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ORIGINAL ARTICLE

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ADULT CARDIAC

Long-term outcomes after coronary artery bypass surgery in patients with diabetes

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Key question

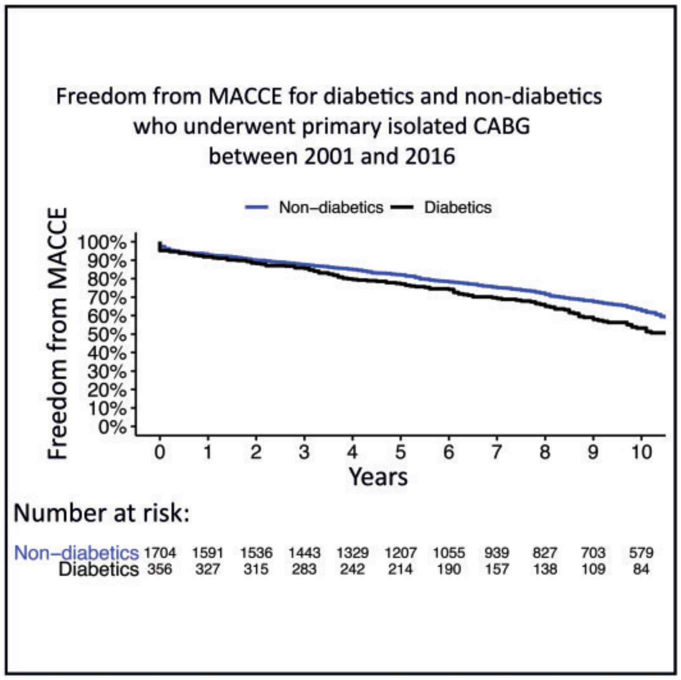
How do long-term outcomes for patients with diabetes compare to those of patients without diabetes following coronary artery bypass grafting (CABG)?

Key finding(s)

Patients with diabetes have worse overall survival and freedom from major adverse cardiac and cerebrovascular events.

Take-home message

Patients with diabetes have increased risk for worse long-term outcomes following CABG.



Abstract

OBJECTIVES: Our aim was to investigate the outcome of patients with diabetes undergoing coronary artery bypass grafting (CABG) surgery in a whole population with main focus on long-term mortality and complications.

METHODS: This was a nationwide retrospective analysis of all patients who underwent isolated primary CABG in Iceland between 2001 and 2016. Overall survival together with the composite end point of major adverse cardiac and cerebrovascular events was compared between patients with diabetes and patients without diabetes during a median follow-up of 8.5 years. Multivariable regression analyses were used to evaluate the impact of diabetes on both short- and long-term outcomes.

RESULTS: Of a total of 2060 patients, 356 (17%) patients had diabetes. Patients with diabetes had a higher body mass index (29.9 vs 27.9 kg/m^2) and more often had hypertension (83% vs 62%) and chronic kidney disease (estimated glomerular filtration rate ≤60 ml/min/1.73 m^2, 21% vs 14%). Patients with diabetes had an increased risk of operative mortality [odds ratio 2.52, 95% confidence interval (CI) 1.27–4.80] when adjusted for confounders. 5-Year overall survival (85% vs 91%, $P < 0.001$) and 5-year freedom from major adverse cardiac and cerebrovascular events were also inferior for patients with diabetes (77% vs 82%, $P < 0.001$). Cox regression analysis adjusting for potential confounders showed that the diagnosis of diabetes significantly predicted all-cause mortality [hazard ratio (HR) 1.87, 95% CI 1.53–2.29] and increased risk of major adverse cardiac and cerebrovascular events (HR 1.47, 95% CI 1.23–1.75).

CONCLUSIONS: Patients with diabetes have significantly lower survival after CABG, both within 30 days and during long-term follow-up.

Keywords: Coronary artery bypass grafting • Diabetes • Outcome • Complications • Long term • Major adverse cardiac and cerebrovascular events • Survival

ABBREVIATIONS

BMI	Body mass index
CABG	Coronary artery bypass grafting
CAD	Coronary artery disease
CI	Confidence interval
CKD	Chronic kidney disease
COPD	Chronic obstructive pulmonary disease
CPB	Cardiopulmonary bypass
HR	Hazard ratio
LVEF	Left ventricular ejection fraction
MI	Myocardial infarction
OR	Odds ratio

INTRODUCTION

Diabetes mellitus is a major risk factor for atherosclerosis and coronary artery disease (CAD) [1, 2]. Furthermore, patients with diabetes have an almost 3 times higher risk of fatal cardiovascular disease compared to patients without diabetes [3]. Landmark studies in the last 2 decades have focussed on finding the optimal revascularization strategy for patients with diabetes, comparing percutaneous coronary intervention (PCI) and coronary artery bypass grafting (CABG) [4]. Both the BARI and SYNTAX studies showed a benefit of CABG in patients with diabetes, and this was further strengthened in the randomized prospective FREEDOM trial where a significant survival benefit of CABG over PCI was demonstrated in patients with diabetes with multivessel disease [5].

CABG is now considered to be the optimal revascularization strategy for patients with diabetes with multivessel CAD. To optimize their operative outcomes, it is important to compare how outcomes for patients with diabetes are compared to patients without diabetes. Studies examining early postoperative complications and 30-day mortality following CABG have shown higher rates of postoperative complications in patients with diabetes [6, 7].

Furthermore, long-term survival has been shown to be inferior, possibly due to long-term complications related to diabetes, such as a higher risk of myocardial infarction (MI) and chronic kidney disease (CKD) [8, 9].

The primary aim of this study was to assess long-term outcomes after CABG, comparing patients with diabetes to patients without diabetes.

MATERIALS AND METHODS

Study design

This was a retrospective cohort study of all patients who underwent isolated CABG surgery in Iceland during 2001–2016. All operations were performed at Landspitali University Hospital, the sole institution performing cardiac surgery in Iceland. The study was approved by the local ethics committee (Ref: VSNb2010010009/03.07, 11 June 2019), and individual patient consent was waived.

Data collection

Patients were identified via operation codes in a digital operation registry, as well as from a centralized cardiac surgery database for all CABG operations. Clinical data were collected retrospectively from medical records. Preoperative variables were registered for each patient, including age, gender, cardiovascular risk factors, recent MI (diagnosed within 30 days) and a previous history of MI or PCI. Information on the severity of CAD was obtained from angiography reports, and EuroSCORE II [10] was calculated for all patients. Diabetes was defined as a preoperative diagnosis of diabetes in the medical records or current use of either oral diabetic medication or insulin. The estimated glomerular filtration rate was calculated from standardized serum creatinine measurements using the Chronic Kidney Disease Epidemiology Collaboration equation [11]. CKD was staged according to the kidney disease outcome quality initiative classification [12] and decreased kidney function defined as an estimated glomerular filtration rate ≤60 ml/min/1.73 m^2. Chronic obstructive pulmonary disease (COPD) was logged if patients had a diagnosis of COPD in the medical records. Echocardiographic reports were used to log preoperative left ventricular ejection fraction (LVEF). Information on preoperative medical therapy, including statins, beta-blockers, anticoagulants and antiplatelet therapy, was obtained from hospital records. Intraoperative factors such as the use of cardiopulmonary bypass (CPB), cross-clamp time and total operative times were registered, as well as the number of distal anastomoses and use of arterial graft conduits.

Study end points

The primary end points of the study were overall survival and freedom from major adverse cardiac and cerebrovascular events (MACCE), defined as the composite end point of all-cause

Table 1: Preoperative patient demographics

Means and standard deviations or *n* (%)	Non-DM (*n* = 1704)	DM (*n* = 356)
Age (years)	66.5 ± 9.4	65.6 ± 9.1
Female gender	299 (18)	59 (19
Hypertension	1051 (62)	296 (83)
CKD (GFR <60 ml/min/1.73 m^2)	247 (14)	76 (21)
BMI (kg/m^2)	27.9 ± 4.2	29.9 ± 5.2
Previous PCI	369 (22)	89 (25)
EuroSCORE II	2.29 ± 3.22	3.07 ± 4.25
Three-vessel CAD	1366 (80)	295 (82)
Left main stem stenosis	731 (43)	126 (35)
LVFEF <35%	113 (7)	36 (10)

BMI: body mass index; CAD: coronary artery disease; CKD: chronic kidney disease; DM: diabetes mellitus; GFR: glomerular filtration rate; LVEF: left ventricular ejection fraction; PCI: percutaneous coronary intervention.

mortality, stroke, MI and/or repeat revascularization. Stroke as a long-term complication was defined as a loss of neurological function that persisted for >24 h and diagnosed with computed tomography or magnetic resonance imaging. Long-term MI was defined as the diagnosis of MI >30 days after surgery. A diagnosis of MI was made if an elevation of cardiac biomarkers was seen in addition to one of the following: new significant ST segment changes, new left bundle branch block or development of Q waves on electrocardiogram, symptoms of ischaemia, diagnostic imaging showing new wall motion abnormalities or identification of an intracoronary thrombus. Repeat revascularization was defined as the need for PCI or re-CABG in the follow-up period. Secondary end point was 30-day mortality, defined as a patient dying within 30 days of all causes.

Follow-up

Statistics Iceland was used to evaluate the survival and cause of death for patients as of 31 December 2018. Unique social security numbers for Icelandic residents allowed for comprehensive follow-up and was completed for all patients (median follow-up 8.5 years, range 0–18 years).

Information on repeat PCI in the follow-up period was obtained from a centralized PCI registry at Landspitali University Hospital, which is the only hospital in Iceland where PCI is performed. Furthermore, the 7 hospitals that cover all parts of Iceland provided medical records to find all patients who had a diagnosis of MI or stroke in the follow-up period.

Statistical analysis

The Mann-Kendall test for monotonic trend in time was used to assess the prevalence of diabetes within the study population between the study years. The Kaplan–Meier method was used to generate survival plots, and the log-rank test was used to compare survival and freedom from MACCE between patients with diabetes and patients without diabetes. Multivariable logistic regression was performed to assess the direct effect of diabetes on operative mortality (<30 days), adjusting for known confounders, age, sex and body mass index (BMI), as well as possible mediators, hypertension, CKD and LVEF <35%. Furthermore, a second regression analysis was performed only adjusting for confounders to investigate the total effect of diabetes on operative mortality. Identical adjustments were done in Cox regression analysis to assess the direct and total effect of diabetes on all-cause death and MACCE. Missing variables were imputed with multiple imputations using the mice package in R.

Statistical analysis was performed using R version 3.2.3 (R Foundation for Statistical Computing, Vienna, Austria) using the survival, epitools, MASS, dplyr, tidyr, ggplot2, mice and survival ROC receiver operating characteristic (ROC) packages.

The study was approved by the Icelandic National Bioethics Committee and the Data Protection Commission.

RESULTS

A total of 2060 patients underwent isolated CABG in Iceland during the 16-year study period. Thereof, 356 (17%) patients had a preoperative diagnosis of diabetes. There was no significant change in the proportion of patients with diabetes between years.

Patient demographics

Demographic factors for patients with diabetes and patients without diabetes are shown in Table 1. Patients with diabetes had a mean BMI of 29.9 kg/m^2 compared to 27.9 kg/m^2 for patients without diabetes. Hypertension was found in 83% and 62% of patients with and without diabetes, respectively; 21% of diabetic and 14% of non-diabetic patients had a history of CKD (class 3–5).

Operative data

Operations were performed off pump (off pump coronary artery bypass grafting, OPCAB) in 18% of patients with diabetes compared to 20% of patients without diabetes. The total operative time for patients with diabetes was longer (225 vs 210 min) as was the CPB time (99 vs 90 min). The median number of distal anastomoses was 3.5 in both groups, and the left internal mammary artery was used as a conduit in 96% and 94% of patients with diabetes and patients without diabetes, respectively. Both patients with diabetes and patients without diabetes received >1 arterial conduit in 2% of cases.

Early complications and operative mortality

Early postoperative complications are listed in Table 2. Superficial wound infections occurred in 13% of patients with diabetes and in 9% of patients without diabetes. Eighteen percent (18%) of patients with diabetes had an acute kidney injury (Kidney Disease: Improving Global Outcomes classes 1–3) compared to 11% of patients without diabetes. Furthermore, 30-day mortality was 4% for patients with diabetes compared to 2% for patients without diabetes.

After adjusting for confounders and mediators in logistic regression analysis, patients with diabetes had a higher risk of operative mortality compared with patients without diabetes [odds ratio (OR) 2.11, 95% confidence interval (CI) 1.02–4.16] and an even higher risk adjusting for confounders only (OR 2.52, 95% CI 1.27–4.80) (Table 3).

Table 2: Postoperative complications, comparison of patients without diabetes and patients with diabetes

n (%)	Non-DM (*n* = 1704)	DM (*n* = 356)
Perioperative MI	70 (4)	11 (3)
Reoperation for bleeding	97 (6)	16 (4)
Superficial wound infection	150 (9)	46 (13)
New postoperative AF	541 (32)	115 (32)
Postoperative pleural effusion	202 (12)	50 (14)
Pneumonia	109 (6)	20 (6)
UTI	54 (3)	14 (4)
DSWI	12 (1)	6 (2)
Stroke	19 (1)	4 (1)
AKI (KDIGO)		
Class 1	142 (8)	49 (14)
Class 2	37 (2)	12 (3)
Class 3	8 (0.5)	6 (1.5)
Multiorgan failure	48 (3)	12 (3)
Operative mortality (30 days)	32 (2)	14 (4)

AF: atrial fibrillation; AKI: acute kidney injury; DM: diabetes mellitus; DSWI: deep sternal wound infection; KDIGO: kidney disease: improving global outcomes; MI: myocardial infarction; perioperative MI: a diagnosis of MI <30 days of operation; UTI: urinary tract infection.

Table 3: The direct and total effect of diabetes on risk of 30-day mortality, overall survival and long-term MACCE when adjusted for confounders

	Direct effect[a]	95% CI	Total effect[b]	95% CI
30-Day mortality	OR 2.11	1.02–4.16	OR 2.52	1.27–4.80
Overall survival	HR 1.83	1.49–2.24	HR 1.87	1.53–2.29
MACCE	HR 1.40	1.17–1.67	HR 1.47	1.23–1.75

[a]Adjusted for age, sex, BMI, smoking, hypertension and left ventricular ejection fraction.

[b]Adjusted for age, sex and BMI.

BMI: body mass index; HR: hazards ratio; MACCE: major adverse cardiac and cerebrovascular event; OR: odds ratio; 95% CIs: 95% confidence intervals.

Overall survival

Long-term overall survival is shown in Fig. 1A. Survival at 1, 5 and 10 years postoperatively was 95% vs 97%, 85% vs 91% and 64% vs 77% for patients with diabetes and patients without diabetes, respectively ($P < 0.001$).

When adjusted for confounders and mediators, diabetes was an independent risk factor for inferior survival with a hazard ratio (HR) of 1.83 (95% CI 1.49–2.24), but when the risk was only adjusted for confounders, diabetes had a slightly higher HR, or 1.87 (95% CI 1.53–2.29) (Table 3).

Long-term complications (major adverse cardiac and cerebrovascular events)

The overall rate of MACCE for both groups at 5 years is shown in Fig. 1B. The freedom from MACCE at 5 years was observed in 77% for patients with diabetes and 82% for patients without diabetes, and that at 10 years was observed in 53% and 63% for patients with diabetes and for patients without diabetes, respectively ($P < 0.01$).

When adjusted for confounders and mediators, diabetes was an independent risk factor for MACCE with an HR of 1.40 (95% CI 1.17–1.67). When only adjusted for confounders, diabetes had an HR of 1.47 (95% CI 1.23–1.75) (Table 3).

DISCUSSION

The present study shows that patients with diabetes had worse long-term survival as compared to patients without diabetes: the 5-year overall survival being 85% vs 91% and the 10-year survival being 64% vs 77% for patients with diabetes and patients without diabetes, respectively. Comparison with other studies is difficult as study populations vary but our survival estimates must be regarded as favourable, both for patients with diabetes and patients without diabetes undergoing CABG [8, 13]. An inferior survival in patients with diabetes is not surprising as the relative risk of mortality for patients with diabetes is 4 times higher than the normal population and even higher in the presence of other comorbidities such as cardiac or kidney disease [14, 15]. Furthermore, in the current study, patients with diabetes had reduced MACCE-free survival after CABG as compared to patients without diabetes.

Most likely the increased risk of long-term MACCE is due to the increased atherosclerotic burden in patients with diabetes compared to patients without diabetes. Numerous studies have shown that patients with diabetes more often have diffuse CAD, and their coronary arteries have smaller luminal diameters [16]. The ability to develop collateral coronary arteries is also inferior in patients with diabetes as compared to patients without diabetes. Both of these factors contribute to an increased atherosclerotic burden in patients with diabetes [17, 18]. In our study, patients with diabetes were more likely to have had a previous coronary artery stent, which further strengthens this notion. Furthermore, patients with diabetes are more likely than patients without diabetes to suffer from silent ischaemia, possibly delaying treatment with PCI and CABG and thereby negatively affecting their prognosis [19]. Alserius *et al.* [20] showed an increased risk of long-term MI for patients with diabetes following CABG compared to patients without diabetes. However, a recent systematic review and meta-analysis by Bundhun *et al.* [21] did not find a difference in rates of MI, repeat revascularization or stroke between patients with diabetes and patients without diabetes; however, only 2 of the included studies had a 10-year follow-up.

Our findings further strengthen that patients with diabetes are at an increased risk for long-term complications and mortality compared to patients without diabetes. Regression analyses showed significantly increased risk of death (HR 1.87) and MACCE (HR 1.47) in patients with diabetes after adjusting for confounders. We considered hypertension, CKD and low LVEF to be mediators, i.e. to lie on the causal pathway between diabetes and the outcome of interest. Since it may be difficult to fully exclude some confounding effect of these mediators through other unmeasured confounders, we have also shown results where we additionally adjust for these factors in the regression analysis. This lowered the risk of death and MACCE minimally in patients with diabetes, whereas it significantly affected the risk of operative mortality, from OR 2.52 to 2.11. This implies that a significant amount of the total effect of diabetes on the risk of operative mortality is mediated through these factors.

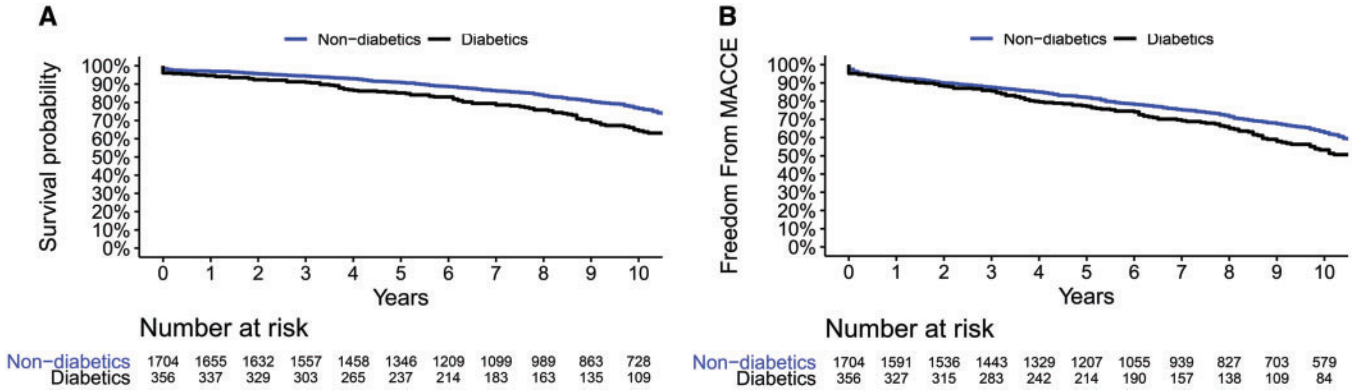


Figure 1: (**A**) Overall survival of patients with diabetes and patients without diabetes who underwent primary isolated coronary artery bypass grafting (CABG) between 2001 and 2016 in Iceland. (**B**) Freedom from MACCE of patients with diabetes and patients without diabetes who underwent primary isolated CABG between 2001 and 2016. MAACE: major adverse cardiac and cerebrovascular event.

In a recent study from Sweden, patients with type 2 diabetes had an HR of 1.11 for death. However, patients with type 1 diabetes had almost double the risk, with an HR of 2.04 for death, and similar ratios for risk of MACCE [13]. Gallagher *et al.* [8] also reported diabetes as a risk factor for inferior 5-year survival following CABG with an HR of 1.30, and the survival was even worse if the patients also had CKD (HR 2.04). There have been conflicting results in the literature regarding the effect of diabetes on operative mortality with Filsoufi *et al.* [6] reporting diabetes not to be a risk factor. Furthermore, a recent study by Kogan *et al.* [22] found no significant difference between patients with diabetes and patients without diabetes in regard to 30-day mortality, that is in contrast to Carson *et al.* [7] that found that diabetes incurs an increased risk for operative mortality in a large cohort study on 146 000 patients from 1997.

The prevalence of diabetes in our cohort was 17%, which is relatively low compared to other studies where it is reported in the 20–30% range [5, 7, 9, 17]. This is probably a reflection of the fact that the overall prevalence of diabetes in Iceland is low compared to countries such as the USA and Germany, where it is ∼3 times higher [23, 24]. Disconcertingly, the prevalence of diabetes in the general population has increased in Iceland from 3% to 6% in males and from 2% to 3% in females in the last 3 decades [24]. Therefore, the prevalence of diabetes in Icelandic CABG patients may be expected to increase in coming years.

Preoperative demographics such as age and sex were similar in patients with diabetes and patients without diabetes. However, patients with diabetes had higher rates of hypertension as well as a higher BMI. Indeed, hypertension was very common in patients with diabetes, with 83% of the patients having the diagnosis and taking antihypertensive medication. Most likely patients with diabetes have hypertension as a part of the metabolic syndrome along with central obesity, insulin resistance and dyslipidaemia [25, 26]. Of note, hypertension in patients with diabetes can also accelerate the development of diabetic nephropathy, a serious complication of diabetes, predisposing to CKD [26]. Today, diabetes is the most common cause of CKD in the developed world and ∼40% of patients with diabetes develop diabetic nephropathy, the risk being even higher for type 1 diabetes than type 2 diabetes [27]. Diabetic nephropathy also increases the risk of developing acute kidney injury, cardiovascular disease and increases the risk of death [28, 29].

The operating time was longer in patients with diabetes, reflecting both in the total operating time and longer CPB time. Operating in patients with diabetes may take longer as their atherosclerotic disease is more diffuse and they have smaller arterial diameters, making the operation more technically challenging [17]. Even so, this did not translate into higher rates of reoperation for bleeding or perioperative stroke. Importantly, there was a slightly increased risk of superficial wound infections (13% vs 9%). Many studies have also reported an increased risk of deep sternal wound infection in patients with diabetes following CABG [6, 7, 30].

Limitations

Our patient cohort is well defined, and centralized registries allowed us to investigate both short- and long-term outcomes for all patients undergoing isolated primary CABG in a single country over a 16-year period. All operations were performed in a single institution, and data on survival were easily attained and complete for all patients with a follow-up of up to 18 years. Detailed follow-up information, such as repeat PCI, was accessible by a nationwide PCI registry in which every PCI performed in Iceland is logged. Furthermore, all individual patient records were reviewed in detail at every hospital in Iceland. The main limitation is the retrospective nature of the study. Furthermore, information was not available on all patients regarding insulin treatment preoperatively and the definition of diabetes relied on information from medical charts and not evaluated prospectively.

CONCLUSIONS

Patients with diabetes have significantly lower survival after CABG, both within 30 days and during long-term follow-up.

Conflict of interest: none declared.

Author contributions

Tomas Andri Axelsson: Investigation; Supervision; Writing—original draft; Writing—review & editing. **Jonas A. Adalsteinsson:** Data curation; Writing—review & editing. **Linda O. Arnadottir:** Conceptualization; Data curation;

Writing—review & editing. **Dadi Helgason:** Data curation; Writing—review & editing. **Hera Johannesdottir:** Conceptualization; Data curation; Writing—review & editing. **Solveig Helgadottir:** Data curation; Writing—review & editing. **Andri Wilberg Orrason:** Formal analysis; Methodology; Writing—review & editing. **Karl Andersen:** Conceptualization; Supervision; Writing—review & editing. **Tomas Gudbjartsson:** Conceptualization; Data curation; Funding acquisition; Project administration; Supervision; Writing—review & editing.

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