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ORIGINAL ARTICLE

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Positive family history of cardiovascular disease and long-term outcomes after coronary artery bypass grafting: a genetic paradox?

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Key question

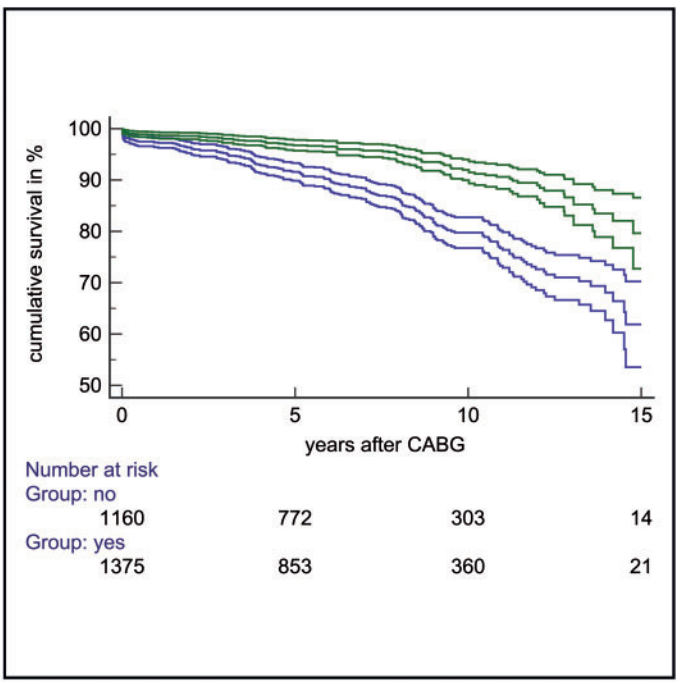
Does a positive family history (PFH) of premature parental cardiovascular disease also affect long-term outcomes after CABG?

Key finding(s)

PFH was associated with improved long-term survival and major adverse cardio- and cerebrovascular event-free survival.

Take-home message

PFH increases the risk of requiring CABG, but this study shows that PFH is also, paradoxically, protective regarding long-term outcomes.



Abstract

OBJECTIVES: Parental cardiovascular disease (CVD) is a known risk factor for premature CVD. It is unknown whether a positive family history (PFH) affects outcomes after coronary artery bypass grafting (CABG).

METHODS: Data come from a retrospective longitudinal study of CABG patients consecutively recruited from 2001 to 2018 ($n = 5389$). From this study, 2535 patients with premature CVD undergoing CABG under the age of 60 years and information on parental CVD were identified. The Framingham offspring study criteria were used to identify PFH of CVD. Multivariable Cox proportional hazards regression models were used to assess the effect of PFH on overall and major adverse cardiovascular and cerebrovascular event-free survival.

RESULTS: A total of 273 deaths and 428 major adverse cardiovascular and cerebrovascular events occurred during follow-up. PFH of CVD was found in 54.2% of patients ($n = 1375$). Within these patients, 66.1% had a father who experienced a premature cardiovascular event ($n = 909$), 27.8% a mother ($n = 382$) and 6.1% both a mother and a father ($n = 84$). In the majority of cases, the patient's parent had experienced a cardiac event (85.9%, $n = 1181$) and 14.1% of patients with PFH reported parental stroke ($n = 194$). Following CABG, PFH was associated with improved overall [adjusted hazards ratio (HR) 0.67, 95% confidence interval (CI) 0.50–0.90; $P = 0.008$] and major adverse cardiovascular and cerebrovascular event-free survival (adjusted HR 0.73, 95% CI 0.68–0.89; $P = 0.01$). Among the covariates adjusted for age, diabetes, renal insufficiency, peripheral arterial disease, ejection fraction, previous cerebrovascular events and previous mediastinal radiation were all associated with poorer outcomes.

CONCLUSIONS: Although it is well established that a PFH increases the risk of requiring CABG at younger ages, this study shows that, paradoxically, PFH is also protective regarding long-term outcomes.

Registration number local IRB: UN4232 297/4.3 (retrospective study).

Keywords: Positive family history regarding cardiovascular disease • Coronary artery bypass grafting • Major adverse cardiovascular and cerebrovascular events

ABBREVIATIONS

BITA	Bilateral internal thoracic arterial
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CIs	Confidence intervals
COPD	Chronic obstructive pulmonary disease
CV	Cardiovascular
CVD	Cardiovascular disease
HR	Hazards ratios
MACCE	Major adverse cardiovascular and cerebrovascular event
PCI	Percutaneous coronary intervention
PFH	Positive family history

INTRODUCTION

Positive (parental) family history (PFH) of cardiovascular disease (CVD), especially when early at onset, is a widely accepted risk factor for offspring cardiovascular (CV) events [1]. The Framingham offspring study has examined the genetic risk among all study participants older than 30 years who were initially free of CVD and both whose parents were in the original Framingham cohort. Compared with participants without PFH of CVD, those with at least 1 parent with premature CVD (onset age <55 years in father, <65 years in mother) had greater risk of CV events. Considering parental history of CVD in addition to conventional risk factors may therefore help clinicians in primary prevention of CVD, particularly in patients at intermediate risk based on levels of single or multiple risk factors, where treatment decisions may be difficult. As a consequence, current guidelines recommend the initiation of antihypertensive and antihyperlipidaemic treatment as a primary preventative measure among patients with PFH of premature CVD [2–4].

Little is known about the prevalence of a PFH of premature CVD in already diseased populations and its effect on patient outcomes. Ertelt *et al.* [5] examined the relationship of PFH with clinical profile and prognosis of patients with ST-elevation myocardial infarction undergoing primary percutaneous coronary intervention (PCI). Although the unadjusted 30-day and 3-year mortality rates were lower in patients with a PFH, this risk factor was not an independent predictor of mortality among PCI patients.

Another study by Esposito *et al.* [6] evaluated whether presenting clinical characteristics, including PFH, were predictive of an increased risk of 30-day CV events in patients with prior revascularization presenting to the emergency department with symptoms of potential acute coronary syndrome. Besides abnormal electrocardiogram (ECG) and positive cardiac troponin, a PFH remained predictive of 30-day CV events.

Moreover, to our knowledge, no prevalence and outcome data exist for patients already suffering from CVD who undergo surgical revascularization by coronary artery bypass grafting (CABG).

Therefore, the aim of this study is to investigate the prevalence of PFH of premature CVD in patients with premature onset of CVD and to evaluate whether PFH of CVD contributes to long-term outcomes following CABG.

MATERIALS AND METHODS

Patients

In this retrospective longitudinal outcome study, 5389 consecutive patients who underwent first, non-emergency CABG at the Innsbruck Medical University were followed up for a median of 8 years between August 2001 and February 2018. Inclusion and exclusion criteria and end point definitions for this study have been described previously [7, 8]. Inclusion criteria were first, non-emergency CABG for multivessel coronary artery disease (CAD). Patients with single-vessel CAD as well as robotically assisted CABG patients were excluded from this investigation. All patients gave informed consent; permission for this study was obtained from the local Institutional Review Board.

A total of 2553 patients with premature CAD, defined as receiving non-emergency multivessel CABG under the age of 60 years, were identified. Eighteen patients (0.7%) were excluded due to a lack of information about family history of premature CVD. Thus, 2535 patients were eligible for this analysis. Follow-up was complete in the study population.

Diagnostic procedures and end point definitions

Patient data including baseline characteristics as well as operative data were prospectively collected in full accordance with the standards of the Quality Control Working Group of the Austrian Society of Cardiothoracic Surgery. Survival, major adverse

cardiovascular and cerebrovascular event (MACCE)-free survival, freedom from angina and repeat revascularization were routinely obtained in 4- to 5-year intervals. MACCE events were defined as combined end points including myocardial infarction, stroke, cardiac-related death and repeat revascularization.

Definition of positive family history of premature cardiovascular disease

The Framingham offspring study criteria were used in order to indicate a PFH of premature CVD. Premature parental CVD was defined as the occurrence of a parental CV or cerebrovascular event before the age of 55 years in the father and/or the age of 65 years in the mother. The occurrence of a CV event included any CV death, non-fatal myocardial infarction, stroke and revascularization by either CABG or PCI. Additionally, premature cardiac events among siblings were also documented in line with Murabito *et al.* [9]. The age of the first CV event of the respective parent, as well as the age at death of the corresponding parent, was recorded.

Statistical analysis

The mean ± standard deviation or median (range) values for continuous variables are presented, with absolute numbers as well as percentages presented for categorical variables. Bivariate associations between categorical variables were tested using the Pearson χ^2 test or Fisher's exact test, where appropriate. For continuous variables, Student's *t*-test or the Mann–Whitney *U*-test was used. Survival and MACCE-free survival of the patients were determined using Kaplan–Meier survival curves together with the associated log-rank test.

Initially, Kaplan–Meier survival analysis was performed to investigate factors associated with survival and MACCE-free survival. Subsequently, multivariable Cox regression analyses were performed to identify independent predictors for both survival and MACCE-free survival. The hazards ratios (HRs) and 95% confidence intervals (CIs) are reported. The selection of variables was based on bivariate comparisons (entry criteria $P < 0.05$). Data management and statistical analysis were performed using SPSS Version 24 (IBM Corporation, Armonk, NY, USA).

RESULTS

Out of 2535 patients undergoing CABG under the age of 60 years, a total of 1375 patients (54.2%) had a PFH of premature CVD. Patients with PFH of CVD were younger (52.6 ± 5.7 vs 53.7 ± 5.2 years, $P < 0.001$) and more likely to have arterial hypertension (78.3% vs 73.4%, $P = 0.005$) than patients without a PFH (Table 1). There was a trend towards higher rates of hypercholesterolaemia (79.1% vs 75.9%, $P = 0.055$) and a statistically significant higher rate of familial forms of dyslipidaemia among patients with a PFH of premature CVD (2.7% vs 0.3%, $P < 0.001$). Patients with PFH were less likely to be current smokers (18.9% vs 23.3%, $P = 0.006$) and less likely to suffer from chronic obstructive pulmonary disease (COPD) (24.5% vs 28.6%, $P = 0.020$). Patients with PFH were also less likely to be diabetic (17.8% vs 31.4%, $P < 0.001$), insulin-dependent (4.0% vs 12.6%, $P < 0.001$), or suffering from type 1 diabetes (0.2% vs 2.8%, $P < 0.001$). Patients with PFH had significantly lower creatinine levels at admission (0.94 ± 0.83 vs 1.09 ± 1.02, $P < 0.001$) and were less likely to require dialysis (0.8% vs 2.6%, $P < 0.001$). Cerebrovascular disease (5.2% vs 7.4%, $P = 0.024$) and peripheral arterial disease (8.1% vs 14.8%, $P < 0.001$) were significantly less prevalent among patients with PFH. However, they were more likely to have previous myocardial infarction (40.3% vs 23.3%, $P < 0.001$) and previous CV interventions (24.9% vs 20.3%, $P = 0.005$).

Table 2 displays the patient demographics regarding PFH of CVD. In 909 cases, a PFH occurred in the father (66.1%), in 382 cases (27.8%) the mother suffered from a premature CVD event and in 84 cases (6.1%), both parents showed premature CVD events. Events were CV in 1181 cases (85.9%), 194 cases (14.1%) reported parental stroke as first premature CVD event. Parental cerebrovascular events were significantly more likely to occur in mothers than in fathers (39.8% vs 2.3%, $P < 0.001$). A positive sibling history of premature CVD was reported among 733 patients (53.3%). Mean age at first CV event was 50.3 ± 4.26 in fathers and was significantly lower than that in mothers (57.02 ± 4.95, $P < 0.001$).

A total of 273 deaths and 428 MACCE events occurred during follow-up. Figure 1 shows the Kaplan–Meier survival analysis of patients with PFH (green line) and patients without PFH (blue line), and patients without PFH experienced impaired overall survival ($P < 0.001$). Table 3 presents the results of the multivariable Cox regression analysis investigating independent predictors for survival after CABG. Age was an independent predictor of impaired survival after CABG (HR 1.069, 95% CI 1.051–1.087; $P < 0.001$). PFH was associated with improved long-term outcome after CABG (HR 0.67, 95% CI 0.50–0.90; $P = 0.008$). Previous mediastinal radiation was an independent risk factor of impaired survival after CABG (HR 5.2, 95% CI 1.84–14.74; $P = 0.002$). Moreover, insulin-dependent diabetes was associated with impaired survival following CABG (HR 1.82, 95% CI 1.13–2.93; $P = 0.013$). Elevated creatinine was associated with impaired long-term survival after CABG (HR 1.25, 95% CI 1.07–1.46; $P = 0.006$). Previous cerebrovascular events (HR 2.12, 95% CI 1.30–3.5; $P = 0.003$), pre-existing peripheral arterial disease (HR 1.70, 95% CI 1.20–2.28; $P = 0.002$) and impaired ejection fraction (HR 0.97, 95% CI 0.95–0.98; $P < 0.001$) were associated with impaired long-term survival after CABG. The use of bilateral internal thoracic arterial (BITA) revascularization was an independent risk factor for improved survival after CABG (HR 0.52, 95% CI 0.36–0.74; $P < 0.001$). COPD was associated with impaired survival after CABG (HR 1.51, 95% CI 1.14–2.00; $P = 0.004$).

Kaplan–Meier survival analysis (Fig. 2) shows improved MACCE-free survival among patients with PFH compared to patients without PFH ($P < 0.001$). Table 4 presents the results of the multivariable Cox regression analysis investigating independent predictors for MACCE-free survival after CABG. PFH of CAD was an independent predictor of improved MACCE-free survival after CABG (HR 0.73, 95% CI 0.68–0.89; $P = 0.01$). Previous mediastinal radiation was associated with impaired MACCE-free survival after CABG (HR 3.90, 95% CI 1.69–9.01; $P = 0.001$). Poor left ventricular function (HR 0.99, 95% CI 0.98–0.99; $P = 0.02$) and peripheral arterial disease (HR 1.48, 95% CI 1.12–1.96; $P = 0.005$) were also associated with impaired MACCE-free survival.

DISCUSSION

To our knowledge, this is the first study investigating the effect of PFH on outcomes following CABG. The results of our study

Table 1: Patient demographic data

	No family history regarding premature CVD (n = 1160 patients)	Positive family history regarding premature CVD (n = 1375 patients)	P-value
Age (years), mean ± SD	53.7 ± 5.2	52.6 ± 5.7	**<0.001**[a]
Male gender, *n* (%)	978 (84.3)	1193 (86.8)	0.079[b]
Migration background, *n* (%)	112 (9.7)	188 (13.6)	**0.002**[b]
Arterial hypertension, *n* (%)	852 (73.4)	1076 (78.3)	**0.005**[b]
Hypercholesterinaemia, *n* (%)	917 (79.1)	1043 (75.9)	0.055[b]
Familial form of dyslipidaemia, *n* (%)	4 (0.3)	37 (2.7)	**<0.001**[b]
Body mass index (kg/m^2), mean ± SD	27.5 ± 4.1	27.6 ± 4.0	0.59[a]
Normal, *n* (%)	315 (27.2)	351 (25.5)	
Overweight, *n* (%)	553 (47.7)	679 (49.4)	
Obese, *n* (%)	292 (25.2)	345 (25.1)	0.60[b]
Previous smoking, *n* (%)	586 (50.5)	659 (47.9)	0.194[b]
Active smoking, *n* (%)	270 (23.3)	259 (18.9)	**0.006**[b]
COPD, *n* (%)	3332 (28.6)	337 (24.5)	**0.019**[b]
Mild	219 (18.9)	232 (16.9)	
Moderate	102 (8.8)	92 (6.7)	
Severe	11 (0.9)	13 (0.9)	0.087[b]
Diabetes, *n* (%)	364 (31.4)	245 (17.8)	**<0.001**[b]
Insulin-dependent diabetes, *n* (%)	146 (12.6)	55 (4.0)	**<0.001**[b]
Type I diabetes, *n* (%)	32 (2.8)	3 (0.2)	**<0.001**[b]
Left ventricular ejection fraction (%), mean ± SD	54.5 ± 11.6	55.6 ± 10.9	**0.010**[a]
Creatinine (mg/dl), mean ± SD	1.09 ± 1.02	0.94 ± 0.83	**<0.001**[a]
Normal (<1.17 mg/dl), *n* (%)	935 (80.6)	1173 (85.3)	
Slightly elevated (1.17 to <2 mg/dl), *n* (%)	182 (15.7)	184 (13.4)	
Elevated (≥2 mg/dl), *n* (%)	43 (3.7)	18 (1.3)	**<0.001**[b]
Dialysis, *n* (%)	30 (2.6)	11 (0.8)	**<0.001**[b]
Cerebrovascular disease, *n* (%)	86 (7.4)	72 (5.2)	**0.024**[b]
Prior cerebrovascular accident, *n* (%)	44 (3.8)	42 (3.1)	0.306[b]
Peripheral arterial disease, *n* (%)	172 (14.8)	111 (8.1)	**<0.001**[b]
Immunosuppressive therapy, *n* (%)	24 (2.1)	9 (0.7)	**0.002**[b]
Previous myocardial infarction, *n* (%)	270 (23.3)	554 (40.3)	**<0.001**[b]
Previous cardiovascular intervention, *n* (%)	235 (20.3)	343 (24.9)	**0.005**[b]
Previous mediastinal radiation, *n* (%)	17 (1.5)	0 (0.0)	**<0.001**[b]
Multiple arterial revascularization, *n* (%)	543 (46.8)	947 (68.9)	**<0.001**[b]
Radial artery used	338 (29.1)	461 (33.5)	0.072[b]
Bilateral internal thoracic artery used	276 (23.8)	644 (46.8)	**<0.001**[b]

Values in boldface indicate statistical significance.

[a]Student's *t*-test.

[b]χ2 test.

COPD: chronic obstructive pulmonary disease; CVD: cardiovascular disease; SD: standard deviation.

clearly show that more than 50% of patients with premature CVD undergoing CABG reported a PFH of premature CVD, indicating that PFH was one of the most prevalent risk factors of premature CVD. However, contrary to our initial assumption, PFH of premature CVD was an independent predictor of improved survival and lower CV and cerebrovascular events after surgical revascularization.

Prevalence of positive family history in younger coronary artery bypass grafting patients

In our study population, the prevalence of PFH was 54.2% and was very high compared to epidemiological studies on healthy subjects [1, 2, 10, 11]. It is also notable that the PFH was inherited from the father in 66.1% of cases, and from the mother in 27.8% cases. The vast majority (85%) of our young patient cohort was male. This proportion is in line with the European coronary heart disease death statistics according to which about 77 000 women and 253 000 men die prematurely from coronary heart disease before the age of 65 years [12].

Is positive family history mediated by modifiable risk factors?

Fritz *et al.* [13] showed large age-dependent sex differences in CVD mortality. Further, they also showed that the extent to which major risk factors contributed to the sex difference regarding CVD mortality decreased with age. A substantial part of the female survival advantage was explained through the pathways of major risk factors, however, only in younger individuals.

In our study, patients with PFH were less likely to present with modifiable risk factors such as smoking and diabetes or renal disease, but were more likely to be hypertensive or to show a familial form of dyslipidaemia. The finding that familial hypercholesterolaemia and hypertension are more prevalent in patients with PFH is in line with the results of a mediation analysis with data from 23 595 participants of the Malmö Diet and Cancer Study [14] In this study, it was reported that only a fraction of the CVD risk associated with family history was mediated through elevated blood lipids and hypertension, but none through diabetes. Indeed, more than 80% of the genetic effect

Table 2: Patient demographics regarding positive family history regarding CVD

	Positive family history regarding premature CVD (n = 1375 patients)
Father, n (%)	909 (66.1)
Cardiovascular event	888 (97.7)
Cerebrovascular event	21 (2.3)
Mother, n (%)	382 (27.8)
Cardiovascular event	230 (60.2)
Cerebrovascular event	152 (39.8)
Both parents, n (%)	84 (6.1)
Mean age of first CVD event parent, mean ± SD	51.23 ± 5.38
Father	50.3 ± 4.26
Mother	57.02 ± 4.95
Mean age of first CVD event patient, mean ± SD	52.1 ± 4.11
Kind of CVD event, n (%)	
Cardiovascular	1181 (85.9)
Cerebrovascular	194 (14.1)
Positive sibling history, n (%)	733 (53.3)

CVD: cardiovascular disease; SD: standard deviation.

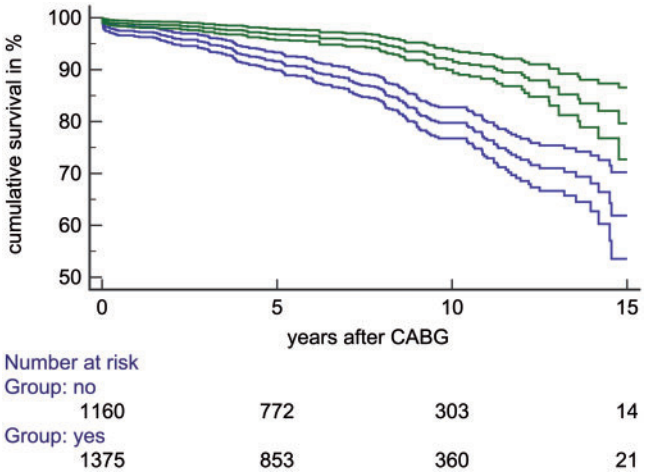


Figure 1: The Kaplan–Meier survival analysis of patients with positive family history (PFH) (green line) and patients without PFH (blue line); patients without PFH experienced impaired overall survival ($P < 0.001$). CABG: coronary artery bypass grafting.

operated independently of established metabolic risk factor pathways.

Familial hypercholesterolaemia confers an increased risk of premature atherosclerotic disease. In the SAVEHEART study, Perez de Isla *et al.* [15] investigated 440 asymptomatic patients with familial hypercholesterolaemia by computed tomography and found that coronary artery atherosclerosis was highly prevalent in these asymptomatic individuals. A meta-analysis published by Mega *et al.* [16] investigated the clinical benefit of statin therapy on coronary disease events. In this study, a genetic risk score identified individuals at increased risk for both incident and recurrent coronary heart disease events. Individuals with the highest burden of genetic risk derived the largest relative and absolute clinical benefit from statin therapy.

Little is known about other pathways, besides via the conventional risk factors, through which a PFH could lead to CVD. Schächinger *et al.* [17] investigated 150 patients with normal or minimally diseased coronary vessels and came up with an alternative explanation for the development of CVD in patients with PFH. Assessing endothelial-dependent vasomotor responses, they demonstrated that a PFH was an important predictor of impaired endothelium-dependent coronary blood flow regulation in humans. They argued that the influence of a PFH is independent of other well-known risk factors and instead aggravates endothelial vasodilator dysfunction associated with hypercholesterolaemia and increased age, suggesting important, interacting effects between genetic and environmental factors.

Explaining the paradox

Contrary to our initial hypothesis, PFH was associated with an improved outcome after CABG. A similar result was shown in an investigation by Preisler *et al.* [18] who evaluated the association between PFH and clinical outcome in patients presenting with ST-elevation myocardial infarction. The study included 1785 subjects of whom 20% had a PFH. In concordance with our study, PFH was associated with better short- and long-term outcomes compared to patients without PFH.

PFH of CVD is associated with increased mortality in the general population [19] but, in our study, paradoxically, with decreased mortality in younger individuals undergoing CABG procedure.

In recent years, awareness that associations observed in epidemiological studies might contradict causal effects, which can sometimes be determined in randomized trials, has rapidly increased. Examples such as the Simpson's [20], the Berkson's [21], the birth weight paradox [22] or the Lord's [23] paradoxes reflect the tension between association and causation. Although already known for decades, it has been only recently that researchers from the field of causal interference have formally clarified all of these paradoxes [24].

In many of these paradoxical findings, so-called colliders, i.e. variables both affected by the exposure of interest but also by other factors, play a decisive role. By selecting populations based on a collider variable, a spurious (i.e. non-causal) association between exposure and outcome can be introduced; this is a special form of selection bias [24]. The observation that obesity is beneficial regarding mortality outcomes among diabetic and heart failure patients arises most likely also due to conditioning on the collider diabetes or heart failure, as Lajous *et al.* [23] recently demonstrated.

The diagrams in Fig. 3 show the causal structure which, we believe, connects PFH and survival outcome variables. PFH as a reason for premature CVD is likely a more benign alternative regarding survival outcomes than some of the other causes that lead to this disease. As not all of these other causes are known, let alone measured, disentangling the association introduced by this 'explain away' effect from the true causal effect of PFH on survival is impossible. Although the survival benefits of patients requiring CABG at younger ages with a PFH are real, we may not conclude that there is a causal relationship between PFH and outcomes following CABG.

Table 3: Results of multivariable Cox regression analysis investigating independent predictors for survival after CABG

	Hazards ratio	95% confidence interval	*P*-value
Age (years)	1.069	1.051–1.087	**<0.001**
Gender	0.81	0.58–1.12	0.204
Migration background	1.27	0.83–1.9	0.273
Positive family history regarding premature CVD	**0.67**	**0.50–0.90**	**0.008**
Previous myocardial infarction	0.98	0.71–1.36	0.91
Familial form of hypercholesterolemia	1.83	0.44–7.56	0.404
Previous mediastinal radiation	5.203	1.84–14.74	**0.002**
Diabetes	1.061	0.76–1.474	0.72
Insulin-dependent diabetes	1.823	1.13–2.93	**0.013**
Type 1 diabetes	0.84	0.32–2.17	0.72
Creatinine (mg/dl)	1.25	1.067–1.46	**0.006**
Dialysis	0.855	0.25–2.99	0.807
Arterial hypertension	1.33	0.96–1.85	0.086
Cerebrovascular accident	2.12	1.30–3.5	**0.003**
Chronic obstructive pulmonary disease	1.51	1.14–2.00	**0.004**
Immunosuppressive therapy	1.84	0.78–4.35	0.164
Peripheral arterial disease	1.70	1.20–2.28	**0.002**
Ejection fraction (%)	0.97	0.95–0.98	**<0.001**
Bilateral internal thoracic artery received	0.52	0.36–0.74	**<0.001**
Year of procedure	1.054	0.97–1.105	0.26

Values in boldface indicate statistical significance.

CABG: coronary artery bypass grafting; CVD: cardiovascular disease.

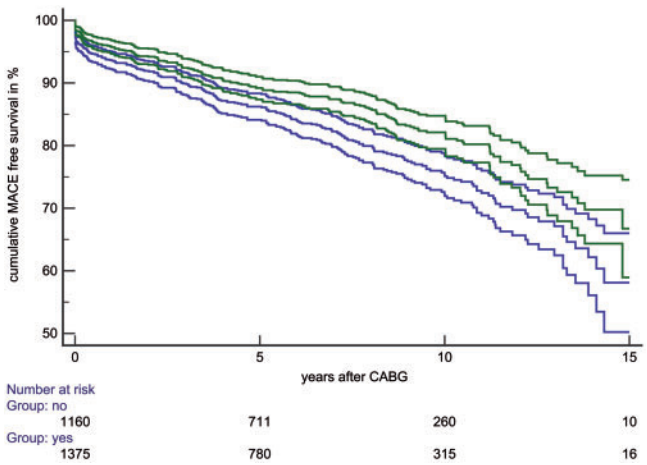


Figure 2: The Kaplan–Meier survival analysis regarding MACCE-free survival of patients with positive family history (PFH) (green line) and patients without PFH (blue line). Patients without PFH experienced impaired MACCE-free survival ($P < 0.001$). CABG: coronary artery bypass grafting; MACCE: major adverse cardiovascular and cerebrovascular events.

Treatment implications of the study

In our study, previous mediastinal radiation was a risk factor for adverse outcome after CABG and was highly significant in the multivariable analyses. Gansera et al. [25] investigated the quality of internal thoracic artery grafts after mediastinal radiation and issued that there is no need for restriction in use of internal thoracic artery grafts. Histomorphological investigations did not identify any severe irradiation-induced fibrosis or damage of internal thoracic artery grafts.

The use of BITA grafts was associated with improved outcomes after CABG, indicating that a more liberal utilization of BITA is warranted among younger patients with or without PFH. In our study, the utilization of BITA, but not the radial artery in order to achieve multiple arterial revascularization, was associated with improved outcomes after CABG. This is in line with previous findings from our study cohort [7, 8]. Moreover, the rate of multiple arterial grafting was 58.7% in the entire study population which was extraordinarily high compared to international registry data [26, 27].

Limitations of the study

Limitations of the study include the potential for recall bias, with premature CVD events being self-reported by offspring which may lead to inflated estimates of risk associated with parental CVD. However, Murabito *et al.* [11] studied offspring reports of parental CVD and found self-reported parental CVD history to be a reliable predictor of poor CVD outcomes in offspring. Moreover, the single-centre experience has inherent limitations that may potentially impair generalizability of the findings. Furthermore, the long intervals (4–5 years) between the follow-ups are a further limitation of our study.

CONCLUSION

In this cohort of younger patients requiring CABG, PFH was highly prevalent. Although it is evident that a PFH increases the risk of requiring CABG at younger ages, this study shows that PFH is also, paradoxically, protective against poor long-term outcomes. Interventional studies on CAD therefore should assess PFH as standard, as it can contribute to the outcome of cardiac interventions.

Conflict of interest: none declared.

Table 4: Results of multivariable Cox regression analysis investigating independent predictors for MACCE-free survival

	Hazards ratio	95% confidence interval	*P*-value
Age (years)	1.013	1.0–1.026	0.057
Gender	0.80	0.60–1.045	0.10
Migration background	1.14	0.83–1.57	0.39
Obesity	1.16	0.93–1.45	0.20
Positive family history regarding premature CVD	**0.73**	**0.68–0.89**	**0.010**
Previous mediastinal radiation	3.90	1.69–9.01	**0.001**
Diabetes	1.13	0.86–1.47	0.38
Insulin-dependent diabetes	1.14	0.74–1.73	0.55
Type I diabetes	1.74	0.80–3.76	0.16
Creatinine (mg/dl)	1.12	0.97–1.29	0.14
Dialysis	0.65	0.20–2.10	0.47
Immunosuppressive therapy	1.66	0.78–3.53	0.19
Peripheral arterial disease	1.48	1.12–1.96	**0.005**
Cerebrovascular disease	1.39	0.96–2.02	0.084
Ejection fraction (%)	0.99	0.98–0.99	**0.02**
Bilateral internal thoracic artery received	0.41	0.31–0.54	**<0.001**
Year of procedure	0.99	0.95–1.047	0.96

Values in boldface indicate statistical significance.

CVD: cardiovascular disease; MACCE: major adverse cardiovascular and cerebrovascular events.

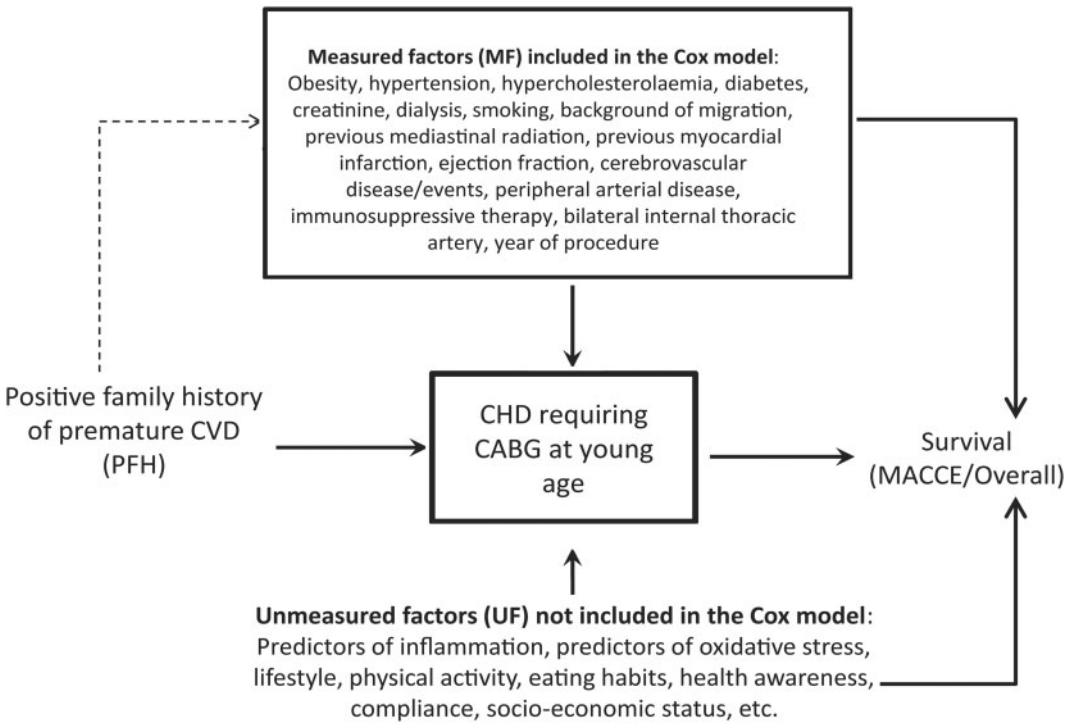


Figure 3: Causal diagram to represent the underlying pathways between PFH of premature CVD and survival outcome. As CVD requiring CABG at young age is affected not only by our main exposure of interest (PFH), but also by MF and UF (thus, 3 arrows enter into the CHD node), CHD requiring CABG at young age qualifies as a collider. For example, cholesterol or hypertension is known to be associated with family PFH, while for diabetes, there is less evidence for such a relationship. CABG: coronary artery bypass grafting; CHD: coronary heart disease; CVD: cardiovascular disease; MACCE: major adverse cardiovascular and cerebrovascular events; MF: measured factors; PFH: positive family history; UF: unmeasured/unknown factors.

Author contributions

Elfriede Ruttmann: Conceptualization; Data curation; Formal analysis; Investigation; Methodology; Supervision; Validation; Visualization; Writing—original draft; Writing—review & editing. **Hannes Abfalterer:** Conceptualization; Data curation; Investigation; Writing—review & editing. **Marion Dietl:** Conceptualization; Data curation; Investigation; Writing—review & editing. **Julian Wagner:** Conceptualization; Data curation; Investigation; Writing—review & editing. **Juliane Kilo:** Data curation; Investigation. **Michael Grimm:** Conceptualization; Investigation; Project administration; Writing—review & editing. **Katie Bates:** Conceptualization; Methodology; Validation; Writing—original draft; Writing—review & editing. **Josef Fritz:** Conceptualization; Methodology; Validation; Writing—original draft; Writing—review & editing. **Hanno Ulmer:** Conceptualization; Formal analysis; Methodology; Supervision; Writing—original draft; Writing—review & editing.

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