









Long-term mortality in patients with ischaemic heart failure revascularized with coronary artery bypass grafting or percutaneous coronary intervention: insights from the Swedish Coronary Angiography and Angioplasty Registry (SCAAR)

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Aims

To compare coronary artery bypass grafting (CABG) and percutaneous coronary intervention (PCI) for treatment of patients with heart failure due to ischaemic heart disease.

Methods and results

We analysed all-cause mortality following CABG or PCI in patients with heart failure with reduced ejection fraction and multi-vessel disease (coronary artery stenosis >50% in ≥ 2 vessels or left main) who underwent coronary angiography between 2000 and 2018 in Sweden. We used a propensity score-adjusted logistic and Cox proportional-hazards regressions and instrumental variable model to adjust for known and unknown confounders. Multilevel modelling was used to adjust for the clustering of observations in a hierarchical database. In total, 2509 patients (82.9% men) were included; 35.8% had diabetes and 34.7% had a previous myocardial infarction. The mean age was 68.1 ± 9.4 years (47.8% were >70 years old), and 64.9% had three-vessel or left main disease. Primary designated therapy was PCI in 56.2% and CABG in 43.8%. Median follow-up time was 3.9 years (range 1 day to 10 years). There were 1010 deaths. Risk of death was lower after CABG than after PCI [odds ratio (OR) 0.62; 95% confidence interval (CI) 0.41–0.96; $P = 0.031$]. The risk of death increased linearly with quintiles of hospitals in which PCI was the preferred method for revascularization (OR 1.27, 95% CI 1.17–1.38, $P_{\text{trend}} < 0.001$).

Conclusion

In patients with ischaemic heart failure, long-term survival was greater after CABG than after PCI.

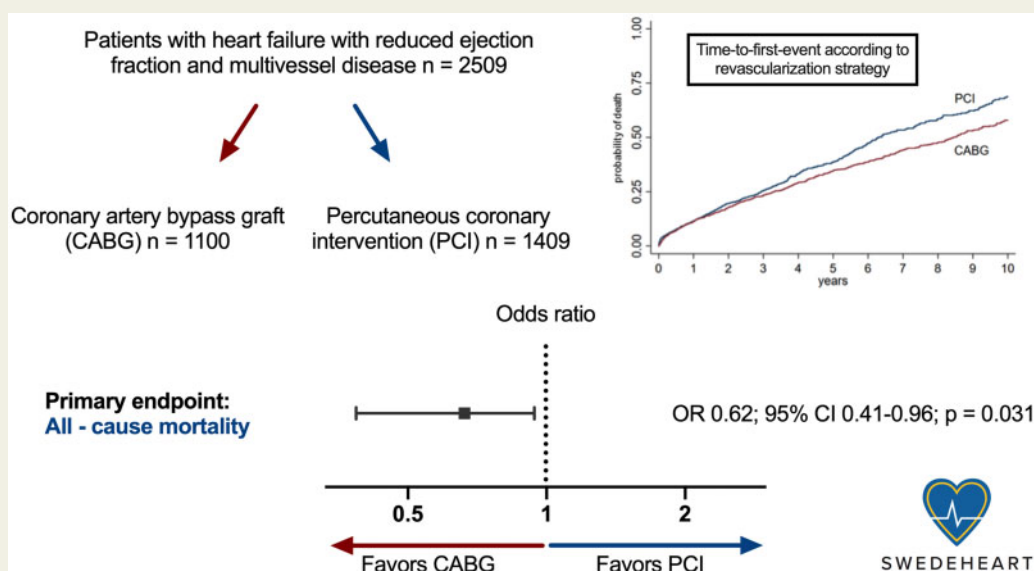
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Graphical Abstract



Study flowchart, time-to-first-event curves through 10-year follow-up and risk-estimate for the primary endpoint – all – cause mortality.

Keywords

Coronary artery bypass grafting • Percutaneous coronary intervention • Heart failure • Diabetes mellitus • Coronary artery disease

Introduction

Ischaemic heart disease is the most common cause of heart failure (HF), accounting for approximately two-thirds of all HF cases.^{1,2} Routine revascularization provides superior outcomes compared with optimal medical therapy (OMT) alone, and current European and American guidelines recommend an invasive approach in addition to OMT in patients with reduced left ventricular ejection fraction (LVEF) and multivessel disease (MVD).^{3,4} Randomized controlled trials in these patients have proven that long-term survival is greater following coronary artery bypass grafting (CABG) than with OMT alone.^{5,6} However, the effects of percutaneous coronary intervention (PCI) in patients with HF and concomitant MVD have not been evaluated in a randomized setting. While European guidelines encourage revascularization with PCI based on observational studies,³ American guidelines deem the available evidence for PCI insufficient.⁴ Furthermore, direct comparisons between PCI and CABG in the context of ischaemic HF are limited to observational studies with inconclusive results.^{7–9} Thus, the optimal revascularization strategy remains a matter of debate.

Our aim was to evaluate the association between CABG vs. PCI and mortality in a national cohort of patients with HF and concomitant MVD.

Methods

Study population

We included all patients who underwent coronary angiography with the primary indication of HF corresponding to International Classification of

Diseases (ICD) 10th revision codes I50.1 (left ventricular failure), I50.2 [systolic (congestive) HF], I50.4 [combined systolic (congestive) and diastolic (congestive) HF], or I50.9 (HF, unspecified) and that showed concomitant MVD (coronary artery stenosis >50% in ≥2 vessels or left main) between 1 January 2000 and 31 March 2018. No patient was hospitalized for acute coronary syndrome (i.e. ST-elevation or non-ST-elevation myocardial infarction) within the 6 months before the index coronary angiography. All patients were included in the Swedish Coronary Angiography and Angioplasty Registry (SCAAR) and Swedish Register of Information and Knowledge about Swedish Heart Intensive Care Admissions (RIKS-HIA), which are part of the Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies (SWEDHEART) registry and was established in 1992. Swedish Coronary Angiography and Angioplasty Registry provides a web-based platform dedicated to data collection from all angiographies and PCIs performed in coronary catheterization laboratories (n = 31) in Sweden (<https://www.ucl.ac.uk/swedeheart/>). Each catheterization procedure is described with ~50 angiographic and 200 PCI, demographic- and procedure-related variables. The registry is financed by the county councils in Sweden and the Swedish state and provides ~100% procedure coverage in Sweden. To obtain information about vital status of the patients, the SCAAR database is continuously merged with the national population registry. More detailed information about SCAAR's organization has been published elsewhere.^{10–14} The study was approved by the ethics committee at the University of Gothenburg (Dnr. 759-13, date of approval 6 May 2014).

Definitions and endpoints

Baseline characteristics, including comorbidities, were obtained from SCAAR and the national patient registry, which includes ICD codes for all

admissions in Sweden since 1987. Patients were considered to have diabetes, hypertension, hyperlipidaemia, previous myocardial infarction, or previous stroke, according to ICD codes.¹² Standard definitions were used for procedure-related information. Only Swedish residents with a unique 10-digit personal identification number were included. The primary endpoint was all-cause mortality. Vital status and date of death were obtained from the Swedish national population registry until 31 March 2018. The population registry in Sweden has nearly 100% completeness within 30 days¹⁵; however, it is not reviewed or adjudicated to establish cardiac vs. non-cardiac causes of death.

Statistical analysis

Continuous variables are presented as median and interquartile range (IQR) and categorical variables as frequencies. The normal distribution of variables was assessed by inspecting the distribution of values on histograms and by the Shapiro–Wilk test. Intergroup differences in continuous variables were tested by linear regression. Differences in categorical variables were tested by logistic regression.

Missing data were imputed using the multiple imputation chain-equation method¹⁶ with five data sets. The calendar year, an indicator of missingness, and an event indicator were included as regular variables. Continuous variables were imputed by ordinary least-squares multiple regression, binary variables by logistic regression, and categorical variables by multinomial logistic regression. The imputation procedure and subsequent analyses were done according to Rubin's protocol¹⁷ under the assumption that missing data are missing at random.

The primary aim of the data analysis was to determine whether the long-term probability of death differed significantly between patients who underwent revascularization with PCI or CABG. Event rates were based on Kaplan–Meier estimates in time-to-first-event analyses. The proportionality of hazards was assessed by including treatment–time interaction in the Cox proportional-hazards regression. However, the underlying assumption of proportional hazards in the Cox model through follow-up was not met (treatment–time interaction, $P < 0.001$). Principal comparisons between treatments were therefore performed by propensity score-adjusted logistic regression with follow-up time included as a log-transformed offset variable, with the use of an estimated standard error for the difference. In a *post hoc* analysis, we evaluated piecewise hazards models separately within 0–3 and 3–10 years, intervals during which proportional hazards were preserved. Given the presence of non-proportional hazards, net treatment effects were also examined with the use of *post hoc* restricted mean survival time and milestone analyses. Restricted mean event-free survival time is the mean time free from an outcome event adjusted for loss to follow-up, reflecting the area under the survival curve.¹⁸ For milestone analysis, the percentage of patients with an event in each group was estimated with the Kaplan–Meier method, and Greenwood's formula was used to estimate standard errors.¹⁹ The difference between groups in the restricted mean survival time and milestone analysis at 10-year follow-up is reported. We used restricted mean survival time to estimate 'lost survival time', depending on the hospital preference for PCI or CABG as a revascularization method.

Propensity score models were used to adjust for differences in patient characteristics. Significant predictors of revascularization method for each patient were identified by fitting a logistic regression model with (i) a binary-dependent variable representing PCI or CABG and (ii) candidate variables consisting of the patient-related predictors of the type of revascularization. The variables in Table 1, calendar year of treatment, and hospital were entered into the logistic model. The estimated propensity score was then used for kernel-based matching²⁰ (based on Epanechnikov function and bandwidth of 0.06) in logistic regression, which was the primary statistical model. Kernel-based matching applies a

non-linear (logit) multiple regression model of the probability and is less sensitive to possible misspecification of the treatment assignment and to violations of positivity assumptions. A frailty term with gamma distribution was included to account for the hierarchical clustering of patients within hospitals.

Sensitivity analysis

For sensitivity analyses, we used modelling with propensity score based on the inverse probability of treatment weighting and instrumental variable analysis.^{21–23} We used instrumental variable analysis to reduce bias due to unmeasured and unknown confounders. This method is a *post hoc* analytic technique based on statistical principles similar to those used in the analysis of randomized controlled trials.^{21,24,25} To use instrumental variable analysis, one must identify a naturally varying phenomenon in the observed data, which like the act of randomization in a randomized controlled trial, predicts the treatment that will be assigned to the individual patient. To become a valid instrument, a variable must fulfil some necessary criteria. First, it must be strongly associated with the received treatment. Second, it must not be associated directly or indirectly with the outcome, except through the effect of the treatment itself. The variable with these statistical qualities is called instrumental variable, or instrument. We used an instrument based on the preference for the use of PCI or CABG at the level of individual hospitals. To create this treatment-preference instrument, we divided hospitals into quintiles based on the total number of procedures in which CABG was used for each year during the study period. Hospital preference is frequently employed as instrument because this type of variable usually fulfils the theoretical criteria for a valid instrument.^{26–28} Variations in the use of the treatment strategy over time in Sweden is a result of changes in guidelines and reimbursement policies as well as changes in physicians' preference due to the release of new effectiveness and safety information. Since the instrument was hospital-based, it might retain an association with the study outcomes, as the quality of care and outcomes are known to vary with a hospital.^{29,30} To mitigate any such association, we controlled for measured hospital characteristics, including size, and teaching vs. non-teaching hospital.

Durbin–Wu–Hausman specification test was used to evaluate the presence of residual confounding (endogeneity). The validity of the instrumental variable was tested with the Sargan test. To test for the strength of the instruments, we examined the partial F test from the first-stage regression, which predicts treatment as a function of instrument and covariates. The partial F-test has the null hypothesis that the coefficient for the effect of the instrument in the first-stage regression model is zero.³¹ An F-statistic greater than 10 indicates that the instrument is not weak. Reported standard errors from instrumental variable two-stage least squares (2SLS) regression are robust and account for the clustering of patients within hospitals using the sandwich estimator. Our primary model was based on instrumental variable 2SLS regression.²¹ The outcome (dependent) variable in the 2SLS regressions was all-cause mortality.

We conducted E-value analysis to assess the robustness of the association between the mode of revascularization and all-cause mortality to address unmeasured confounding.³² If the strength of unmeasured confounding was weaker than indicated by the E-value, then the study result could not be cancelled by unmeasured confounders.

Goodness-of-fit (calibration) for the propensity score models was assessed with the Hosmer–Lemeshow test and with Groennesby and Borgan test for the Cox proportional hazards models. Multicollinearity between the variables in the models was evaluated by calculating the variance inflation factor. All reported P-values are two-sided and are not adjusted for multiple testing.

Table 1 Patients' characteristics at baseline

	PCI (N = 1409)	CABG (N = 1100)	Missing (%)	Crude absolute standardized difference	Adjusted absolute standardized difference
Male sex (%)	83.4	82.7	0	0.01	0.07
Age (years, mean ± SD)	69 ± 9	67 ± 9	0	0.26	0.07
BMI (kg/m ² , mean ± SD)	28 ± 0.2	27 ± 0.2	26.5	0.09	0.00
Diabetes (%)	35.0	38.4	9.8	0.05	0.01
Creatinine (mmol/L, mean ± SD)	108 ± 2	107 ± 2	23.5	0.08	0.00
Hypertension (%)	68.5	60.9	10.3	0.21	0.05
Hyperlipidemia (%)	63.1	52.5	10.5	0.19	0.05
Smoking status (%)			13.6	0.07	0.02
Current smoker	18.9	23.1			
Previous smoker	46.5	43.2			
Previous MI (%) ^a	39.5	26.3	12.4	0.22	0.02
Previous PCI (%) ^a	20.1	5.6	3.2	0.38	0.05
Previous CABG (%)	15.6	1.8	3.2	0.46	0.01
Left ventricular function (%) ^b			46	0.09	0.01
EF 30–49%	28.1	24.1			
EF <30%	71.9	75.9			
Extent of CAD (%)			0.7	1.04	0.01
Multivessel	53.3	10.5			
Left main	46.7	89.5			
Medication at discharge (%)			26		
Beta-blocker	88.8	87.3		0.04	0.07
ACEI/ARB	87.7	86.6		0.07	0.06
MRA	40.3	39.5		0.01	0.03
Statins	78.4	80.7		0.07	0.05
Diuretics	63.9	67.4		0.16	0.07

ACEI, angiotensin-converting enzyme inhibitors; angiotensin II receptor antagonists; BMI, body mass index; CABG, coronary artery bypass grafting; CAD, coronary artery disease; EF, ejection fraction; MI, myocardial infarction; MRA, mineralocorticoid receptor antagonists; PCI, percutaneous coronary intervention; SD, standard deviation.

^aRevascularization procedure prior to index diagnostic angiography.

^bEvaluation of EF was performed at the time of hospitalisation for diagnostic angiography.

Stata software (version 16.1, StataCorp) was used for all statistical analyses. $P < 0.05$ was considered statistically significant.

Results

Baseline characteristics and treatment modalities

In total, 2509 patients [2080 (82.9%) men and 429 (17.1%) women] were included in the study; 35.8% had diabetes, and 34.7% had a previous myocardial infarction. The mean age was 68.1 ± 9.4 years (47.8% were >70 years old), and 64.9% had three-vessel or left main disease. The primary designated therapy after coronary angiography was PCI in 1409 (56.2%) and CABG in 1100 (43.8%) individuals. The baseline characteristics of the patients are presented in Table 1. Patients in the PCI group were, on average, 2 years older and were more likely to have hypertension, hyperlipidaemia, previous myocardial infarction, previous PCI, or previous CABG. Patients in the

CABG group were more likely to have a left main disease. The groups were balanced regarding sex, body mass index, diabetes, creatine clearance, smoking status, ejection fraction, and medication at discharge. The majority of patients revascularized with PCI received drug-eluting stents (Table 2). Waiting time from angiography to revascularization was shorter in the PCI group (median 2 days; IQR 1–5) than in the CABG group (median 11 days; IQR 5–18, $P < 0.001$). There were no deaths during the waiting time between coronary angiography and revascularization.

The number of revascularized patients with PCI or CABG increased by 7.5% per calendar year ($P_{\text{trend}} < 0.001$; Figure 1A). Between 2000 and 2008, CABG was the preferred method for revascularization. In 2009, PCI surpassed CABG as the preferred method. The number of revascularized patients with PCI increased by 13.3% per calendar year ($P_{\text{trend}} < 0.001$), and in 2018 PCI was used 3.4 times more often than CABG. There was a considerable variation between hospitals in the preference for procedures, ranging from 27% to 86% of all procedures for PCI and from 14% to 73% of all procedures for

Table 2 Patients' characteristics related to percutaneous coronary intervention procedure

PCI (N = 1409)	
DES (%)	79.0
Second- or third-generation DES (%)	70.4
Intracoronary pressure wire (%)	33.9
Radial artery access (%)	70.3
Chronic total occlusion (%)	9.4
Lesion classification (%)	
A	13.5
B1	32.5
B2	22.3
C	31.7
Bivalirudin (%)	4.2
GP IIb/IIIa receptor inhibitor (%)	2.0
UFH/LMWH (%)	91.4
Complete revascularization (%)	39.7
P2Y12 receptor antagonist (%)	
Clopidogrel	68.4
Ticagrelor	30.4
Prasugrel	1.2

DES, drug-eluting stent; GP, glycoprotein; LMWH, low molecular weight heparin; PCI, percutaneous coronary intervention; UFH, unfractionated heparin.

CABG ($P < 0.001$) (Figure 1B). An additional 1150 patients who had HF and MVD during the study period did not receive either PCI or CABG but were treated medically. Percutaneous coronary intervention increased annually by 13.6% [95% confidence interval (CI) 12.1–15.1, $P < 0.001$] compared with CABG and by 14.3% (95% CI 12.7–15.8, $P < 0.001$) compared with medical treatment.

Clinical outcome

The primary endpoint was all-cause mortality. Median follow-up time was 3.9 years (range 1 day to 10 years). Over the study period, there were 1010 (40.5%) deaths. Coronary artery bypass grafting was associated with a lower risk of death compared with PCI [odds ratio (OR) 0.62; 95% CI 0.41–0.96; $P = 0.031$] (Figure 2A). In piecewise hazards models, CABG did not associate with risk of death at 3 years (HR 0.79; 95% CI 0.62–1.00; $P = 0.052$) but was associated with a lower risk of death between 3 and 10 years after treatment (hazard ratio 0.72; 95% CI 0.55–0.96; $P = 0.027$) (Figure 2B). Analyses of the restricted mean (Figure 2C) and milestones survival time (Figure 2D) showed that the benefit of CABG increased gradually starting 4 years after revascularization. Mean event-free survival was 0.59 years (95% CI 0.21–0.98) longer after CABG than after PCI ($P = 0.002$) over 10 years. We found significant effect modification between diabetes and CABG ($P_{\text{interaction}} = 0.041$, Figure 3). There was no interaction between the revascularization method and age, sex, calendar year, and the severity of coronary artery disease (Figure 3). The risk of death increased (OR 1.27, 95% CI 1.17–1.38, $P_{\text{trend}} < 0.001$) linearly with quintiles of hospitals in which PCI was the preferred method for revascularization (Supplementary material online, Figure S1). Compared with hospitals with the lowest preference for PCI, 'lost

survival time' increased from 2.2 to 9.6 months in hospitals with a higher preference for PCI (Supplementary material online, Table S1).

Sensitivity analysis

Modelling with propensity score matching based on the inverse probability of treatment weighting showed similar results to the primary model (OR 0.58; 95% CI 0.40–0.86; $P = 0.007$). Instrumental variable analysis based on the treatment-preference instrument showed a significant risk reduction for all-cause mortality with CABG (HR 0.61; 95% CI 0.43–0.86; $P = 0.001$). The exclusion of patients with previous CABG or PCI did not change risk estimates substantially (HR 0.61; 95% CI 0.39–0.94; $P = 0.026$). We tested different scenarios to quantify when the lower limit of the 95% CI for CABG would reach 1 in the primary model.³³ The observed OR of 0.62 in the primary model could be explained away by an unmeasured confounder associated with both the treatment and the outcome by OR of 2.6 each, above and beyond the measured confounders, but weaker confounding could not do so.

Data analysis and post-estimation diagnostics

Data were missing for one or several variables in 900 (34.7%) patients: 446 (30.6%) in the PCI group and 454 (40.1%) in the CABG group (Table 1). Post-estimation analysis for the logistic regression models, including propensity score estimation, by Hosmer–Lemeshow and Groennesby and Borgan tests showed adequate goodness-of-fit for the models ($P > 0.05$). Squared covariate terms had no explanatory power in any of the models (link test, $P > 0.05$). Balancing properties of the calculated propensity scores were evaluated by multivariate linear and binary and multinomial logistic regressions. After propensity score adjustment, we found no statistical difference in baseline characteristics between groups (Table 1). There was an adequate overlap between groups after propensity score matching (Supplementary material online, Figure S2). The average variance inflation factor was below 5.0 for all models, indicating a lack of multicollinearity between the variables. Durbin–Wu–Hausman test for endogeneity was statistically significant at $P < 0.001$ for all dependent variables modelled with the 2SLS regression. The validity (overidentification) test yielded the Sargan–Hansen statistic of 1.17 with a P -value of 0.76, which indicates that the instruments were valid. Treatment–time interaction in the piecewise Cox proportional-hazards models was not significant for the period between 0 and 3 years ($P = 0.979$) or 3–10 years ($P = 0.508$).

Discussion

Among 2509 patients undergoing revascularization therapy due to ischaemic HF, treatment with CABG was associated with a lower risk of all-cause mortality as compared with PCI (Graphical abstract). Our findings confirm current guideline recommendations for patients with ischaemic HF.^{3,4}

The most important result of this study—the superior outcome with CABG in ischaemic HF—indirectly supports the findings from the STICH (Surgical Treatment for Ischaemic Heart Failure) trial,^{5,6} the pivotal trial assessing the effects of CABG compared with OMT. Our finding that CABG was more favourable for patients with

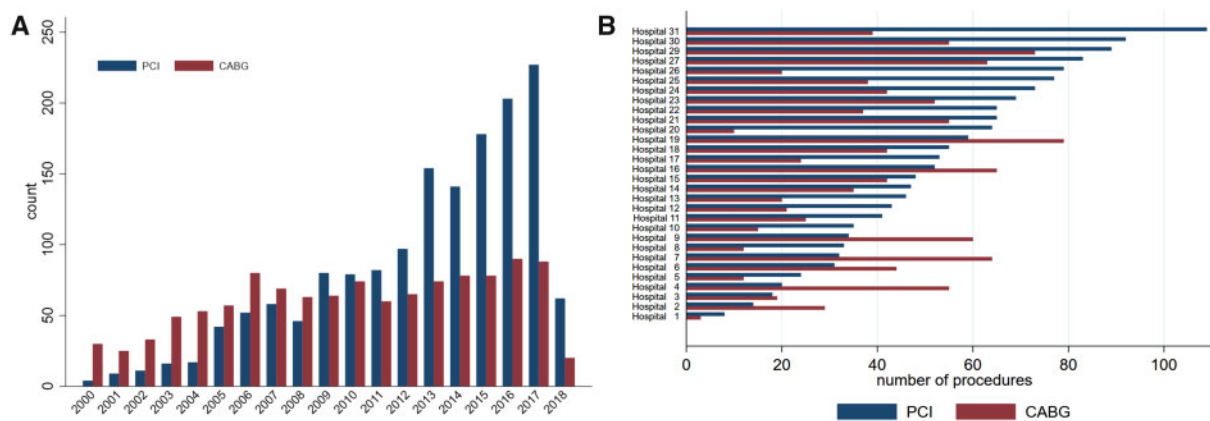


Figure 1 (A) Number of revascularized patients with ischaemic heart failure in Sweden between 2000 and 2008. The number of revascularized patients with percutaneous coronary intervention or coronary artery bypass grafting increased by 7.5% per calendar year ($P_{\text{trend}} < 0.001$). Between 2000 and 2008, coronary artery bypass grafting was the preferred method for revascularization of patients with ischaemic heart failure in Sweden. In 2009, percutaneous coronary intervention became the preferred revascularization method. The number of revascularized patients with percutaneous coronary intervention increased by 13.3% per calendar year ($P_{\text{trend}} < 0.001$). In 2018, percutaneous coronary intervention was used 3.4 times more often than coronary artery bypass grafting. (B) Number of percutaneous coronary intervention and coronary artery bypass grafting per hospital 2000–18. There was large variation between the hospitals in the preference for revascularization method ranging between 27–86% for percutaneous coronary intervention and 14–73% for coronary artery bypass grafting.

diabetes mellitus is congruent with data from previous studies.^{34,35}

The survival curves started to separate after 4 years, thus reflecting the timeline of events from the STICH trial. The late departure of the curves in the STICH trial was explained by an early increase in peri-procedural mortality of CABG, which was then offset by beneficial effects of the surgical revascularization.⁶ Our study shows that this timeline is similar even for the comparison between CABG and PCI and confirms previously demonstrated robustness of surgical revascularization in patients with MVD, with and without HF.^{34–36} The lower risk of death with CABG translates on average into 0.5 years of event-free survival time over 10 years. However, the gain in event-free survival time decreases substantially with shorter life expectancy. Given the risk-benefit of CABG vs. PCI, this information should be considered wisely during the decision-making process within heart teams as well as for informed consent to patients.

Due to the observational nature of our study, we cannot establish a causal relationship on the basis of the present analysis. However, previous studies have shown that the beneficial long-term outcome of CABG in comparison with PCI may be mediated by a higher degree of completeness of revascularization and lower risk for future myocardial infarction—a finding which has been consistent in several major studies.^{37–39} Also, different from PCI, CABG targets both flow-limiting and no-flow-limiting stenoses, the latter being responsible for a significant proportion of future myocardial infarction.^{40,41}

Our findings contrast results in an observational study from the USA of comparable size and design. Using data from a New York registry, Bangalore *et al.* assessed outcomes of PCI vs. CABG in patients with reduced LVEF. They found no statistical difference in all-cause mortality between the two treatment strategies.⁷ However, the follow-up time in their study was limited to a median of 2.9 years

compared with 3.9 years in our study. With a follow-up time up to 10 years, our study provides a significant extension resulting in a three-fold higher number of events. Consequently, the substantially higher number of events generates greater statistical power to detect a difference in mortality and may, therefore, explain the discrepancy between the two studies. Our study is congruent with Sun *et al.*,⁴² who recently reported that CABG was associated with better long-term survival based on data from the Ontario province. However, the most important differences between our study and the Ontario study are (i) we used an unselected population from one whole nation, and (ii) we confirmed our results by modelling with instrumental variable analysis, which is one of the best methods to account for residual confounding in observational studies. Moreover, our data are supported by results from a recently published meta-analysis in which CABG, PCI, and OMT were compared in the setting of ischaemic HF.⁸ Wolff *et al.* performed a comprehensive, pooled analysis of 3 randomized and 18 observational studies, which showed a survival benefit of CABG compared with PCI in patients with ischaemic HF.

Over the 19 years of this study, there was a steady rise of revascularization procedures in patients with ischaemic HF in Sweden. While the use of CABG remained stable over the past decade, PCI procedures increased continuously at a steep rate of 13.3% per year, thus surpassing CABG and ultimately tripling in rate compared with CABG in the most recent years. However, this development is not supported by the current guidelines and available evidence.³ One explanation for this trend may be the extrapolation of the findings from the STICH study by physicians presuming a class effect of coronary revascularization. Also, we noted a considerable variation in the preference of revascularization modality across the 31 study centres in Sweden with PCI/CABG ratios ranging from 0.2 to 5. Indeed, patients

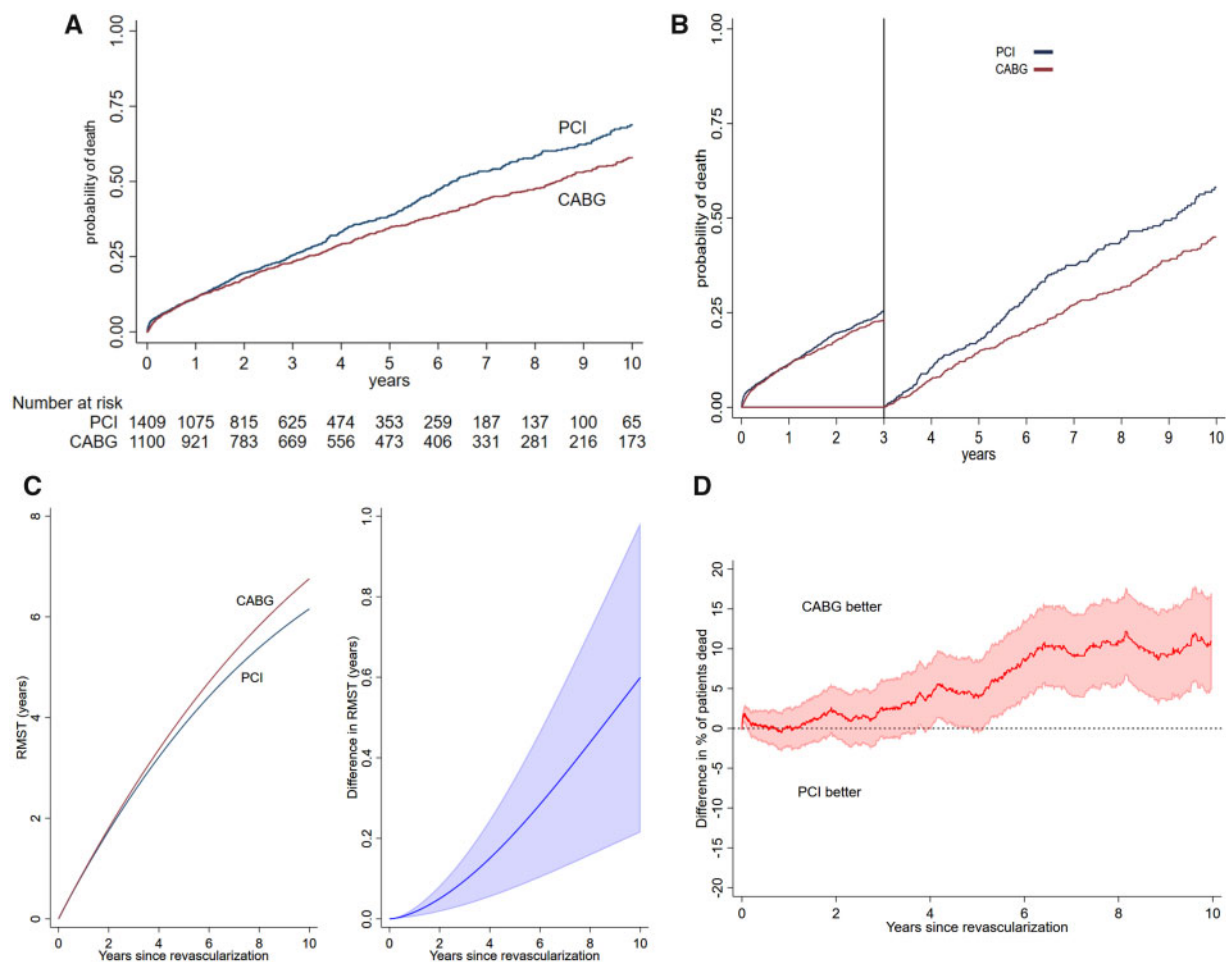


Figure 2 (A) Time-to-first-event curves for all-cause mortality through 10-year follow-up. Survival curves start separating after the 3rd year. Given non-proportional hazards during the follow-up period, logistic regression with follow-up time included as a log-transformed offset variable was used to calculate the odds ratios with 95% confidence intervals as a primary analysis. (B) Piecewise analysis for all-cause mortality from 0 to 3 years days, and 3 year to 10 years. Time-to-first event curves with landmarks at 3 years. Hazard ratios with 95% confidence intervals in the two intervals were determined by Cox proportional-hazards regression. (C) Milestone and restricted mean survival time analyses for all-cause mortality during the 10-year follow-up period. Difference in restricted mean event-free survival time between percutaneous coronary intervention and coronary artery bypass grafting. Dashed lines represent 95% confidence intervals. Mean event-free survival through 10 years was 0.59 years longer after coronary artery bypass grafting than after percutaneous coronary intervention (95% CI 0.21–0.98 years). (D) Milestone analysis representing the difference in probability of event-free survival over time (dark red line) between percutaneous coronary intervention and coronary artery bypass grafting. Light red area represents 95% confidence intervals.

with ischaemic HF treated in hospitals in which PCI was the preferred revascularization method had higher long-term mortality and significant loss in survival time. A similar finding was reported previously when comparing Swedish hospitals in general.⁴³ Factors that are important determinants of treatment preference among decision-making physicians include a lack of high-quality evidence comparing PCI and CABG in the setting of HF, local tradition, technical expertise, and access to a surgical unit. Other reasons for the discrepancy between guidelines and clinical practice have been investigated and include operator-specific inertia of previous practice, lack of familiarity, and disagreement with current guidelines.⁴⁴ Data from other

countries are scarce, but the same trend is reflected in one previous study which identified PCI to be the most common revascularization method in US patients with HF and MVD.⁴⁵

Data from randomized controlled trials investigating PCI in ischaemic HF will not be available for some time. The results from the ongoing REVIVED (REvascularization for Ischaemic VENTricular Dysfunction) trial, which assesses the comparative effectiveness of PCI vs. OMT in patients with reduced systolic LVEF,⁴⁶ are not expected before 2023. Of note, the REVIVED trial does not include a CABG arm and focuses only on patients who are not eligible for surgery. There are ongoing initiatives for a pivotal, head-to-head

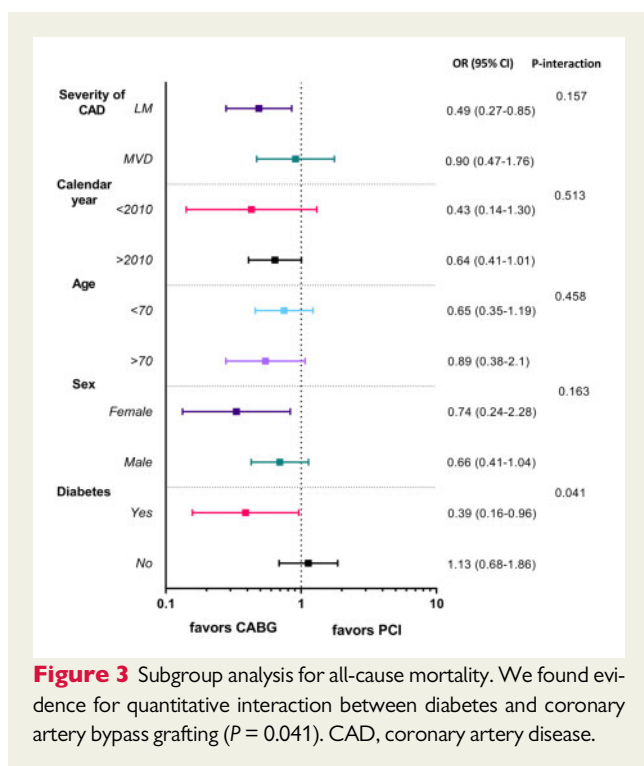


Figure 3 Subgroup analysis for all-cause mortality. We found evidence for quantitative interaction between diabetes and coronary artery bypass grafting ($P = 0.041$). CAD, coronary artery disease.

comparison of PCI and CABG in ischaemic HF. Data from our observational study may provide valuable information for the planning of such a study.

Several limitations need to be addressed. The present study is based on an intention-to-treat analysis, and thus a minority of the included patients may have eventually crossed over to a different revascularization modality. We do not have data about New York Heart Association class, Canadian Cardiovascular Society class, or SYNTAX score. Lack of data about implantable cardioverter-defibrillator/cardiac resynchronization therapy is a major limitation. As our patient inclusion was based on diagnostic coding only, data resolution did not allow differentiation between reversible and irreversible alteration in cardiac structure and function. We do not present outcome data for patients treated medically because of the difficulty in ascertaining whether HF was primarily due to ischaemic heart disease or cardiomyopathy. In a number of medically treated patients, there was an apparent and sizeable discrepancy between the extent and grade of impairment of left ventricular function and the area at risk supplied by the coronary arteries with significant stenoses (i.e. vessels <2 mm), which suggests that cardiomyopathy rather than ischaemic heart disease is the primary cause of HF. Many patients treated medically were unsuitable for revascularization due to coronary anatomy or high procedural risk. A recent meta-analysis by Bangalore *et al.*⁴⁷ evaluating the importance of revascularization vs. medical treatment in stable coronary artery disease patients without HF did not demonstrate prognostic benefit from revascularization therapy irrespective of type. However, the effect of revascularization therapy vs. medical treatment in patients with HF differs from stable coronary artery disease. The STICH trial has established the superiority of CABG over

medical treatment. The remaining question is whether revascularization with PCI confers beneficial prognostic effects similar to CABG. A substantial number of patients were revascularized with an older stent generation and without intracoronary evaluation with a pressure-wire. We acknowledge that the observational design of our study carries an inherent risk for residual confounding. However, stringent statistical modelling with propensity score method and instrumental variable analysis has minimized the risk of substantial bias in risk estimates. Indeed, the quantification of residual confounding with E -value³² confirmed the robustness against bias. The events in the study were not independently adjudicated. However, regular external monitoring and data validation are performed in SWEDEHEART and have previously shown high data accuracy.¹⁴ Our data do not allow the differentiation between cardiac and non-cardiac death. All-cause death is a robust, clinically significant endpoint and, in contrast to cause-specific death, it does not require a complex adjudication process. Administrative databases reliably capture death events in Sweden, and nearly 100% of all deaths are registered within the first month.¹⁵

In conclusion, in patients with ischaemic HF, CABG was associated with superior long-term survival compared with PCI. This finding was supported by centre-level data showing that inclination towards performing PCI rather than CABG was associated with a worse prognosis. However, PCI is still the preferred revascularization method in the majority of Swedish hospitals in these patients. Our study supports the current European and American guidelines for revascularization of patients with HF due to ischaemic heart disease.^{3,4} There is a need for a randomized trial to resolve the question of which revascularization method should be the treatment of choice for patients with ischaemic HF.

Supplementary material

Supplementary material is available at *European Heart Journal* online.

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Data availability

The data underlying this article will be shared on reasonable request to the corresponding author.

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Conflict of interest: E.O. reported receiving institutional research grant from AstraZeneca, consultancy fees from Bayer and Novartis and speakers honorarium from MSD. A.J. reported speakers honorarium from AstraZeneca, Boehringer-Ingelheim, Octapharma, LFB and consultancy fees from LFB, XVIVO. D.E. reported speaker fees from AstraZeneca. No other disclosures were reported. All others authors reported no conflict of interests.

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