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Impact of Extracardiac Vascular Disease on Vein Graft Failure and Outcomes After Coronary Artery Bypass Surgery

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Abstract

Background—While extracardiac vascular disease (ECVD), defined as a history of peripheral vascular disease (PVD) or cerebrovascular disease (CBVD), is common in patients undergoing coronary artery bypass graft (CABG) surgery, there are limited data available on the association between ECVD, vein graft failure (VGF), and clinical outcomes.

Methods—Using data from the Project of Ex-vivo Vein Graft Engineering via Transfection IV (PREVENTIV) trial (n = 3,014), 1-year angiographic follow-up and 5- year clinical outcomes (death, myocardial infarction, and revascularization) were determined in patients with and without ECVD. Logistic regression was used to assess risk of VGF. Generalized estimating equations methods were used to account for correlations in a graft level analysis. Kaplan-Meier estimates and Cox hazards regression were used to compare clinical outcomes. We similarly explored the association of the individual components CBVD and PVD with both VGF and clinical outcomes in an additive model.

Results—Patients with ECVD (n=634, 21%) were older, more commonly female, and had more comorbidities, lower use of internal thoracic artery grafting, and overall worse graft quality than patients without ECVD. VGF rates tended to be higher (patient-level: odds ratio [OR]: 1.23, 95% confidence interval [CI] 0.96 to 1.58, p = 0.099; graft-level: OR: 1.23, 95% CI: 1.00 to 1.53, p = 0.053) in patients with ECVD. VGF rates were significantly higher among CBVD patients (OR: 1.42, 95% CI: 1.03 to 1.97, p = 0.035; graft-level: OR: 1.40, 95% CI: 1.06 to 1.85, p = 0.019). Patients with ECVD had a higher risk of death, myocardial infarction, or revascularization 5 years after CABG surgery (hazard ratio [HR]: 2.96, 95% CI: 2.02 to 4.35, p < 0.001). This relationship was driven by the subset of patients with PVD (HR = 3.32, 95% CI: 2.16 to 5.09, p < 0.001) and not by those with CBVD (HR = 1.10, 95% CI: 0.88 to 1.37, p = 0.40).

Conclusions—ECVD is common among patients undergoing CABG surgery and is associated with similar short-term but increasingly worse long-term clinical outcomes. This higher risk may be partly, but not exclusively, due to higher rates of VGF among these patients.

Patients undergoing coronary artery bypass graft (CABG) surgery represent a heterogeneous group in terms of cardiovascular risk factors, coronary anatomy, and the quality of available graft material [1–4]. Some patients have isolated coronary artery disease, while others have extensive extracardiac vascular disease (ECVD), including cerebrovascular disease (CBVD) and peripheral vascular disease (PVD). Several studies have associated PVD with worse outcomes in patients after CABG surgery [5–7]. This association seems less clear in patients with carotid disease or CBVD. Although studies have focused on clinical outcomes, few have investigated the relationship between ECVD and risk for graft failure, despite the high prevalence of vein graft failure (VGF) and the increasing number of high-risk patients undergoing CABG surgery [4]. Such data are important as they could potentially influence the surgeon's choice to opt for arterial graft use instead of vein graft conduits in those with ECVD. Additionally, given the increased incidence of graft failure, it may help heart teams and patients balance expected risks and benefits of CABG surgery, including likelihood of successful complete revascularization, by identifying patients who will be prone to graft failure or adverse clinical outcomes. In this analysis, we investigated the relationship between ECVD and both VGF and clinical outcomes in patients undergoing CABG surgery.

Patients and Methods

Study Population

We conducted a retrospective analysis using data from the Project of Ex-vivo Vein Graft Engineering via Transfection IV (PREVENT IV) trial database. The design, primary results, and long-term follow-up have been published previously [2, 8, 9]. In short, PREVENT IV was a phase 3, multicenter, randomized, double-blind, placebo-controlled trial of ex vivo treatment of vein grafts with the E2F transcription factor decoy edifoligide in patients undergoing CABG surgery. The trial enrolled 3,014 patients at 107 US sites between 2002 and 2003. Eligibility criteria for the trial included age between 18 and 80 years, and first isolated CABG surgery for coronary artery disease with at least 2 planned vein grafts. Exclusion criteria included prior cardiac surgery or planned concomitant valve surgery, non-atherosclerotic causes of coronary artery disease, and a life expectancy less than 5 years due to comorbid illness. The first 2,400 patients enrolled in PREVENT IV were assigned to an angiographic cohort and scheduled to return for angiography 12 to 18 months after surgery. For VGF-related outcomes we included patients who underwent angiographic follow-up ($n = 1,828$ patients, with 4,343 vein grafts). The analysis of clinical outcomes utilizes the complete PREVENT IV population ($n = 3,014$).

Population and Outcome Event Definitions

In our study ECVD was defined as a history of the following: (1) CBVD or (2) PVD. CBVD was defined as stroke, transient ischemic attack, greater than 75% carotid stenosis, or prior carotid surgery. PVD was defined as the following: claudication (on exertion or at rest); amputation for arterial insufficiency; aortoiliac occlusive disease reconstruction; peripheral vascular bypass surgery, angioplasty, or stent; documented abdominal aortic aneurysm, abdominal aortic aneurysm repair, or stent; or other positive noninvasive testing documentation of PVD.

Outcomes included angiographic VGF and clinical outcomes including death and composites of death or myocardial infarction (MI) and death, MI, or repeat revascularization through 5 years. VGF was defined as stenosis of at least 75% of the diameter of the graft. Patients in the angiographic cohort who underwent angiography for clinical reasons and had VGF before programmed angiographic follow-up were exempt from additional angiography. All angiograms were analyzed at a core laboratory (PERFUSE Angiographic Core Laboratory, Boston, MA); the laboratory personnel who analyzed the angiograms were blinded to baseline characteristics, including history of ECVD.

Clinical outcomes were assessed annually through mail and telephone contact with the patients. Five-year followup was complete in 95.1% of patients; consent for participation was withdrawn by 2.0% of patients, and an additional 2.9% were lost to follow-up [8]. For reported events, medical records were collected, and the events were adjudicated by an independent clinical events committee using prespecified criteria.

Statistical Analysis

Categoric baseline and surgical characteristics are summarized by ECVD status at baseline as percentages and compared using a Pearson χ^2 test. Continuous characteristics are reported as median and (25th, 75th) percentiles, and were compared using Wilcoxon rank-sum tests.

VGF was assessed according to patient and according to graft. Patients were considered to have VGF if at least 1 graft had VGF. Logistic regression assessed the association between ECVD and graft-failure outcomes at the patient level adjusted for possible confounders including the patient's weight, duration of surgery, use of cardiopulmonary bypass pump, use of endoscopic vein graft harvesting, worst target artery quality (as assessed by the surgeon at time of implantation), and use of a composite graft. Graft-level analyses used generalized estimating equations to account for correlation among grafts within a patient [10, 11] and adjusted for weight, duration of surgery, cardiopulmonary bypass pump use, and graft-specific endoscopic vein graft harvesting, target artery quality, and composite grafting. We similarly explored the association of the individual components CBVD and PVD with VGF in an additive model.

Kaplan-Meier estimated event rates were calculated by ECVD status for clinical outcomes. Cox hazards regression further assessed the association of ECVD with clinical outcomes, adjusting for potential confounders including age, sex, diabetes, congestive heart failure, chronic lung disease, atrial flutter or fibrillation, MI within prior 30 days, creatinine clearance, preoperative ejection fraction, preoperative cardiogenic shock, use of endoscopic vein graft harvesting, use of internal thoracic artery, worst target artery quality, worst graft quality, time on cardiopulmonary bypass pump, any prior MI, and peri-index CABG MI. Linearity and proportional hazards assumptions were checked for all covariates and transformations applied when necessary. For each clinical outcome, a nonproportional hazard was identified for ECVD. A timevarying transformation was applied such that the hazard ratio (HR) could change with increased time from baseline; estimated HRs for ECVD are plotted as a function of time from baseline and reported at key fixed time points. Similarly, we assessed the association of CBVD and PVD with clinical outcomes in an

additive model. For PVD, a non-proportional hazard was identified similar to the main analysis for ECVD; we present the HR at key time points.

Finally, we sought to assess whether the relationship between ECVD and clinical outcomes might be mediated by VGF. Recognizing that this analysis might suffer from selection bias, we conducted a landmark analysis from the time of follow-up angiography, allowing a similar non-proportional hazard over time and adjusted for baseline covariates and VGF status. All statistical tests were 2-tailed, and p values less than 0.05 were considered statistically significant.

Results

Demographic and Operative Characteristics

Baseline demographic and operative characteristics are described by ECVD status in Table 1. ECVD at baseline was identified in 634 (21.0%) of patients. Among patients with ECVD, 382 (60.3%) had CBVD, 369 (58.2%) had PVD, and 117 (18.5%) both. Patients with ECVD were older, more frequently female, and had a lower body mass index and more comorbidities. Marked differences in operative characteristics were also observed. Use of the internal thoracic artery as a bypass graft was significantly lower in patients with ECVD, and intraoperative assessment of the target artery and graft quality were less favorable in ECVD patients. Median surgery duration was also significantly longer in ECVD patients.

Postoperative Events and Medication Use Up to 30 Days

Table 2 compares postoperative care, adverse events through 30 days, and medications through 30 days after surgery. Patients with ECVD required more time to wean off the ventilator, and postoperative recovery was longer. Adverse events, including stroke, atrial fibrillation, and renal failure, were markedly higher in patients with ECVD. Postoperative use of aspirin was lower in patients with ECVD, while use of adenosine diphosphate receptor inhibitors was higher. The use of warfarin, digoxin, and other antiarrhythmic drugs, including sotalol and amiodarone, was higher in patients with ECVD.

Vein Graft Failure

Angiographic follow-up was completed for 1,828 of patients, representing 4,343 vein grafts. Unadjusted rates of VGF were higher among ECVD patients; after adjustment, a nonsignificant trend was observed in both the patient level ($p = 0.099$) and graft level ($p = 0.053$) analyses (Fig 1). We also assessed the association of VGF and the individual components CBVD and PVD. CBVD was associated with increased risk of VGF (patient level: odds ratio [OR]: 1.42, 95% confidence level [CI]: 1.03 to 1.97, $p = 0.035$; graft-level: OR: 1.40, 95% CI: 1.06 to 1.85, $p = 0.019$). PVD, however, was not associated with VGF (patient level: OR: 0.90, 95% CI: 0.66 to 1.23, $p = 0.52$; graft level: OR: 0.90, 95% CI 0.68 to 1.19, $p = 0.45$).

Death, MI, or Revascularization at 30 Days and 5 Years

After adjustment, the estimated risk associated with ECVD and the composite of death, MI, and revascularization increased over time from surgery. At 30 days, the association between

ECVD and the composite outcome was nonsignificant (HR: 0.91, 95% CI: 0.69 to 1.22, $p = 0.27$). However, at 5 years, patients with ECVD had significantly worse outcomes (HR: 2.96, 95% CI: 2.02 to 4.35, $p < 0.001$). Panel A in Figure 2 shows the Kaplan-Meier event curves as well as the estimated adjusted HRs for ECVD over time from baseline surgery. When looking at the individual and additive associations of PVD and CBVD with the composite outcome, an increasing non-proportional hazard was found for PVD (at 30 days, HR: 0.83, 95% CI: 0.58 to 1.18, $p = 0.15$; at 5 years, HR: 3.32, 95% CI: 2.16 to 5.09, $p < 0.001$), whereas CBVD was not associated with the 5-year composite outcome throughout the follow-up period (HR: 1.10, 95% CI: 0.88 to 1.37, $p = 0.40$).

Death or MI at 30-Day and Long-Term Follow-Up

As with the composite outcome of death, MI, or revascularization, the estimated risk associated with ECVD and the composite of death and MI increased over time from surgery. A nonsignificant trend toward increased risk associated with ECVD and death or MI was identified at 30 days (HR: 1.29, 95% CI: 0.89 to 1.87, $p = 0.092$). At 5 years, ECVD was associated with a threefold increased risk (HR: 3.11, 95% CI: 2.05 to 4.72, $p < 0.001$). Panel B in Figure 2 shows the Kaplan-Meier event curves and the estimated HRs for ECVD over time. Like ECVD, PVD showed a similar association with death or MI over time (at 30 days, HR: 1.00, 95% CI: 0.64 to 1.57, $p = 0.50$; at 5 years, HR: 3.12, 95% CI: 1.98 to 4.93, $p < 0.001$). CBVD was associated with a constant increased risk for death or MI over the 5-year follow-up period after surgery (HR: 1.49, 95% CI: 1.14 to 1.95, $p = 0.004$).

All-Cause Mortality at 30-Day and Long-Term Follow-Up

All-cause mortality was not associated with ECVD status at 30 days (HR: 1.28, 95% CI: 0.84 to 1.95, $p = 0.12$). As with the composite endpoints, the estimated risk for death associated with ECVD increased over time from surgery, resulting in an almost threefold higher risk after 5 years (HR: 2.81, 95% CI: 1.81 to 4.37, $p < 0.001$). Panel C in Figure 2 shows the Kaplan-Meier event curves and the estimated HRs for ECVD over time.

Landmark Analysis From Angiography

Those surviving to undergoing follow-up angiography were subsequently followed for a mean of 3.75 years from their angiogram. After adjusting for VGF status, ECVD was associated with more death, MI, or revascularization after angiography such that the HR increased with time from angiogram (30-day HR: 0.83, 95% CI: 0.56 to 1.22; 3.75-year HR: 3.82, 95% CI: 2.23 to 6.52). Similar results were observed for the composite death and MI and death alone (3.75-year HR: 4.07, 95% CI: 2.21 to 7.48, and HR: 4.45, 95% CI: 2.24 to 8.45, respectively).

Comment

In this study we investigated the association between ECVD and both vein graft patency and 5-year clinical outcomes after CABG surgery. We found that, compared with patients who did not have ECVD, patients with ECVD were older and had higher rates of comorbidities. These characteristics have probably influenced the intraoperative parameters as well, as suggested by lower use of internal thoracic artery grafting and poorer vein graft quality.

After adjustment for these baseline differences, ECVD was still associated with a trend toward more graft failure at 12 to 18 months and significantly worse clinical outcomes through 5 years.

Our findings suggest that there may be factors other than associated comorbidities that influence long-term outcomes in patients with ECVD after CABG surgery. Although our hypothesis included that the relationship should be partly mediated by more VGF, our findings suggest that there are likely other factors involved as well. Our data also suggest that in patients with CBVD this relationship with VGF seems to be stronger than in patients with PVD. Apart from VGF, ECVD may be a marker for more severe associated coronary atherosclerosis. Patients with ECVD may have more diffuse, small-vessel coronary disease not amenable to complete surgical revascularization, which could contribute to the poorer long-term outcomes. Visual assessment of the quality of the target artery by the surgeon at time of graft implantation also suggests worse target arteries. Patients with ECVD may have more aggressive coronary artery disease that progresses faster than coronary disease in patients without ECVD. Although we did not collect information on the cause of death, our data suggest it could have been mediated through MI and more disease progression as measured by more revascularization. However, the increased risk for mortality could also be explained in part by noncardiac causes that are associated with ECVD, including cancer, and renal and neurologic diseases. Lastly, our data also suggest that recommended medical therapy with agents that have been shown to decrease recurrent ischemic events could be optimized in patients with ECVD who underwent CABG surgery.

Previous research on ECVD has focused on the individual components PVD and carotid disease or CBVD. Previous studies on carotid artery disease and CBVD show that a history of stroke or transient ischemic attack [12], as well as the presence of symptomatic carotid artery stenosis [13], increases the risk of a perioperative stroke in patients undergoing CABG. Perioperative stroke in turn is associated with increased mortality (19% vs 3.7%) in patients undergoing CABG, which persisted at long-term follow-up [14]. In our study, we found that patients with ECVD had increased risk for stroke during index hospitalization. Also, our study corroborates with previous studies in showing that CBVD patients were at increased risk for short-term as well as long-term adverse outcomes, including death. To our knowledge there have been 2 recent studies assessing PVD on early and late survival after CABG using adjustment for potential confounding factors [7, 15]. The largest study, from a contemporary Dutch population ($n = 10,504$), found that PVD ($n = 1,222$, 11.6%) is an independent risk factor for late mortality (HR: 1.67, 95% CI: 1.43 to 1.95) but not for early mortality [7]. Similarly, in a contemporary US cohort of 1,162 patients who underwent primary isolated CABG, investigators showed that although patients with PVD (31.8%) have more comorbidities and worse longterm survival (HR: 1.7, 95% CI: 1.2 to 2.4, $p = 0.004$), the presence of PVD did not predict increased 30-day mortality or major adverse cardiac events [15]. Our findings are similar, as we found an increasing hazard for all-cause mortality in patients with PVD that was only significantly increased after greater than 2 years of clinical follow-up. This raises the question whether PVD should be used as one of the predictive risk elements for short-term outcomes in patients undergoing isolated CABG as is currently the case in the additive or logistic EuroSCORE (European System for Cardiac Operative Risk Evaluation) [16, 17], EuroSCORE II [18], and Society of Thoracic Surgeons

risk scores [19]. In accordance with prior findings on PVD, our analysis suggests that early after surgery there is little relationship between ECVD and outcomes, but that over a longer follow-up, survival is substantially worse. Although the underlying mechanisms remain unclear, it could be that PVD patients undergoing CABG may be different from the populations from which the various risk models are derived. Also it could be that patients with PVD may have more rapidly progressive coronary artery disease that does not affect short-term outcomes as much as it does long-term outcomes.

Limitations

This was a retrospective, observational analysis of clinical trial data. The trial may have inclusion and exclusion criteria that limit the generalizability of these findings. The main outcome included all-cause mortality; using cause-specific mortality instead would have allowed us to further elucidate the cause of increased mortality observed after CABG in patients with ECVD. Also, the assessment of the criteria for PVD and CBVD were site physician reported and not based on strict definitions. Although information on completeness of revascularization was not available, data on number of diseased vessels and implanted coronary bypass grafts were collected.

Conclusions

ECVD is common and associated with similar short-term and increasingly worse long-term clinical outcomes after CABG surgery. A constant increased risk was seen in patients with prior CBVD, while prior PVD was associated with an increasing risk for adverse events at followup. The higher risk of long-term adverse outcomes is likely due, in part, to higher rates of graft failure. Further research is warranted on how to improve the outcomes of patients with ECVD undergoing CABG surgery.

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Fig 1. Adjusted vein graft failure rates on (A) patient level and (B) graft level stratified by extracardiac vascular disease (ECVD). Numbers in parentheses are 95% confidence intervals. (OR = odds ratio; VGF = vein graft failure.)

Fig 2.

Kaplan-Meier curves in patients with or without extracardiac vascular disease (ECVD) for the composite endpoints (A) death, myocardial infarction, or revascularization, (B) death or myocardial infarction, and (C) mortality with non-proportional hazard ratios (and 95% confidence interval) for each clinical outcome for extracardiac vascular disease over 5 patient years after index coronary artery bypass surgery.

Table 1

Baseline Characteristics in Patients With and Without Extracardiac Vascular Disease (ECVD)

Characteristics	Total (n = 3,014)	ECVD (n = 634)	No ECVD (n = 2,380)	p Value
Age, median, years	64 (56, 71)	67 (60, 73)	62 (55, 70)	<0.001
Female, %	20.9	25.9	19.5	<0.001
Race, non-white, %	9.1	7.1	9.6	0.052
BMI, median, kg/m ²	28.9 (26.0, 32.6)	28.4 (25.7, 31.9)	29.0 (26.1, 32.8)	0.003
Systolic BP, median, mm Hg	134 (120, 149)	139 (125, 153)	132 (120, 147)	<0.001
Heart rate, median, bpm	70 (62, 80)	71 (62, 80)	70 (62, 80)	0.15
Current NYHA heart failure class, %				0.45
I	40.2	37.4	40.9	
II	33.3	34.4	33.0	
III	18.0	19.3	17.7	
IV	8.5	8.9	8.4	
Cardiogenic shock, %	0.8	0.6	0.8	0.60
Cigarette smoker, %				<0.001
Never	31.4	23.7	33.5	
Former	45.7	51.7	44.1	
Current	22.9	24.6	22.4	
Hypertension, %	75.1	86.9	71.9	<0.001
History of diabetes mellitus, %	37.8	44.0	36.1	<0.001
Hypercholesterolemia, %	76.3	80.9	75.1	0.002
Prior MI, %	42.2	43.2	42.0	0.57
Renal failure, %	2.2	4.6	1.5	<0.001
Prior PCI, %	25.9	26.5	25.7	0.69
Preoperative atrial fibrillation/flutter, %	7.0	11.4	5.9	<0.001
LVEF, median, %	50 (40, 60)	50 (40, 60)	50 (40, 60)	0.15
Creatinine clearance, median, mL/minute	88.5 (69.6, 112.1)	77.9 (60.2, 96.8)	91.6 (73.2, 114.8)	<0.001
Total CK, median, ratio to ULN	0.4 (0.3, 0.7)	0.4 (0.2, 0.6)	0.4 (0.3, 0.8)	0.002
CK-MB, median, ratio to ULN	0.4 (0.2, 0.8)	0.3 (0.2, 0.7)	0.4 (0.2, 0.9)	0.062
Surgery				
Elective surgery, %	48.5	49.0	48.4	0.84
Endoscopic vein graft, %	58.4	58.3	58.5	0.92
Internal thoracic artery graft, %	92.3	89.3	93.2	0.001
Number of vein grafts used, median	2 (2, 3)	2 (2, 3)	2 (2, 3)	0.42
Multiple distal target vein grafts, %	34.7	34.7	34.7	0.99
Worst target artery quality				0.14
Good	43.0	40.6	43.6	
Fair	35.9	35.5	36.1	
Poor	21.1	23.9	20.4	
Worst vein graft quality				<0.001
Good	70.8	63.7	72.8	

Characteristics	Total (n = 3,014)	ECVD (n = 634)	No ECVD (n = 2,380)	p Value
Fair	24.1	28.2	23.0	
Poor	5.0	8.0	4.2	
Surgery duration, median, minutes	231 (193, 272)	238 (199, 280)	229 (191, 270)	0.001
CPB duration, median, minutes	100 (79, 123)	100 (81, 122)	100 (79, 123)	0.59

Values in parentheses are 25th and 75th percentiles.

BMI = body mass index; BP = blood pressure; CK = creatine kinase; CK-MB = MB fraction of creatine kinase; CPB = cardiopulmonary bypass; LVEF= left ventricular ejection fraction; MI= myocardial infarction; NYHA = New York Heart Association; PCI= percutaneous coronary intervention; ULN = upper limit of normal.

Table 2

Hospital Care and Adverse Events During Index Hospitalization in Patients With and Without Extracardiac Vascular Disease (ECVD)

Characteristics	Total (n = 3,014)	ECVD (n = 634)	No ECVD (n = 2,380)	p Value
ICU stay, median, hours	26 (22, 47)	27 (23, 53)	25 (21, 46)	<0.001
Ventilator, median, hours	7.5 (4.6, 13.8)	9.0 (5.5, 16.0)	7.0 (4.5, 13.0)	<0.001
Hospital stay, median, days	6 (5, 8)	7 (6, 9)	6 (5, 7)	<0.001
Stroke, %	1.5	2.7	1.2	0.008
Bleeding requiring reoperation, %	2.5	3.3	2.3	0.15
Atrial fibrillation, %	25.9	31.5	24.4	<0.001
Renal failure, %	3.3	5.8	2.6	<0.001
Pneumonia, %	2.3	3.0	2.1	0.21
Adult respiratory distress syndrome, %	0.9	1.3	0.8	0.22
Mediastinitis, %	0.7	0.3	0.8	0.28
Medications continued at 30 days, %				
Aspirin, %	90.5	86.5	91.6	<0.001
Clopidogrel/ticlopidine, %	21.9	28.0	20.3	<0.001
Warfarin, %	9.0	13.0	7.9	<0.001
ACE/ARB inhibitor, %	41.7	43.3	41.3	0.36
Beta-blocker, %	78.7	75.9	79.5	0.054
Statin, %	72.9	70.0	73.6	0.068
Nitrates, %	6.8	8.2	6.4	0.11
Digoxin, %	8.8	12.0	7.9	0.001
Other antiarrhythmic drugs, %	14.9	17.8	14.1	0.021

Values in parentheses are 25th and 75th percentiles.

ACE = angiotensin-converting enzyme; ARB = angiotensin receptor blocker; ICU = intensive care unit.