

Off-pump Coronary Artery Bypass Surgery with Multiple Arterial Grafts in Diabetic Patients: Short and Long-term Results.

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ABSTRACT

Introduction

Diabetes mellitus has been identified as a strong independent predictor of cardiovascular disease onset and progression and acknowledged as a mortality risk factor after coronary artery surgery. Off-pump coronary artery bypass grafting has been established as an efficient alternative to coronary revascularization, comparable to the conventional technique, with results evidencing a reduction in procedure morbidity and, in high risk patients, lower postoperative mortality.

Objective

The aims of this study were to compare short and long-term postoperative results of off-pump coronary artery revascularization surgery with multiple arterial grafts in patients with or without diabetes mellitus and to determine if postoperative hyperglycemia is an independent predictor of early morbidity and mortality.

Methods

Off-pump coronary revascularization surgery with multiple arterial grafts was consecutively performed on 1002 patients between January 2004 and December 2008. The population was divided in diabetes mellitus (n: 234) and non-diabetes mellitus (n: 768) patients. Post-operative complications were analyzed and independent predictors of in-hospital mortality were identified. The average follow-up period of 1038 ± 517 days was completed by 95.7% of patients.

Results

Diabetes mellitus patients had lower cardiac output (p=0.005), atrial fibrillation (p=0.005) and deep sternal wound infection (p=0.005). Age (OR= 1.11), non-elective surgery (OR=5.88) and blood glucose level > 200 mg/dL (OR= 6.9) were significant predictors of in-hospital mortality. Five-year survival was lower in diabetes mellitus patients (p=0.01). Diabetes mellitus (HR = 2.1), age (HR= 1.06), left ventricular ejection fraction <40% (HR=2.45) and postoperative creatinine > 1.6 mg/dL (HR=2.46) were significant predictors of decreased long-term survival.

Conclusions

Diabetes mellitus and non-diabetes mellitus patients had similar in-hospital mortality rates. Postoperative hyperglycemia was a predictor of greater in-hospital mortality. Diabetes mellitus and creatinine > 1.6 mg/dL were independent predictors of decreased long-term survival.

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Key words >

Coronary Disease - Coronary Artery Bypass - diabetes mellitus

Abbreviations >

ADA	Anterior descending artery	LAD	Left anterior descending artery
AMI	Acute myocardial infarction	LIMA	Left internal mammary artery
CABG	Coronary artery bypass grafting	MACCE	Major adverse cardiac and cerebrovascular event
CAT	Computed axial tomography	RIMA	Right internal mammary artery
CVA	Stroke	RCA	Right coronary artery
CxA	Circumflex artery	TCA	Transluminal coronary angioplasty
DM	Diabetes mellitus		
EF	Ejection fraction		

INTRODUCTION

Diabetes mellitus (DM) has been identified as a strong independent predictor of onset and progression of cardiovascular disease (1) and has been acknowledged as a risk factor for mortality after coronary artery bypass grafting (CABG). (2) Diabetes mellitus alters many physiological parameters, including lipid metabolism and the inflammatory cascade components. These changes would be responsible for the high incidence of comorbidities in this group of patients: diffuse disease of small coronary vessels, peripheral vascular disease, hypertension, renal failure, obesity and propensity to infection.

Off-pump CABG has been established as an effective approach to coronary revascularization comparable to the conventional on-pump CABG technique. Results show a decrease in procedure morbidity and a reduced postoperative mortality in high-risk patients. (3-9)

Recent publications have shown that patients with bilateral internal mammary arteries as arterial conduits for revascularization have higher survival and event-free period in long-term follow-up. The use of multiple arterial conduits seems to be the current way of performing CABG with a longer lasting effect. (10-12)

The presence of hyperglycemia in critically ill patients is a "normal" stress phenomenon. Van den Berghe et al. showed that keeping blood glucose levels between 80 and 110 mg/dL with the use of intensive IV insulin was accompanied by a marked reduction in these patients' mortality. (13)

The aim of this work was: a) to investigate in-hospital and long-term outcome in a consecutive group of patients with and without DM undergoing off-pump CABG, and b) to determine whether postoperative hyperglycemia is an independent predictor of increased postoperative risk.

METHODS

Between January 2004 and December 2008, 1002 patients underwent off-pump CABG using both mammary arteries for exclusive arterial revascularization. The group of patients operated with this technique represents 45.7% of the total off-pump CABG surgeries performed at our institution (1002 / 2191). All patient data were prospectively obtained from the database (Microsoft Access@Microsoft) used in daily practice to record clinical data.

A comparative analysis of postoperative risk and long-term follow-up was performed between DM (n: 234) and non-DM (n: 768) patients. Patients with DM were those under pharmacological treatment with any oral hypoglycemic drug and/or subcutaneous insulin; patients only under diet control were excluded from the study. Complete arterial revascularization was performed with arterial grafting to any coronary artery presenting >70% stenosis. The arterial graft / lesion >70% relationship was assessed for every coronary artery (ADA, CxA and RCA) in patients with and without DM. Preoperative, intraoperative and postoperative data were obtained from the retrospective systematic review of surgical records and clinical histories.

Postoperative complications were: acute myocardial infarction (AMI) (or presence of a new Q wave or loss of the R wave progression in precordial leads or >10% increase in creatine kinase (myocardial band); low cardiac output requiring intra-aortic balloon counterpulsation and/or use of inotropic drugs for > 48 h; postoperative bleeding demanding surgical reexploration; respiratory failure needing mechanical respiratory assistance for > 48h; renal failure with creatinine level > 2 mg/dL or 100% increase from preoperative value, with or without need for dialysis; stroke, defined as central neurological disorder persisting > 24 h with or without computed tomography (CT) scan confirmation. Mediastinitis was defined as deep sternal wound infection demanding surgical reexploration.

Prevalence of postoperative hyperglycemia was analyzed in DM and non-DM patients. Mobile scale insulin infusion was used in all patients during the procedure, immediately after surgery or during hospitalization, to keep blood glucose levels below 150 mg/dL. In most cases, intravenous infusion was discontinued after 48 h, with subsequent oral treatment. Postoperative glucose levels were assessed in all patients, registering the highest level recorded during patient stay in intensive care. Patients were divided into two groups according to their blood glucose levels (> or < 200 mg/dL). These values represented the 75th percentile of the total group of patients.

All patients were operated with the intention of performing off-pump CABG (intention to treat) and the criteria to switch to on-pump CABG were: hemodynamic and electrical instability and calcified, thin (< 1.5 mm) and/or intramyocardial coronary arteries.

The surgical technique for off-pump CABG has been previously reported (14) and consists in using bilateral internal mammary arteries (LIMA-RIMA) as exclusive conduits for coronary revascularization. No other arterial or venous vessel was used. The most common technical configuration used was in situ LIMA with anastomosis to the left anterior descending artery (LAD); then RIMA was used for sequential revascularization of the CxA and RCA system. No aortic

anastomosis was performed in any patient of this series.

Multivariate analysis was done to identify independent predictors of in-hospital mortality and presence of major adverse cardiovascular and cerebrovascular events (MACCE, involving death, AMI, CVA and mediastinitis) in both groups of patients.

Long-term follow-up was carried out by telephone contact with the patient, his/her family and/or family doctor during a six-month interval. Long-term survival as well as prevalence of readmission due to cardiovascular complications as: new episodes of chest pain, new AMI and or congestive heart failure were analyzed. Also, the incidence of new revascularization procedures (transluminal coronary angioplasty (TCA) and/or CABG) was analyzed during follow-up. Multivariate analysis was performed to identify independent predictors of long-term survival and combined adverse events (death, hospital readmission and reintervention).

Postoperative angiographic studies were performed in patients having informed consent to evaluate the long-term patency of the arterial graft. In patients developing symptoms during follow-up, the angiography was performed at the moment of symptom occurrence. The Fitzgibbon classification was used to assess the graft, (15) analyzing patency indexes in all the population and separately for DM and non-DM patients. Confirmation of new coronary lesion and/or graft occlusion was opportunely treated by means of TCA or CABG as required. Cardiac surgeons and interventional cardiologists reviewed and evaluated angiographic studies.

The institutional Ethics Committee approved the study and an informed consent concerning the surgical method and postoperative evaluations was obtained from each patient.

Statistical analysis

Categorical variables were expressed as percentages and compared using the chi-square test. Continuous variables were expressed as mean and standard deviation or median and interquartile range. Comparisons were performed using Student's *t* test or Wilcoxon's test according to normal or non normal distribution, respectively. Early and long-term postoperative results as long-term survival free from hospital readmission, reintervention and combined cardiovascular events were analyzed. Multiple logistic regression analysis was used to explore the association between baseline characteristics and perioperative results, and expressed as OR with the corresponding 95% CI. The Kaplan-Meier method was applied to build survival curves which were compared using the log-rank test. Cox multivariate analysis was used to adjust for initial differences between groups and obtain independent predictors of results. In all cases, a *p* value < 0.05 was considered statistically significant. Stata 9.0 was employed to perform the statistical analyses.

RESULTS

In-hospital results

Table 1 shows baseline population characteristics. From the total number of patients, 234 were DM and 768 non-DM patients. Diabetes mellitus patients had a significantly greater incidence of hypertension, hyperlipidemia, chronic renal failure and previous myocardial infarction than non-DM patients. A greater number of non-DM patients underwent non-elective surgery compared to DM patients. Table 2A summarizes surgical results. The switch ratio to on-pump

CABG was 0.59% (6 / 1002). There were no differences in the total number of distal anastomoses between both groups (3.28 vs. 3.21). Diabetes mellitus patients received more than one distal anastomosis on the CxA territory than non-DM patients (*p* = 0.02). Complete revascularization could be performed in 91.8% of non-DM and in 89.3% of DM patients (*p* = 0.078). More than 96% of DM and non-DM patients underwent ADA and CxA revascularization. Conversely, RCA complete revascularization could only be performed in 68.3% of DM patients and 75.5% of non-DM patients (*P* = ns). Table 2B shows results of postoperative angiographies.

In-hospital mortality (30 days) was similar in both groups, while low cardiac output, atrial fibrillation and mediastinitis were more frequent in DM patients. Hospital stay showed no significant differences between both groups (Table 3).

Independent predictors for in-hospital mortality were: age (OR 1.11, 95% CI: 1.02-1.21, *p* = 0.01), non-elective procedure (OR 5.88, 95% CI: 1.36-25, *p* = 0.01) and blood glucose level > 200 mg/dL (OR 6.9, 95% CI: 1.27-37.38, *p* = 0.02). Significant MACCE predictors were: age (OR 1.04, 95% CI: 1.01-1.07, *p* = 0.01), urgent surgical procedure (OR 1.93, 95% CI: 1.22-3.05, *p* = 0.005), aortic calcification (HR 5.02, 95% CI: 1.82-13.8, *p* = 0.002), and time of "skin to skin" (OR 1.006, 95% CI: 1.00-1.01, *p* = 0.014). Univariate analysis did not identify DM as an independent predictor of in-hospital mortality and MACCE during hospitalization (Table 4A).

Long-term results

Long-term follow-up was performed in 990 patients, representing 95.7% of the total study population. Forty-six patients (4.3%) were lost to follow-up. Mean follow-up of the remaining 944 patients was 1038 ± 517 days. Twenty-seven (2.7%) late deaths occurred during this period and 14 patients (1.4%) died of cardiac causes at 5 years. Overall actuarial survival was significantly lower in DM patients compared with the non-DM population (91% vs. 96%, *p* = 0.011) (Figure 1).

Significant long-term predictors of mortality were: DM (HR 2.1; 95% CI: 1.0 – 4.5, *p* = 0.04), age (HR 1.1, 95% CI, 1.01 – 1.11, *p* = 0.01), EF <40% (HR 2.45, 95% CI: 1.15 – 5.48, *p* = 0.01), and creatinine > 1.6 mg/dL (HR 2.46, 95% CI: 1.10 – 5.48, *p* = 0.03) (Table 4 B).

No significant differences were found in the free from hospital readmission and reintervention period between both groups.

Independent predictors for the incidence of combined events (death, hospital readmission, and reintervention) were: DM (HR 1.94, 95% CI: 1.16-3.25, *p* = 0.01) and creatinine > 1.6 mg/dL (HR 2.13, 95% CI: 1.25-3.63, *p* = 0.005).

Postoperative control angiography could be performed in only 216 (21.5%) of the total group of pa-

Table 1. Baseline Characteristics

	DM	Non-DM	p
Patients (n)	234	768	
Age (years)	65 ± 7	62 ± 9	1.0
Male/Female	213/21	702/66	0.4
Hypertension	195 (83%)	563 (73%)	0.001
Hyperlipidemia	194 (82%)	586 (76%)	0.01
Smoking	148 (63%)	499 (65%)	
Unstable angina	133 (56%)	445 (57%)	0.4
Chronic renal failure	18 (7.7%)	28 (3.6%)	0.01
Peripheral vascular disease	25 (10.7%)	73 (9.5%)	0.5
Previous CVA	8 (3.4%)	27 (3.5%)	0.9
Previous AMI	90 (38%)	217 (28%)	0.003
EuroScore (average)	3.1±2	2.7±3	0.9
Previous TCA	54 (23%)	133 (20%)	0.2
Previous CABG	4 (1.8%)	3 (0.3%)	
Non-elective CABG	82 (35.04%)	243 (31.64%)	0.3
Previous counterpulsation balloon	7 (3%)	14 (1.8%)	0.2
LV dysfunction (EF < 40%)	56 (23%)	146 (19%)	0.08
Main vessel disease	44 (18%)	159 (20%)	0.09
Two-vessel disease	40 (17.1%)	165 (21%)	0.1
Three-vessel disease	194 (82%)	603 (79%)	0.1
Preoperative glucose (mg/dL)	133 ± 52	101 ± 26	0.1
Preoperative creatinine	1.17 ± 53	1.16 ± 47	0.6
With preoperative aspirin	188 (80%)	590 (76%)	0.2
With preoperative clopidogrel.	26 (11%)	97 (12%)	0.5

DM: Patients with diabetes mellitus; Non-DM: Patients without diabetes mellitus; CVA: Stroke; AMI: acute myocardial infarction; TCA: Transluminal coronary angioplasty; CABG: Coronary artery bypass grafting; LV: Left ventricular; EF: Ejection fraction.

tients. Studies were performed 24.7 ± 15 months after CABG. Total patency of the 663 grafts examined (Fitzgibbon A+B) was 97.08%. In the 87 DM patients studied, arterial graft patency was 96.7% and in the 129 non-DM patients, it was 97.4% ($p=0.07$) (Table 2B). The main reasons for lack of postoperative angiograms in all patients were: renal failure (creatinine level > 2.5 mg/dL), concomitant pathologies and lastly, an important group of patients refused to undergo the study due to their asymptomatic condition.

DISCUSSION

The effectiveness of off-pump CABG has been demonstrated by many surgical groups, with outcomes comparable to those of on-pump CABG. (16) Previous studies have reported conflicting outcomes on the adverse effect of DM in off-pump CABG. (17) This may be due to several factors such as the extent of coronary disease, the small diameter of the coronary arteries, the type of conduit selection and the surgical technique used. In our study, the DM population represents 23% of the entire series, similar to other studies. (18-20) Only 30 patients had type 1 DM in our

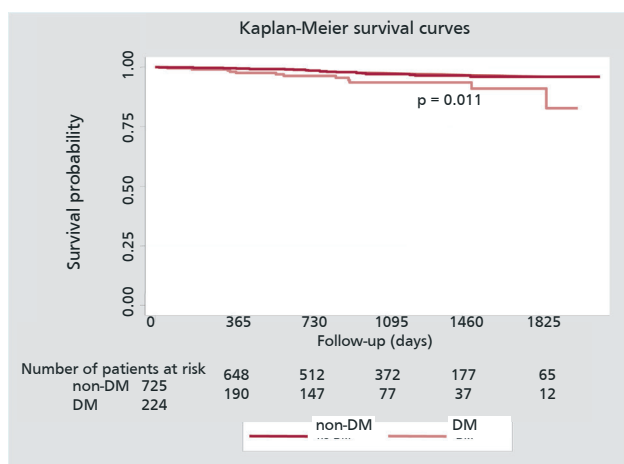


Fig. 1. Long-term survival curves with diabetes mellitus (DM) and without diabetes mellitus (non-DM).

series, and although it is considered a high risk population, its small number prevented us from analyzing their post CABG outcome. (21)

Table 2. Intraoperative data.**A: Complete revascularization (coronary lesion / arterial graft) and number of distal anastomoses.**

	DM (n: 234)	NonDM (n: 768)	p
Complete revascularization(#)	89.3%	91.8%	0.07
ADA	99.4 %	100 %	---
CxA	96,9 %	97.5 %	---
RCA	68.3 %	75.5 %	0.2

Number of distal anastomoses			
2	17 (7.1%)	73 (9.5%)	
3	144 (61.5%)	473 (61.5%)	
4	63 (26.9%)	206 (26.8%)	
5	10 (4.2%)	16 (2.0%)	0.2
Anastomosis/patient	3.28 ± 0.6	3.21 ± 0.6	0.9
Skin to skin time (minutes)	203 ± 41.3	200 ± 42	0.9

DM: Patients with diabetes mellitus; Non-DM: Patients without diabetes mellitus; ADA: Anterior descending artery; CxA: Circumflex artery; RCA: Right coronary artery.

B: Series of postoperative angiograms

	Fitzgibbon A		Fitzgibbon B		Occlusion		Permeability %	
	DM	non-DM	DM	non-DM	DM	non-DM	DM	non-DM
LIMA ADA	83	117	3	12	1	0	98.8	100.00
RIMA CxA1	69	108	5	3	4	2	94.8	98.20
RIMA CxA2	40	44	4	4	2	2	95.60	96.00
RIMA CxA1-2	109	152	9	7	6	4	95.10	97.50
RIMA RCA	61	78	3	10	2	6	96.90	93.60
Complete	253	347	15	29	9	10	96.75	97.41

DM: Patients with diabetes mellitus; Non-DM: Patients without diabetes mellitus; LIMA: left internal mammary artery; ADA: Anterior descending artery; RIMA: right internal mammary artery; CxA: Circumflex artery; RCA: Right coronary artery.

Table 3. Postoperative results.

	DM	NonDM	p
In-hospital mortality (30 days)	3 (1.28%)	12 (1.58%)	0.7
Perioperative AMI	2 (0.85%)	6 (0.78%)	0.9
Reoperation due to bleeding	1(0.4%)	20(2.6%)	0.04
Low cardiac output	11 (4.70%)	12 (1.56%)	0.005
Acute renal failure	20 (8.5%)	52 (6.77%)	0.3
Atrial fibrillation	35 (14.9%)	66 (8.6%)	0.005
CVA	1 (0.4%)	5 (0.6%)	0.6
Respiratory failure	4 (1.71%)	21 (2.7%)	0.3
MACCE	23 (9.8%)	63 (8.2%)	0.4
Mediastinitis	5.1%	1.3%	0.001
Hospital stay (days)	6.5	6.3	0.8

DM: Patients with diabetes mellitus; Non-DM: Patients without diabetes mellitus; AMI: Acute myocardial infarction; CVA: Stroke; MACCE: Major adverse cardiac and cerebrovascular event (death, stroke, renal failure, myocardial infarction)

Table 4. Independent predictors from logistic regression multivariate analysis:

A: Postoperative complications.

In-hospital mortality	OR	95% CI	p
Age	1.11	1.02 - 1.21	0.01
Elective CABG	0.17	0.04 - 0.73	0.01
Glycemia >200 mg/dL	6.9	1.27 - 37.38	0.02
MACCE	OR	95% CI	p
Age	1.04	1.01 - 1.07	0.01
Emergency surgery	1.93	1.22 - 3.05	0.005
Skin to skin time	1.006	1.001 - 1.011	0.01
Calcified aorta	5.02	1.82 - 13.8	0.002

OR: odds ratio. 95% CI: 95% confidence interval; CABG: Coronary artery bypass surgery; MACCE: Major adverse cardiovascular and cerebrovascular event (death, stroke, renal failure, myocardial infarction)

B: Long-term complications.

Follow-up mortality	HR	95% CI	p
DM	2.1	1.0 - 4.5	0.04
Age	1.1	1.01 - 1.11	0.01
LV function	2.45	1.15 - 5.48	0.01
Creatinine >1.6mg/dL	2.46	1.10 - 5.48	0.03
Combined events	HR	95% CI	p
DM	1.94	1.16 - 3.25	0.01
Creatinine >1.6mg/dL	2.13	1.25 - 3.63	0.005

HR: Hazard ratio. 95% CI: 95% confidence interval; DM: diabetes mellitus; LV: Left ventricular. Combined events: death, readmission and reoperation.

Total arterial grafting has shown better mid- and long term outcome with regard to the recurrence of angina, AMI and the need for reoperation when compared with CABG using venous grafts. (22)

In our study, we were able to perform off-pump CABG with exclusive use of arterial grafts in all patients, with a low incidence of on-pump CABG conversion, similar both for patients with or without DM

In our series, DM was not identified as an independent predictor of in-hospital mortality, confirming that off-pump CABG and multiple arterial grafting is a low risk technique and comparable in patients with and without DM. Kubal et al. reported similar observations, with higher incidence of complications in patients with type 1 DM. (23-25) An increased incidence of atrial fibrillation and low cardiac output was found in DM patients, probably associated with greater extent of coronary artery disease and prior myocardial infarction. (26)

Despite perioperative strict control of blood glucose, patients with DM had a higher incidence of mediastinitis, though this complication was not a cause of increased postoperative mortality. The latter might be attributed to the direct interference of excess blood glucose with the function of monocytes and neutrophils, enhancing the risk of infection. Moreover, bilateral removal of the mammary artery could be associ-

ated with decreased sternum vascularization favoring sternal infection or dehiscence.

Postoperative glucose level > 200 mg/dL was an independent predictor of in-hospital mortality and MACCE, more significant in non-DM patients (OR = 6.9). Jones et al. consider that the greatest risk of complications observed in non-DM patients with postoperative hyperglycemia may be related to a preclinical DM condition. (27) Adverse effects associated with hyperglycemia were observed after AMI and CABG. Doenst et al. (28) found higher mortality in post CABG patients with or without DM with blood glucose levels > 360 mg/dL. In our series, as in most publications, DM patients had lower long-term survival and far less combined event-free survival than non-DM patients. (29-31) Despite data collection was performed prospectively, the study is retrospective and this is its main limitation.

CONCLUSIONS

The use of off-pump CABG with multiple arterial grafts presented the same in-hospital mortality in patients with and without DM. DM patients had lower survival than non-DM patients. Hyperglycemia in the postoperative period is a predictor of in-hospital mortality, but is not related to the presence or absence of DM.

RESUMEN

Cirugía coronaria sin circulación extracorpórea con puentes arteriales múltiples en pacientes diabéticos: resultados tempranos y alejados**Introducción**

La diabetes mellitus se ha identificado como un fuerte predictor independiente de iniciación y progresión de la enfermedad cardiovascular y se ha reconocido como un factor de riesgo de mortalidad luego de la cirugía coronaria. La cirugía de revascularización miocárdica sin circulación extracorpórea se ha establecido como una alternativa eficaz de revascularización coronaria comparable a la técnica convencional, con resultados que muestran una disminución en la morbilidad del procedimiento y, en pacientes de riesgo alto, una mortalidad posoperatoria menor.

Objetivos

Comparar los resultados posoperatorios tempranos y alejados de pacientes con y sin diabetes mellitus luego de cirugía de revascularización miocárdica sin circulación extracorpórea con puentes arteriales múltiples y determinar si la hiperglucemia posoperatoria es un predictor independiente de morbimortalidad temprana.

Material y métodos

Entre enero de 2004 y diciembre de 2008 se efectuó cirugía de revascularización miocárdica sin circulación extracorpórea con puentes arteriales múltiples en 1.002 pacientes en forma consecutiva. La población se dividió en pacientes con diabetes mellitus ($n = 234$) y sin diabetes mellitus ($n = 768$). Se efectuó un análisis de las complicaciones posoperatorias y se identificaron predictores independientes de mortalidad hospitalaria. El seguimiento promedio fue de 1.038 ± 517 días y fue completo en el 95,7%.

Resultados

Los pacientes con diabetes mellitus presentaron mayor incidencia de bajo gasto cardíaco ($p = 0,005$), fibrilación auricular ($p = 0,005$) e infección esternal profunda ($p = 0,005$). Fueron predictores de mortalidad hospitalaria la edad ($OR = 1,11$), la cirugía no electiva ($OR = 5,88$) y la glucemia posoperatoria > 200 mg/dl ($OR = 6,9$).

Los pacientes con diabetes mellitus tuvieron menor sobrevida alejada a los 5 años ($p = 0,01$). Fueron predictores de menor sobrevida alejada la diabetes mellitus ($HR = 2,1$), la edad ($HR = 1,06$), la fracción de eyección del ventrículo izquierdo $< 40\%$ ($HR = 2,45$) y la creatinina posoperatoria $> 1,6$ mg/dl ($HR = 2,46$).

Conclusiones

Los pacientes con diabetes mellitus tuvieron igual mortalidad hospitalaria que los no diabéticos. La presencia de hiperglucemia posoperatoria fue un predictor de mayor mortalidad hospitalaria. La diabetes mellitus y la creatinina $> 1,6$ mg/dl fueron predictores independientes de menor sobrevida alejada.

Palabras clave > Cirugía coronaria, sin circulación extracorpórea - Diabetes mellitus

Conflicts of interest

None declared.

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