

Coronary surgery in patients with diabetes mellitus: a risk-adjusted study on early outcome

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Abstract

Objectives: We aimed at determining the effect of diabetes mellitus (diabetes) on short-term mortality and morbidity in a cohort of patients with ischemic disease undergoing coronary artery bypass surgery (CABG) at our institution. **Material and methods:** A total of 4567 patients undergoing isolated CABG in a 10-year period were studied. Diabetes mellitus was present in 22.6% of the cases but the percentage increased from 19.1% in the beginning to 27% in the end of the study period ($p < 0.0001$ for the decade time-trend). Compared with non-diabetic patients, the group with diabetes was older (61.5 ± 8.4 years vs 60.4 ± 9.5 years), had a higher body mass index (26.4 ± 2.2 vs 26.0 ± 2.2), comprised more women (17.5% vs 10.1%), and had a greater incidence of peripheral vascular disease (13.3% vs 8.8%), cerebrovascular disease (8.3% vs 4.3%), renal failure (2.7% vs 1.1%), cardiomegaly (14.0% vs 10.9%), class III–IV angina (43.4% vs 39.0%), triple-vessel disease (80.9% vs 73.7%) and patients with left ventricular dysfunction (all $p < 0.05$). Demographic and peri-procedural data were registered prospectively in a computerized institutional database. Multivariate logistic regression was performed to assess the influence of diabetes as an independent risk factor for in-hospital mortality and morbidity. **Results:** The overall in-hospital mortality was 0.96% [$n = 44$; diabetics: 1.0%, non-diabetics: 0.9% ($p = 0.74$)]. The mortality of patients with diabetes decreased from 2.7% in the early period to 0.7% in the late period ($p = 0.03$ for the time-trend). Postoperative in-hospital complications were comparable in the two groups in univariate analysis, with only cerebrovascular accident and prolonged length of stay being significantly higher in the diabetic patients (all $p < 0.05$). In multivariate analysis, diabetes was not found to be an independent risk factor for in-hospital mortality (OR = 0.61; 95% CI = 0.28–1.30; $p = 0.19$), but predicted the occurrence of mediastinitis (OR = 1.80; 95% CI = 1.01–3.22; $p = 0.049$). **Conclusions:** Despite worse demographic and clinical characteristics, diabetic patients could be surgically revascularized with low mortality and morbidity, comparable with control patients. Hence, our data do not support diabetes as a risk factor for significantly adverse early outcome following CABG.

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Keywords: Coronary artery bypass grafting (CABG); Diabetes mellitus; Risk factors; Early outcome

1. Introduction

Diabetes mellitus is most often recognized as a risk factor for adverse outcomes after coronary artery bypass graft surgery (CABG), with regard to both early postoperative results and long-term survival [1–4]. Hence, there is a need for continuously evaluating the performance of surgical revascularization in diabetic patients, because (1) diabetes is present in approximately one-quarter of the patients undergoing CABG [1,3,5,6], and its prevalence is steadily increasing [7,8]; and (2) over the years, several reports have attested the superiority of CABG over percutaneous coronary intervention for coronary revascularization in diabetic patients [9–12].

However, the impact of diabetes in the short-term mortality and morbidity in patients undergoing CABG is unclear and remains a subject of debate. While some studies reported a significant negative influence of diabetes in early postoperative outcomes [2,5], others have even suggested a better outcome in this group of patients [1,3,4].

In this report we assess the impact of diabetes in the early mortality and morbidity in a large series of patients subjected to CABG in a single institution, adjusting for patient and disease characteristics.

2. Materials and methods

2.1. Study design and population

We performed a retrospective study of patients who underwent CABG during a 10-year period at our institution. All patients undergoing isolated first operations and reopera-

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tions were included and those who had CABG combined with heart valve repair or replacement, resection of a ventricular aneurysm, or other surgical procedures were excluded. All operations were performed without cardioplegia, under hypothermic ventricular fibrillation or empty beating heart, a technique described in detail in a previous report from our group [13].

2.2. Study variables and definitions

The study included the following preoperative, operative and outcome variables:

- (1) *Preoperative*: age; body mass index; gender; hypertension; dyslipidemia; recent smoking; peripheral vascular disease; cerebrovascular disease; renal failure; anemia; chronic obstructive pulmonary disease; cardiomegaly; previous myocardial infarction; recent myocardial infarction; unstable angina; Canadian Cardiovascular Society (CCS) class; non-elective surgery; previous percutaneous coronary intervention (PCI); prior CABG; ejection fraction; left ventricular dysfunction; left main disease; and extent of coronary disease (1–2 vessel or 3 vessel). Definitions of these variables are presented in [Appendix A](#).

- (2) *Operative*: number and type of grafts, the use of coronary endarterectomy and the cardiopulmonary bypass (CPB) time.
- (3) *Outcome variables*: in-hospital mortality and the following postoperative complications: cerebrovascular accident, mediastinitis, acute renal failure, reoperation for bleeding, myocardial infarction, atrial and ventricular arrhythmias, inotropic support, mechanical support, and prolonged length of stay.

Definitions of these complications are presented in [Appendix B](#).

Diabetes was defined as a history of the disease and the patient currently receiving treatment with either oral medications or insulin. In-hospital mortality was defined as death during hospital stay, unlimited in time.

2.3. Data collection

Data were collected prospectively on a standardized written form by the involved surgeon and validated and inputted in a computerized database by the first author. Data collection and storage was supervised by the project coordinator (MJA) for consistency, and aggregate outputs were periodically crosschecked against an independent

Table 1
Demographic and clinical characteristics (n = 4567)

Variable	Diabetic (N = 1030)	% (22.6)	Non-diabetic (N = 3537)	% (77.4)	p value
Mean age (years)	61.52 ± 8.41		60.39 ± 9.46		0.001
Mean body mass index	26.39 ± 2.22		26.02 ± 2.22		<0.001
Female sex	180	17.5	357	10.1	<0.001
Hypertension	612	59.4	1991	56.3	0.074
Dyslipidemia	668	64.9	2011	56.9	<0.001
Recent smoking	87	8.4	438	12.4	<0.001
Peripheral vascular disease	158	13.3	311	8.8	<0.001
Cerebrovascular disease	85	8.3	153	4.3	<0.001
Renal failure ^a	15	2.7	21	1.1	0.005
Anemia	57	5.5	122	3.4	0.002
COPD	42	4.1	110	3.1	0.13
Cardiomegaly	144	14.0	386	10.9	0.007
Previous myocardial infarction	588	57.1	2021	57.1	0.99
Recent myocardial infarction	57	5.5	176	5.0	0.47
Unstable angina	74	7.2	237	2.7	0.59
CCS class					
I–II	583	56.6	2157	61.0	0.012
III–IV	447	43.4	1380	39.0	
Previous PCI	46	4.5	189	5.4	0.26
Prior CABG	20	1.9	50	1.4	0.23
Left main disease	181	17.6	573	16.2	0.30
Non-elective surgery	80	7.8	223	6.3	0.097
Ejection fraction					
>60%	551	53.5	2003	56.6	0.007
40–60%	309	30.0	1098	31.0	
30–39%	126	12.2	326	9.2	
<30%	44	4.3	110	3.1	
Extent of coronary disease					
1–2 vessel	197	19.1	929	26.3	<0.001
3 vessel	833	80.9	2608	73.7	

^a n = 2481; 553 diabetic and 1928 non-diabetic patients.

Table 2
Operative data

Variable	Diabetic (N = 1030)	% (22.6)	Non-diabetic (N = 3537)	% (77.4)	p value
N of distal anastomoses per patient (mean \pm SD)					
Total	2.88 \pm 0.79		2.80 \pm 0.81		0.005
Arterial	1.15 \pm 0.41		1.28 \pm 0.49		<0.001
LIMA use	1021	99.1	3517	99.4	0.55
RIMA use	136	13.2	934	26.4	<0.001
BIMA use	134	12.6	896	25.6	<0.001
Coronary endarterectomy	86	8.3	238	6.7	0.075
CPB time, mean \pm SD (min)	62.8 \pm 19.9		63.0 \pm 24.3		0.80

clinical database. The data collection instruments included questions regarding demographic characteristics, preoperative risk factors, previous interventions, preoperative cardiac status, cardiac catheterization results, intraoperative management and postoperative complications.

2.4. Patient and operative data

The study cohort included 4567 patients undergoing isolated CABG surgery. Of these, 1030 (22.6%) patients were classified as diabetic using the definition indicated above. The percentage of patients with diabetes increased from 19.1% in the early to 27% in the late period ($p < 0.001$ for the decade time-trend).

The distribution of baseline characteristics between the two groups is shown in Table 1. Comparing with the non-diabetic, the diabetic group was characterized by a higher mean age, a higher mean body mass index, a higher proportion of females and of patients with dyslipidemia, anemia, cardiomegaly, renal failure, peripheral vascular disease, cerebrovascular disease, severe angina (CCS class III–IV), triple-vessel disease and left ventricular dysfunction (ejection fraction <40%).

The distribution of operative variables is shown in Table 2. The number of distal anastomoses per patient was significantly higher in the diabetic group (2.9 \pm 0.8 vs 2.8 \pm 0.8; $p = 0.005$). Although the group of diabetic patients received fewer arterial grafts, similar percentages of patients in the two groups were revascularized with LIMA grafts, in both cases as a consequence of the protocol implemented in these patients.

2.5. Perioperative glycemc control

We aimed at maintaining the blood glucose levels in diabetic patients between 120 and 160 mg/dl. Preopera-

tively, diabetic patients were started on a standard sliding scale subcutaneous insulin injection. In the operating room and in the ICU they received continuous intravenous insulin infusions. They were then switched back to the sliding scale subcutaneous insulin injection until discharge, even after the resumption of their preoperative glucose control regimen. For non-diabetic patients, the use of sliding scale insulin infusion was triggered by blood glucose levels greater than 180 mg/dl.

2.6. Statistical methods

Normally distributed continuous variables are represented as mean \pm standard deviation (SD) or as the percentage of the sample. The χ^2 -test and Fisher's exact test were used to determine differences in patient characteristics by univariate analysis. Multivariate logistic regression was performed to assess the influence of diabetes as an independent risk factor for hospital mortality and postoperative morbidity. Variables included in the adjusted analyses were chosen because they showed imbalance between the two groups and/or they were thought to affect the outcome. The same variables were included in the entire risk-adjusted analyses presented (see Table 4 footnote for details). Taken into consideration the presence of a small effective sample size on the outcome death ($n = 44$), the entire database was initially used to develop the predictive logistic model. Survivors and non-survivors were compared by univariate analysis. Variables with a p value less than 0.2 by univariate analysis were used as independent variables in a stepwise logistic regression analysis, with in-hospital mortality as the binary dependent variable. Because of the relatively small effective sample size, a p value less than 0.1 was selected for variable retention in the final regression model. A bootstrap analysis was used in combination with the

Table 3
Postoperative outcomes

Variable	Diabetic (N = 1030)	% (22.6)	Non-diabetic (N = 3537)	% (77.4)	p value
In-hospital deaths	9	0.9	35	1.0	0.74
Cerebrovascular accident	37	3.6	79	2.2	0.015
Mediastinitis	18	1.7	38	1.1	0.084
Myocardial infarction	32	3.1	121	3.4	0.62
Renal dysfunction	28	5.2	108	5.7	0.68
Inotropic support	88	8.5	244	6.9	0.074
Mechanical support	10	1.0	29	0.8	0.64
Reoperation for bleeding	27	2.6	85	2.4	0.69
Atrial arrhythmias	246	23.9	869	24.6	0.65
Prolonged length of stay	109	10.6	289	8.2	0.016

Table 4
Risk-adjusted analysis of the effect of diabetes on clinical outcomes

Outcome	Adjusted ^a effect size		
	Odds ratio	95% confidence interval	<i>p</i> value
In-hospital death	0.61	0.28–1.30	0.19
Cerebrovascular accident	1.27	0.84–1.92	0.26
Mediastinitis	1.80	1.01–3.22	0.049
Myocardial infarction	0.93	0.62–1.39	0.71
Renal dysfunction	0.83	0.53–1.29	0.40
Inotropic support	1.01	0.83–1.43	0.53
Mechanical support	1.05	0.47–2.13	0.99
Reoperation for bleeding	1.01	0.65–1.59	0.96
Atrial arrhythmias	0.90	0.76–1.06	0.20
Prolonged length of stay	1.20	0.94–1.52	0.14

^a Adjusted for age, sex, body mass index, Canadian Cardiovascular Society class, previous myocardial infarction, anemia, dyslipidemia, recent smoking, cardiomegaly, peripheral vascular disease, cerebrovascular disease, prior CABG, ejection fraction, non-elective surgery, hypertension, and extent of coronary disease.

logistic regression analysis to select the final set of risk factors included in the model. In the bootstrap procedure, 200 samples of 4567 patients (the same number of observations as the original database) were sampled with replacement. A stepwise logistic regression analysis was applied to every bootstrap sample. If the predictors occurred in more than 50% of the bootstrap models, they were judged to be reliable and were retained in the final model. Unreliable variables, if present, were removed from the final model.

The statistical significance of time-trends, prevalence of diabetes and in-hospital mortality during the 10-year period was determined by logistic regression. A *p* value <0.05 was considered significant for all tests.

3. Results

Postoperative outcomes are shown in Table 3. The overall in-hospital mortality was 0.96% (*n* = 44). There was no difference in the mortality rate of the diabetic and non-diabetic groups (0.9% and 1.0%, respectively; *p* = 0.74). The mortality of patients with diabetes decreased from 2.7% in the early period to 0.7% in the late period (*p* = 0.03 for the decade time-trend).

Table 4 shows the influence of diabetes on the mortality and postoperative morbidity after adjustment for potential confounders. The presence of diabetes was not found to be an independent predictor of in-hospital mortality on multivariate analysis (OR = 0.61; 95% CI 0.28–1.30; *p* = 0.19) (Table 4). By contrast, age (increasing), reoperation, peripheral vascular disease, left ventricular dysfunction (ejection fraction <40%) and non-elective surgery were identified as independent predictors of in-hospital death (Table 5).

In-hospital morbidity events were mostly comparable in the two groups by univariate analysis, with only cerebrovascular accident and prolonged length of stay showing a significantly higher incidence in the diabetic patients. Requirement for inotropic support (*p* = 0.074) and mediastinitis (*p* = 0.084) approached statistical significance. However, by multivariate analysis, diabetes had an independent

Table 5
Predictors of in-hospital mortality in the total population

Variable	<i>p</i> value	Odds ratio	95% CI (OR)	
Age (per 1-year increase)	0.006	1.054	1.015	1.094
Peripheral vascular disease	<0.001	4.831	2.590	9.010
LV dysfunction (EF < 40%)	0.055	1.989	0.985	4.016
Non-elective surgery	0.002	3.323	1.556	7.097
Reoperation	0.009	5.040	1.486	17.090

influence only in the development of mediastinitis (OR = 1.80; 95% CI 1.01–3.22; *p* = 0.049), whereas the association with cerebrovascular accident (*p* = 0.26) and prolonged length of stay (*p* = 0.14) disappeared.

4. Discussion

Most reports indicate that diabetes is present in approximately one-quarter of the patients undergoing revascularization for coronary artery disease, for which it is considered a risk factor [1,3,5,6], but there has been a steady increase in the incidence. Analysis of the data from the Society of Thoracic Surgeons National Adult Cardiac Database and from the Society of Cardiothoracic Surgeons of Great Britain and Ireland showed an increase in the prevalence of diabetes in patients referred for CABG (21% in 1990 to 33% in 1999, and 18% in 1994 to 23.5% in 2001, respectively) [7,8]. In our contemporary series, we observed a similar percentage of diabetic patients referred for CABG with an overall prevalence of 22.6% and a significant increase in the prevalence of diabetes, from 19.1% in the beginning to 27% in the end (*p* < 0.0001 for the decade time-trend).

Our diabetic patients had a similar preoperative higher risk profile as patients from other reported series [1,3–6]. Patients with diabetes were more likely to be older and female, and to have a higher mean body mass index, severe angina, peripheral vascular disease, cerebrovascular disease, renal failure, anemia, dyslipidemia, cardiomegaly, triple-vessel disease, as well as a decreased LV ejection fraction, all factors which are well known for their negative impact on outcome.

It is generally accepted that diabetic individuals subjected to CABG have a higher early mortality, but the influence of diabetes per se on this outcome has been under debate. In the study reported by Thourani et al. [2], the mortality was significantly higher among the diabetic (3.9%) compared to the non-diabetic population (1.6%). The North American Multicenter Registry data of 146,786 patients who underwent CABG surgery in 1997 indicates a 30-day mortality of 3.7% in diabetic patients compared to 2.7% in non-diabetic patients [5]. In both studies, diabetes was found to be an independent predictor of early (in-hospital or 30-day) mortality. However, more recent studies have challenged these findings by reporting more favorable results, crude and adjusted, in diabetic patients undergoing CABG. Szabo et al. [1], Rajakaruna et al. [3] and Filsoufi et al. [4] reported mortality rates of 2.6%, 2.2% and 2.4%, respectively, in diabetic patients and did not isolate diabetes as an independent predictor of early mortality. Our in-hospital mortality for diabetic patients was 1.0%, only marginally higher than in non-diabetics (0.9%) and we could also not

identify diabetes as an independent predictor of early mortality. This could be related to the small number of events (44 deaths) in the series. Although there is no consensus on sample size, as a rule of thumb in studies deriving multivariable prognostic models, 10 or more events per variable are usually required in order to get a robust estimation of the coefficients. The ratio of events to risk factors included in our local model presented in Table 5 was approximately 9–1 (44 events; 5 variables), therefore, the data of the multivariate analysis should be interpreted with caution.

There is now clear evidence that the impact of diabetes on in-hospital mortality has changed over time. According to the Society of Cardiothoracic Surgeons of Great Britain and Ireland, in 1997 diabetic patients were twice as likely to die after CABG compared to non-diabetics (5.9% vs 3.0%), but by 2001 there had been an important reduction in the operative mortality (2.9% vs 2.2%), practically eliminating diabetes as an additional risk [7]. In the study reported by Filsoufi et al. [4], the mortality rate among diabetics decreased significantly, from 3.1% in the period 1998–2002 to 1.0% in 2003–2005. Similarly, our study shows a decrease in in-hospital mortality among diabetic patients over the decade in analysis from 2.7% in 1992 to 0.7% in 2001 ($p = 0.03$ for the decade time-trend). Better knowledge of the pathophysiology and improved pre- and perioperative control of the disease may have contributed to this evolution.

In this series, the incidences of morbidity events analyzed were also similar in the two groups by univariate analysis, with only cerebrovascular accident and prolonged length of stay showing a significantly higher incidence in diabetic patients. However, by multivariate analysis, diabetes had only an independent influence on the development of mediastinitis (OR = 1.80). The studies reported by Filsoufi et al. [4], Kubal et al. [14] and Shroyer et al. [15] also demonstrated that diabetes had an independent influence on the development of sternal infection.

The independent influence of diabetes in the development of a cerebrovascular accident has been described by some authors [1,3]. Although univariate analysis had shown a significantly higher incidence of cerebrovascular accidents in our diabetic patients, this association disappeared in the multivariate analysis. This finding is also in accordance with those of some recent studies [4,14].

In contrast with the previously published studies of Szabo, Rajakaruna and Kubal and their co-workers [1,3,14], we could not identify diabetes as an independent predictor of acute renal failure or prolonged length of stay. Additionally, diabetes was also not associated with the rate of post-operative myocardial infarction, with increased requirement for inotropic or mechanical support, the occurrence of atrial arrhythmia and need for re-exploration for bleeding in our patients.

There is now evidence to suggest that a better blood glucose management in the perioperative period improves early outcomes in diabetic patients subjected to CABG [16]. Estrada, Fish, Furnary and their co-workers demonstrated that controlling blood glucose levels at values lower than 200 mg/dl in diabetic patients leads to significantly fewer postoperative complications, including in-hospital death [17–19]. During the 10-year study interval in our series,

we aimed at maintaining the blood glucose levels between 120 and 160 mg/dl in diabetic patients, and below 180 mg/dl in non-diabetic patients, during the perioperative period. We believe that this approach has contributed to the good surgical outcomes observed in these patients.

There are some limitations in this study, which may affect its conclusions. This is an observational study and, by its retrospective nature (although the data was prospectively collected), it cannot account for the unknown variables affecting the outcomes that are not correlated strongly with the variables used in the risk adjustment. However, multivariate analysis is a theoretically sound statistical method of accounting for differences between groups in the absence of random allocation. Also, this study was based on a large cohort of patients from a single institution, which adds strength to the power of the analysis.

In conclusion, despite the worsening case-mix, in our experience diabetic patients could be surgically revascularized with low mortality and morbidity rates, comparable to those of non-diabetic patients. Hence, our data do not support the conclusions by other authors who found diabetes to be a risk factor for significantly adverse early outcome following CABG. Better knowledge of the disease and improved management of blood glucose levels led to a significant improvement in the results during the study-period and beyond.

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Appendix A. Definition of preoperative variables

Hypertension	Blood pressure exceeding 140/90 mmHg, or a history of high blood pressure, or the need of antihypertensive medications
Renal failure	Creatinine >2.0 mg/dl and no dialysis dependency
Recent smoking	Up to less than 4 weeks of surgery
Anemia	Hematocrit ≤34%
Cardiomegaly	Cardiothoracic ratio >0.50 on a chest X-ray-film
Pulmonary obstructive chronic disease	Patient requires pharmacologic therapy for the treatment of chronic pulmonary compromise, or patient has a FEV1 <75% of predicted value

Peripheral vascular disease	Claudication either with exertion or at rest; amputation for arterial insufficiency; aorto-iliac occlusive disease reconstruction; peripheral vascular bypass surgery, angioplasty or stent; documented abdominal aorta aneurysm, repair or stent; or non-invasive carotid test with >75% occlusion
Cerebrovascular disease	Unresponsive coma >24 h, CVA, or TIA <30 days
Recent myocardial infarction	Preoperative use of iv nitrates until arrival in the anesthetic room
Unstable angina	Ejection fraction <40%
Left ventricular dysfunction	Urgent or emergent surgery
Non-elective surgery	

Appendix B. Definition of postoperative complications

Cerebrovascular accident (CVA)	Global or focal neurological deficit lasting less (transient ischemic attack) or more than 24 h (reversible ischemic neurologic deficit; stroke)
Mediastinitis	At least one of the following: (1) an organism isolated from culture of mediastinal tissue or fluid; (2) evidence of mediastinitis seen during operation; (3) one of the following conditions: chest pain, sternal instability, or fever (>38 °C), in combination with either purulent discharge from the mediastinum or an organism isolated from blood culture or culture of mediastinal drainage
Myocardial infarction	New Q-wave postoperatively in two or more contiguous leads of the ECG
Inotropic support	Use of one or more inotropic drugs, for any length of time
Mechanical support	Use of intra-aortic balloon pumping or ventricular assistance
Acute renal failure	A postoperative creatinine serum level ≥2.1 mg/dl plus an increase in the serum creatinine level ≥0.9 mg/dl from preoperative to maximum postoperative values in patients who had no significant pre-existing renal disease (creatinine ≤2.0 mg/dl and no dialysis-dependence)
Reoperation for bleeding	Bleeding or cardiac tamponade that required intervention after admission into the ICU
Prolonged postoperative length of stay	≥10 days