, or revascularization at 5 years included diabetes, sex, worst graft quality, peri-index CABG MI, and ejection fraction.

Conclusions—Up to a quarter of patients undergoing CABG will have a major cardiac event or repeat revascularization procedure within 5 years of surgery. Edifoligide does not affect outcomes

following CABG; however, common identifiable baseline and procedural risk factors are associated with long-term outcomes following CABG.

Keywords

vein graft failure; coronary artery bypass graft surgery; transcription factor decoy; outcomes

Autologous vein is the most widely used conduit for coronary artery bypass graft (CABG) surgery [1]. Although data are limited regarding the precise relationship between aortocoronary saphenous vein graft failure and subsequent clinical outcomes [2], vein graft occlusions are known to occur frequently following CABG surgery and the prevention of these occlusions is an active area of scientific inquiry [3, 4]. The pathogenesis of vein graft failure involves intimal injury, smooth muscle migration, and neointimal hyperplasia, leading to an accelerated atherosclerotic process and ultimately thrombosis of arterialized veins [5]. In this process, the E2F transcription factor plays an important role in gene expression and accelerated atherosclerosis [6–8]. Thus, inhibition of E2F function was hypothesized to inhibit cellular proliferation and neointimal lesion formation [9].

Despite promise, ex vivo treatment of vein grafts with the E2F transcription factor inhibitor edifoligide did not prevent vein graft failure in a large randomized controlled trial comparing ex vivo treatment of autologous vein grafts with edifoligide versus placebo [3]. However, at the end of initial trial follow-up, there was a trend toward improved short-term clinical outcomes (death, myocardial infarction, or revascularization with vein graft failure) among patients treated with edifoligide compared with placebo (6.7% vs. 8.1%; $p=0.16$) [3]. The objective of this study was to compare the 5-year clinical outcomes of patients treated with edifoligide and placebo. In addition, this study provides unique information on the contemporary long-term clinical outcomes following CABG surgery and identifies the major baseline clinical factors associated with these outcomes.

METHODS

Study Population

These analyses were conducted using the PROject of Ex-vivo Vein graft ENgineering via Transfection IV (PREVENT IV) clinical trial database. Details of the PREVENT IV trial design have been published previously [10]. In summary, PREVENT IV was a phase 3, multicenter, randomized, double-blind, placebo-controlled trial of ex vivo treatment of vein grafts with edifoligide in patients undergoing primary isolated CABG with at least 2 planned vein grafts. The trial enrolled 3014 patients between 2002 and 2003 at 107 sites in the United States. All patients were between the ages of 18 and 80 years and suffered atherosclerotic coronary artery disease. Exclusion criteria included prior cardiac surgery, planned concomitant valve procedure, and presence of an additional existing comorbid illness making survival to 5 years unlikely. The first 2400 patients enrolled made up an angiographic cohort scheduled to return for angiographic follow-up 12 and 18 months following CABG surgery. Vein graft failure was defined as a $\geq 75\%$ stenosis or occlusion at follow-up angiography. Angiograms were analyzed using quantitative coronary angiography at a core laboratory (PERFUSE Angiographic Core Laboratory, Boston, MA). The primary outcome for the trial was death or angiographic vein graft failure 12–18 months following surgery. The main angiographic results and clinical outcomes at 1 year have been previously reported [3]. Institutional review boards of participating medical centers approved the PREVENT IV protocol and all patients gave written informed consent.

The authors of this manuscript have certified that they comply with the Principles of Ethical Publishing in the International Journal of Cardiology: Shewan LG and Coats AJ. Ethics in the authorship and publishing of scientific articles [11].

Treatment of Vein Grafts

The study drug edifoligide was delivered via a pressure-mediated delivery system consisting of a trough inserted in a polypropylene tube and attached to a pressure syringe. Veins were harvested according to usual practice, placed on the trough, and inserted into the tubing, which was then filled with either edifoligide or placebo solution. Six pounds per square inch of nondistending pressure was applied to the sealed tube for 10 minutes. The treated vein graft was then removed from the tubing, rinsed, and grafted using standard techniques. Other than the administration of study drug, all interventions were left to the discretion of the treating physician.

Study Outcomes

All PREVENT IV patients were followed by mail and telephone follow-up through 5 years for death, myocardial infarction, and repeat revascularization up to 5 years after CABG surgery. For patients who reported possible myocardial infarction or repeat revascularization procedures, relevant medical records were collected and the events were adjudicated by an independent clinical events committee.

Statistical Analyses

The distributions of baseline demographic and operative characteristics were summarized with medians and 25th and 75th percentiles for continuous variables and percentages for categorical variables. Treatment group differences were assessed with the Wilcoxon rank-sum test (for continuous variables) and the chi-square test (for categorical variables). All tests of significance were 2-tailed. Cumulative event rates were characterized with Kaplan-Meier event curves, with time from surgery to the first event as the outcome variable. The significance of the difference between treatment groups was assessed with the log-rank test.

For each clinical outcome (death or myocardial infarction or repeat revascularization; death or myocardial infarction; death), a Cox proportional hazards model was developed for the purpose of identifying potential confounding factors to be used in conducting subsequent covariate-adjusted analyses. Note that the major objective of this modeling exercise was to identify and adjust for any potential imbalances in baseline characteristics that might bias the comparison of future observational analyses. Variables considered included sex, age, history of cardiogenic shock, ejection fraction, history of atrial fibrillation, history of congestive heart failure, chronic lung disease, peripheral and/or cerebrovascular disease, diabetes mellitus, prior myocardial infarction, myocardial infarction within 30 days prior to enrollment, whether the patient was placed on cardiopulmonary bypass, time on cardiopulmonary bypass, internal mammary artery use, use of endoscopic harvest technique, worst target artery quality, worst graft quality, creatinine clearance, and peri-index CABG myocardial infarction. The linearity of each predictor was evaluated and an appropriate transformation was applied, when necessary.

Variable selection for final model inclusion was performed using the method of Fast FSR [12]. This method controls the percentage (10% in this study) of variables that are incorrectly identified as being associated with the outcome. This approach was more conservative than traditional selection methods, resulting in the inclusion of additional adjustment variables (alpha for inclusion >0.05 for each outcome). Missing data in the covariates were addressed through multiple imputation. We used a weighted approach during the variable selection process to account for the variability resulting from multiple

imputation [13]. The proportional hazards assumption was evaluated for each of the selected covariates and time-varying coefficients were used to address any violations detected.

RESULTS

Clinical Follow-up

Five-year follow-up was complete in 95.1% of patients, including 94.8% in the edifoligide group and 95.3% in the placebo group. Consent for participation was withdrawn by 2.0% of enrolled patients (2.4% edifoligide and 1.7% placebo groups) and 2.9% of patients were lost to follow-up (2.8% edifoligide and 3.1% placebo group). Figure 1 displays the flow of patients through the trial.

Demographic and Operative Characteristics

Baseline demographic and operative characteristics of the PREVENT IV population have been previously detailed [3]. There were no differences between patients randomized to edifoligide versus placebo.

5-Year Clinical Outcomes

At 5 years, patients randomized to edifoligide and placebo had similar observed rates of death (11.7% and 10.7%), myocardial infarction (2.3% and 3.2%), revascularization (14.1% and 13.9%), and rehospitalization (61.6% and 62.5%). The composite outcome of death, myocardial infarction, or revascularization occurred at similar rates among patients randomized to edifoligide and placebo (26.3% and 25.5%, respectively) (Figure 2A). No difference was observed between the edifoligide and placebo groups for the endpoint of death alone (Figure 2B) or for the composite of death or myocardial infarction (Figure 2C). The observed 5-year rates of revascularization, percutaneous coronary intervention, and repeat CABG surgery were 14.0%, 13.3%, and 0.8%, respectively. No differences were observed between the edifoligide and placebo groups for these outcomes. Table 1 displays observed rates of 5-year clinical outcomes in addition to results for the placebo and edifoligide groups.

Relationship Between Evidence-Based Medication Use at 1 Year and Clinical Outcome at 5 Years

In the overall population, the use of aspirin, angiotensin-converting enzyme inhibitors or angiotensin receptor blockers, beta-blockers, and statins or other lipid-lowering agents at 1 year after CABG surgery was 92.5%, 56.6%, 71.7%, and 82.7%, respectively. Patients using aspirin, beta-blockers, and statins or other lipid-lowering agents at 1 year had better unadjusted 5-year outcomes than patients who were not using these medications at 1 year after CABG surgery (data not shown). When adjusted for baseline differences, however, patients taking and not taking aspirin (hazard ratio [HR] 0.89, 95% confidence interval [CI] 0.75–1.05; $P=0.17$), angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (HR 0.93, 95% CI 0.84–1.02; $P=0.10$), beta-blockers (HR 1.05, 95% CI 0.95–1.16; $P=0.35$), and lipid-lowering therapy (HR 1.01, 95% CI 0.89–1.14; $P=0.94$) at 1 year had similar 5-year outcomes.

Baseline Factors Associated with 5-year Clinical Outcomes

Baseline variables associated with subsequent clinical outcomes are listed in Table 2, with predictors associated with smaller P values appearing earlier in the list. Hazard ratios and associated 95% confidence intervals were computed for each predictor at 5 years; for continuous variables, the hazard ratio is given at the median value. The results presented in Table 2 are for the composite outcome of death, myocardial infarction, or revascularization.

Models for death alone and death or myocardial infarction yielded similar results and are included in the Appendix.

DISCUSSION

Although edifoligide exhibited a trend towards improved clinical outcomes at 1 year of follow-up [3], the agent does not have delayed beneficial effects on 5-year clinical outcomes after CABG surgery. In this contemporary CABG surgery population, major adverse cardiac events continued to occur at similar rates for patients in both arms of the trial. Multivariable models revealed several important baseline variables associated with death and other clinical endpoints at 5 years.

The results of PREVENT IV should be put into context with findings from earlier trials [14–16]. Randomized prospective evaluation of CABG surgery as a therapy to relieve symptoms and prolong life in patients with advanced coronary artery disease has been repeated in every decade since the first studies enrolled patients in the 1960s following development of the procedure [14–18]. Between 1974 and 1979, the Coronary Artery Surgery Study (CASS) randomized 780 patients to CABG surgery versus medical therapy [19]. Mortality among those CASS patients receiving CABG surgery was 11% at 5 years [20]. However, the CASS trial enrolled a younger patient population (51 years) with fewer comorbidities and excluded patients with a left ventricular ejection fraction <35% and those with clinical symptoms of heart failure. Other landmark studies, including the classic 1984 report of the Veterans Administration Coronary Artery Bypass Surgery Cooperative Study Group, have also found similar 5-year mortality rates, particularly in patients >55 years of age [17, 21].

In contrast to these healthier trial populations, the recently completed Surgical Treatment for Ischemic Heart Failure (STICH) trial [22] enrolled 1000 patients with a left ventricular ejection fraction $\leq$ 35% and left ventricular dysfunction amenable to surgical ventricular reconstruction. The overall rate of death at 5 years in the STICH cohort was 28% [22, 23]. In terms of patient risk, the PREVENT IV population is somewhere in between these earlier trials and the recent STICH trial. Notably, mean patient age in PREVENT IV was older than in CASS (51 years), Veterans Administration Cooperative (58 years), and STICH (60 years) trial cohorts. Additionally, the median left ventricular ejection fraction among patients in PREVENT IV was 50% yet up to 20% had an ejection fraction <35%. Thus, the 11.2% mortality through 5-year follow-up observed in PREVENT IV is impressive given the risk of the patients included. The contemporaneous SYNTAX trial (SYNergy between PCI with TAXus and Cardiac Surgery) results appear to be on pace with PREVENT IV findings, with all cause mortality among CABG patients found to be only 8.8% through 4 years follow-up [Kappetein AP. *SYNTAX Trial Update*. Society of Thoracic Surgeons Annual Meeting. Ft. Lauderdale, FL. January 30, 2012]. Despite the benefits of revascularization, patients continue to have recurrent ischemic events following CABG surgery. Ongoing use of appropriate, evidence-based medical therapy is critical to improving these patient outcomes. In PREVENT-IV, at 1 year following surgery, there was high, but not ubiquitous, use of antiplatelet therapy (93%), angiotensin-converting enzyme inhibitors or angiotensin receptor blockers (57%), beta-blockers (72%), and lipid-lowering therapy (83%) [24]. Although after adjusting for baseline characteristics, no significant relationship was observed between the use of these evidence-based therapies at 1 year after CABG surgery and the 5-year incidence of death, myocardial infarction, or revascularization, we believe there still might be unmeasured confounders affecting our results. Low-density lipoprotein (LDL) values were not obtained at 5 years to assess whether optimal medical management was being achieved (i.e. LDL levels <100mg/dl). Thus, further research is needed into how to improve the medical management of patients following CABG surgery [25, 26].

The multivariable models generated from this study confirm the contemporaneous importance of several major risk factors on long-term survival after CABG surgery including: diabetes mellitus, female sex, bypass graft quality, left ventricular ejection fraction, previous and peri-CABG myocardial infarction, and internal mammary artery use [27–31]. The prognosis for women compared with men undergoing CABG surgery has been a point of debate in the medical literature [32, 33]. Female sex was significantly associated with the composite outcome of death, myocardial infarction, or revascularization but did not retain significance in the prognostic models for death or the composite of death or myocardial infarction. Further investigation is needed to specifically evaluate the comparative effectiveness of treatment options for coronary artery disease in women [34, 35]. We note that while not all variables in the model were significantly associated with the outcome, they were identified as variables to be used for adjustment in future observational analyses. For age in particular, we do see statistical evidence that this variable is a confounder in the analysis however age does not emerge as a statistically significant variable because of our composite endpoint which included not only death (higher in older patients) but also revascularization rate (higher in younger patients).

The present study establishes that edifoligide does not further improve clinical outcomes for CABG patients through 5 years of follow-up. This finding is not unexpected given recent advances in the understanding of vein graft biology, including the identification of multiple unique E2F transcription factors since PREVENT IV was initiated [36]. Some of these transcription factors promote neointimal hyperplasia, while others are believed to inhibit this process, and edifoligide serves as an effective decoy for both [37–39]. Selective inhibition of E2F transcription factors may still be a viable approach to the prevention of vein graft failure. Although arterial grafts are generally preferred for aortocoronary anastomoses [40], autologous vein grafts remain the most widely used CABG surgery conduits and are an important aim for future therapeutics. Additional research is needed in understanding the role of platelets in the subsequent development of intimal hyperplasia and arteriosclerosis within vein grafts. Investigation is also warranted into the prevention of intimal injury during graft harvesting with refinement of techniques for graft harvesting and handling. Finally, the techniques of direct targeted tissue therapy used successfully in PREVENT IV represent an exciting frontier for future surgical interventions [41].

Limitations

The pressurized delivery system and other vein graft handling techniques that were used in both edifoligide- and placebo-treated patients were unique to the PREVENT IV trial. These techniques could have contributed to higher rates of vein graft failure and/or adverse clinical outcomes and may limit the generalizability of these findings. In addition, the field of cardiac surgery continues to evolve and much has changed in the care of patients undergoing CABG surgery since the first patients were enrolled in PREVENT IV, including the increased use of evidence-based secondary prevention medications following CABG surgery [25].

Conclusions

Up to a quarter of patients undergoing CABG surgery will have a major cardiac event or repeat revascularization procedure within 5 years of surgery. Edifoligide had no effect on clinical outcomes through 5 years following CABG surgery. Common identifiable baseline and procedural risk factors are associated with subsequent clinical events following CABG surgery.

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Figure 1.
Flow of patients through the trial.

B

Figure 2. Kaplan–Meier estimates of event rates for (A) death; (B) the composite of death or MI; and (C) the composite of death, MI, or revascularization in the edifoligide and placebo groups.

Table 1

Summary of clinical events through 5 years of follow-up in the PREVENT IV trial

	Edifoligide (n=1508)	Placebo (n=1506)	All Patients (n=3014)
Death	176 (11.7)	161 (10.7)	337 (11.2)
Post-CABG myocardial infarction	34 (2.3)	48 (3.2)	82 (2.7)
Repeat revascularization	213 (14.1)	210 (13.9)	423 (14.0)
Revascularization with vein graft failure	148 (9.8)	156 (10.4)	304 (10.1)
Revascularization without vein graft failure	54 (3.6)	49 (3.3)	103 (3.4)
Revascularization with unknown vein graft failure	12 (0.8)	7 (0.5)	19 (0.6)
Repeat CABG	12 (0.8)	12 (0.8)	24 (0.8)
Percutaneous coronary intervention	202 (13.4)	200 (13.3)	402 (13.3)
Rehospitalization			
0	579 (38.4)	564 (37.5)	1143 (37.9)
1	303 (20.1)	338 (22.4)	641 (21.3)
2	233 (15.5)	227 (15.1)	460 (15.3)
3	155 (10.3)	128 (8.5)	283 (9.4)
4	83 (5.5)	87 (5.8)	170 (5.6)
5–9	135 (9.0)	148 (9.8)	283 (9.4)
10 or more	20 (1.3)	14 (0.9)	34 (1.1)
Hospitalizations per year, median (25th, 75th)	0.2 (0.0, 0.6)	0.2 (0.0, 0.6)	0.2 (0.0, 0.6)

Values presented as no. (%), unless otherwise indicated. CABG indicates coronary artery bypass grafting.

Table 2

Results of Cox proportional hazards model for the composite outcome of death, myocardial infarction, or revascularization

Parameter	Chi-Square	HR (95% CI)	P Value
Diabetes mellitus	17.38	1.57 (1.27, 1.95)	<0.001
Female Sex	6.40	1.26 (1.05, 1.50)	0.011
Worst graft quality (poor vs. good)	4.97	1.23 (1.02, 1.48)	0.026
Peri-index CABG myocardial infarction	4.71	1.27 (1.02, 1.59)	0.030
Ejection fraction (per 10% increase)	4.24	1.07 (1.00, 1.14)	0.040
Previous myocardial infarction	4.16	1.21 (1.01, 1.44)	0.041
Internal mammary artery use	3.88	0.78 (0.62, 1.00)	0.049
Creatinine clearance (per 10ml/min increase)	12.12	0.81 (0.18, 3.65)	0.059
Time on cardiopulmonary bypass (per 10 min increase)	31.98	1.07 (1.00, 1.15)	<0.001
Lung disease	21.08	1.97 (1.31, 2.96)	<0.001
Atrial fibrillation	1.28	1.16 (0.90, 1.49)	0.260
Endoscopic vein harvest	1.19	1.09 (0.94, 1.26)	0.277
Age (per 10 year increase)	0.94	0.95 (0.86, 1.05)	0.333
Recent myocardial infarction	0.64	0.91 (0.74, 1.14)	0.425
Peripheral and/or cerebrovascular disease	35.76	2.86 (1.98, 4.12)	<0.001
Worst graft quality (poor vs. fair)	0.52	0.89 (0.65, 1.22)	0.469
Congestive heart failure	15.94	2.21 (1.37, 3.59)	<0.001
Worst target artery (poor vs. fair)	0.48	1.07 (0.88, 1.31)	0.482
Worst target artery (poor vs. good)	0.09	1.03 (0.87, 1.21)	0.761

CABG indicates coronary artery bypass grafting; CI, confidence interval; HR, hazard ratio.