Effect of diabetes on early and late survival after isolated first coronary bypass surgery in multivessel disease

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Objective: Diabetes has not yet been investigated as a risk factor for early and late cardiac-related death.

Methods: Patients operated on from January 1988 to December 1999 were considered; 767 were diabetic (group D) and 2593 were nondiabetic (group ND). Patients with preoperative hemodynamic deterioration were excluded. Early (30-day) mortality (any causes and cardiac causes) was evaluated with univariate analysis and stepwise logistic regression. Ten-year actuarial freedom from death of any cause and cardiac death was also assessed with univariate and Cox analyses.

Results: Early mortality was 2.2% (group D, 3.3%; group ND, 1.9%; P = .023). Early cardiac mortality was 1.3% (group D, 2.2%; group ND, 1.1%; P = .0016). Diabetes was an independent risk factor only for cardiac death and not for death of any cause. Five-year survival was 93.5% ± 0.5% (group D, 92.5% ± 1.1%; group ND, 93.9% ± 0.6%; P = .0304). Diabetes was not an independent risk factor. Five-year freedom for cardiac death was 96.3% ± 0.4% (group D, 94.9% ± 0.9%; group ND, 96.6% ± 0.4%; P = .0155). Diabetes was an independent risk factor. However, if only the patients who survived the first 30 days are considered, diabetes disappears as a risk factor (5-year freedom for cardiac death, 97.8% ± 0.3%; group D, 97.3% ± 0.8%; group ND, 97.9% ± 0.4%; P = 0.2389).

Conclusions: Diabetes is an independent risk factor for early cardiac death only. Long-term survival in patients who survive the first 30 days is not statistically significantly different for diabetic and nondiabetic patients. In fact, the rates appear very similar.

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Diabetes is a widely recognized risk factor for increased early and late mortality after myocardial revascularization in patients with multivessel disease.[1-17] Even if better results after coronary artery bypass grafting (CABG) than after percutaneous transluminal coronary angioplasty had been demonstrated in the Bypass Angioplasty Revascularization Investigation trial,[1] further studies were not able to confirm this finding.[13,14] Therefore it seems that diabetes is a risk factor independent from the strategy used. However, in other studies diabetes seems to be weakly related to higher early and late mortality after CABG,[15-22] leaving the problem open to further evaluation.

During the past decade, different surgical techniques, such as normothermic perfusion,[23] CABG on a beating heart without cardiopulmonary bypass (CPB),[24,25] and extensive use of arterial conduits,[26,27] became popular. We reviewed our

TABLE 1. Preoperative data in diabetic (group D) and nondiabetic (group ND) patients

	Group ND (n = 2593)	Group D (n = 767)	*P* value
Age (y)	62.0 ± 9.5	63.2 ± 8.8	.001
≥75	217 (8.4%)	58 (7.6%)	.474
EF (%)	59.1 ± 12.9	57.0 ± 14.0	<.001
≤35	133 (5.1%)	62 (8.1%)	.002
Female sex	327 (12.6%)	206 (26.9%)	<.001
Urgent	678 (26.1%)	209 (27.2%)	.543
Left main	309 (11.9%)	88 (11.5%)	.817
Hypertension	1133 (43.7%)	402 (52.4%)	<.001
Previous AMI	1445 (55.7%)	454 (59.2%)	.407
Carotid disease	278 (10.7%)	128 (16.7%)	<.001
CRF (cr ≥2.0 mg/dL)	38 (1.5%)	14 (1.8%)	.478
CHF	49 (1.9%)	23 (3.0%)	.062

EF, Ejection fraction; *AMI,* acute myocardial infarction; *CRF,* chronic renal failure; *cr,* creatininemia; *CHF,* chronic heart failure.

experience in patients with multivessel coronary disease who underwent surgical revascularization during a 12-year period to evaluate (1) whether diabetes is a risk factor for early or late survival and, if so, (2) whether there is any technical factor that can improve survival in diabetic patients.

Methods

From January 1988 to December 1999, 3392 patients with multivessel disease underwent first isolated surgical myocardial revascularization. Thirty-two patients who had preoperative low-output syndrome were not included because their status could influence the early outcome more than any other risk factor. Globally, 3360 patients were entered into this study. Among them, 767 patients (22.8%) were diabetic (group D) and receiving oral (group OT, n = 596 [77.7%]) or insulin (group IT, n = 171 [22.3%]) treatment, and 2593 (77.2%) were nondiabetic (group ND). Patients on diet because of mild fasting hyperglycemia were considered in group ND. Table 1 shows some of the preoperative characteristics of both groups.

Surgical Details

CPB was used in 2181 (65.4%) patients and not used in 1179 (34.6%) patients. Perioperative technical data are shown in Table 2. Simultaneous carotid endoarterectomy was performed in 65 patients (1.9%; 47 [1.8%] in group ND and 18 [2.3%] in group D; $P = .345$).

Postoperative Course

After the operation, all the patients were admitted to the intensive care unit and later sent to the regular ward. They were then followed up at our outpatient clinic. The follow-up deadline was June 30, 2000. Recent information about their clinical status was obtained directly from the referring physician or by telephone. Mean follow-up was 50 ± 38 months (median, 41 months; minimum, 3 months; maximum, 150 months; 25th percentile, 20 months; 75th percentiles, 67 months), 43 ± 34 months in diabetic patients (median, 33 months; minimum, 3 months; maximum, 149 months; 25th percentile, 17 months; 75th percentile, 67 months), and 53 ± 39 months in nondiabetic patients (median, 44 months; minimum, 3 months; maximum, 150 months; 25th percentile, 21 months; 75th percentile, 72 months; $P < .001$). Follow-up was 98.9% completed.

Study Method

The real survival at 30 days after the operation was analyzed by using a variety of risk factors (appendix). Patients were first considered as a whole; as a second step, rates were given overall and by diabetes group to illustrate the association of factors on outcomes within the patients in groups D and ND.

The same variables were used to analyze 5-year actuarial survival, inclusive of the first month, for all patients. As a second step, the first month was withdrawn from the analysis, and the 5-year survival of patients who survived 1 month was evaluated to explore the weight of early mortality on late survival. All the analyses were repeated to evaluate the influence of diabetes on freedom from cardiac death. When some perioperative surgical strategies were evaluated, survival and freedom from cardiac death were considered at 10 years.

Definitions of Terms

Need of inotropic agents was defined as infusion of greater than 5 $\mu g \cdot kg^{-1} \cdot min^{-1}$ dobutamine or any dose of epinephrine or norepinephrine for more than 12 hours.

Cerebrovascular accident (CVA) was defined as global or focal neurologic deficit lasting less (transient ischemic attack) or more (stroke) than 24 hours that could be evident after emergence from anesthesia or after first awaking without any neurologic deficits. CVA was diagnosed by a neurologist and confirmed with a brain computed tomographic scan.

Acute myocardial infarction was defined as enzymatic elevation, electrocardiographic signs of necrosis, new akinetic segments at echocardiography, and non–K^+-related ventricular arrhythmias.

Acute renal failure was defined as a postoperative creatinine value of greater than 2.0 mg/dL for more than 24 hours if the preoperative value was less than 1.4 mg/dL or a 1-unit creatinine increase if the preoperative value was greater than 2.0 mg/dL.

Early major events were defined as the sum of death of any cause, CVA, acute myocardial infarction, low-output syndrome (defined as need for an intra-aortic balloon pump, inotropic drugs

TABLE 2. Operative data according to groups ND and D

	Group ND (n = 2593)	Group D (n = 767)	*P* value
CPB	1699 (65.5%)	482 (62.8%)	.174
Anastomoses/patient	2.6 ± 1.1	2.6 ± 1.0	.949
LITA	2351 (90.7%)	717 (93.5%)	.015
RITA	1210 (46.7%)	352 (45.9%)	.707
RGEA	359 (13.8%)	97 (12.6%)	.395
RA	200 (7.7%)	53 (6.9%)	.459
IEA	107 (4.1%)	18 (2.3%)	.022
SVG	1045 (40.3%)	326 (42.5%)	.276
BITA	1178 (45.4%)	346 (45.1%)	.876
SVG to LAD	230 (8.9%)	53 (6.9%)	.086
TAMR	1093 (42.2%)	308 (40.2%)	.325

LITA, Left internal thoracic artery; *RITA,* right internal thoracic artery; *RGEA,* right gastroepiploic artery; *RA,* radial artery; *IEA,* inferior epigastric artery; *BITA,* bilateral internal thoracic artery; *TAMR,* total arterial myocardial revascularization.

TABLE 3. Early postoperative data according to groups ND and D

	Group ND (n = 2593)	Group D (n = 767)	*P* value
Deaths	49 (1.9%)	25 (3.3%)	.023
CVA	29 (2.1%)	8 (1.0%)	.861
AMI	23 (0.9%)	8 (1.0%)	.089
Inotropes	57 (2.2%)	26 (3.4%)	.065
IABP	14 (0.5%)	7 (0.9%)	.370
Transfused patients	549 (21.2%)	189 (24.6%)	.041
CK-MB peak	38.8 ± 59.0	34.6 ± 46.7	.089
ICU stay (h)	22.2 ± 21.6	20.8 ± 24.4	.142
Hospital stay (d)	5.7 ± 5.2	5.4 ± 4.9	.123

AMI, Acute myocardial infarction; *IABP,* intra-aortic balloon pump; *CK-MB,* creatine kinase muscle and brain; *ICU,* intensive care unit.

for >12 hours, or both), need for mechanical ventilation for more than 24 hours in the absence of low-output syndrome, acute renal insufficiency (defined as blood creatinine level >2.0 mg/dL and 2 times the preoperative value), or acute renal failure (need for ultrafiltration without a related operation), gastrointestinal complications with or without related surgery.

Cardiac death was defined as any cardiac-related death, sudden and unknown.

Statistical Analysis

All continuos variables were expressed as means ± SD. Groups were compared by means of unpaired 2-tailed *t* testing in case of normally distributed factors, whereas Mann-Whitney tests were used in case of nonnormally distributed variables, and χ^2 tests (Pearson χ^2 and Fisher exact tests) were used for categoric variables. Stepwise logistic regression was used to select the independent variables that could predict death of any cause. Actuarial survival curves were obtained with the Kaplan-Meier method. Statistical significance was calculated with the log-rank test. Cox analysis was used to evaluate the independent risk factors for reduced late survival. All the multivariable analysis included univariate variables with *P* values of less than .2. Results of stepwise logistic regression were expressed as odds ratios with associated 95% confidence limits and *P* values. Results of Cox analysis were expressed as hazard ratios, 95% confidence limits, and *P* values. The SPSS software (SPSS, Chicago, Ill) was used for all analyses in this study.

Results

Early Mortality

During the first 30 days after the operation, 72 (2.2%) patients died, 25 (3.3%) in group D and 49 (1.9%) in group ND (*P* = .023). Table 3 summarizes the postoperative data. The results of stepwise logistic regression are shown in Table 4. Diabetes was not a risk factor for higher 30-day mortality.

The incidence of cardiac-related 30-day mortality was 1.3% (45 patients), 2.2% (17 patients) in group D and 1.1% (28 patients) in group ND (*P* = .016). The incidence of cardiac deaths was higher in group D (17/25 [68.0%]) than in group ND (28/49 [57.1%]) but not significantly (*P* = .511). Results of stepwise logistic regression are also summarized in Table 4. The analysis showed that diabetes was an independent factor for increased 30-day cardiac-related mortality. Again, early survival was not influenced by any technical aspect.

Late Actuarial Survival

During the follow-up period, 137 (4.1%) patients died, 32 (4.2%) in group D and 105 (4.0%) in group ND. Five-year overall actuarial survival, first month included, was 93.5% ± 0.5%, 93.9% ± 0.6% in group ND and 92.5% ± 1.1% in group D (*P* = .0304, Figure 1). Table 5 shows the independent predictors of lower survival at the Cox analysis. Diabetes was not an independent predictor of higher late mortality.

Seventy-three (2.2%) patients died of cardiac causes, 20 (2.6%) in group D and 53 (2.0%) in group ND. The incidence for cardiac death was higher in group D (20/32 [62.5%]) than in group ND (53/105 [50.5%]). Freedom from cardiac death, first month included, was 96.3% ±

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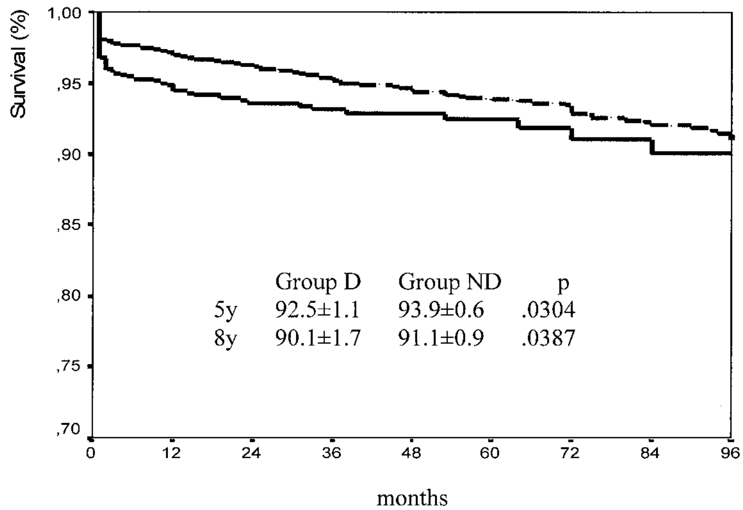

D group	767	656	495	363	274	176	117	94	82
ND group	2593	2279	1861	1520	1195	864	660	513	434

Figure 1. Five-year actuarial survival (first month included): group D *(solid line)* versus group ND (*dashed line)*.

TABLE 4. Stepwise logistic regression: Independent risk factors for increased early mortality, any death, and cardiac deaths

	Any death			Cardiac deaths		
Variable	All patients, OR (95%CL)	Group D, OR (95%CL)	Group ND, OR (95%CL)	All patients, OR (95%CL)	Group D, OR (95%CL)	Group ND, OR (95%CL)
Untouchable ascending aorta	2.9 (1.3-6.8) $P = .0116$	2.1 (0.5-8.3)	3.5 (1.2-10.3)	1.9 (0.8-4.2) $P = .1545$	1.7 (0.5-6.2)	2.0 (0.7-6.0)
Carotid disease	2.1 (1.2-3.7) $P = .0107$	1.5 (0.6-4.0)	2.2 (1.1-4.4)	1.2 (0.7-2.0) $P = .3324$	1.2 (0.5-2.8)	1.2 (0.6-2.3)
EF ≤35%	2.2 (1.1-4.5) $P = .0250$	8.2 (0.9-3.8)	3.0 (1.3-6.9)	2.0 (1.1-3.6) $P = .2598$	1.6 (0.6-4.4)	2.0 (0.98-4.2)
CHF	4.2 (1.8-9.6) $P = .0006$	8.9 (3.0-26.9)	2.4 (0.7-8.5)	4.5 (1.7-12.1) $P = .0029$	1.1 (0.2-5.7)	5.5 (1.5-19.2)
Urgent	2.0 (1.2-3.2) $P = .0042$	2.3 (1.0-5.2)	1.7 (0.9-3.1)	2.3 (1.2-4.2) $P = .0089$	2.1 (0.9-4.3)	2.3 (1.0-4.9)
SVG to LAD	2.2 (1.1-4.4) $P = .0168$	2.8 (0.9-9.0)	2.1 (0.9-4.7)	2.8 (1.3-6.0) $P = .0068$	3.6 (0.5-8.9)	2.7 (1.1-6.8)
Female sex	1.4 (0.8-2.6) $P = .1932$	0.8 (0.3-2.0)	2.3 (1.2-4.6)	0.9 (0.6-1.6) $P = .2482$	0.7 (0.3-1.6)	2.5 (1.1-5.8)
CRF (cr > 2.0 mg/dL)	1.1 (0.2-4.9) $P = .9251$	0.8 (0.4-1.1)	4.4 (1.3-15.5)	3.8 (0.6-9.0) $P = .2571$	0.9 (0.8-7.9)	5.3 (1.2-24.2)
Previous AF	1.6 (0.4-2.6) $P = .1932$	3.2 (0.5-21.4)	0.8 (0.1-7.2)	1.9 (0.7-5.0) $P = .2598$	9.0 (1.7-45.8)	1.7 (0.5-6.2)
Age ≥75 y	1.5 (0.7-2.9) $P = .4602$	2.9 (0.9-8.7)	1.0 (0.4-2.6)	2.4 (1.1-5.1) $P = .0223$	5.7 (1.9-17.1)	1.03 (0.5-2.2)
Diabetes	1.4 (0.8-2.4) $P = .1803$	–	–	2.0 1.1-3.7) $P = .0320$	–	–

HR, Hazard ratio; *CL,* confidence limit; *EF,* ejection fraction; *AMI,* acute myocardial infarction; *CHF,* chronic heart failure; CRF, chronic renal failure; *AF,* atrial fibrillation.

0.4%, 94.9% ± 0.9% in group D and 96.6% ± 0.4% in group ND ($P = .0155$, Figure 2). The results of Cox analysis are also shown in Table 5. Now diabetes is again a risk factor for increased incidence of cardiac deaths. Interestingly, the use of saphenous vein graft (SVG) on the left anterior descending artery (LAD) appeared as a new risk factor, emphasizing a direct effect of this graft on late cardiac mortality.

Late Actuarial Survival of Patients Who Survived for 30 Days

Five-year actuarial survival, with the exclusion of the first month, was 95.7% ± 0.4%, 95.6% ± 0.9% in group D and 95.7% ± 0.5% in group ND (Figure 3, $P = .3642$). Results of Cox analysis are shown in Table 6.

Freedom from cardiac death was 97.8% ± 0.3%, 97.3% ± 0.8% in group D and 97.9% ± 0.4% in group ND (Figure 4, $P = .2389$). Results of Cox analysis are also shown in Table 6. Diabetes was no longer a risk factor once patients who died in the first 30 days were excluded.

Results According to Preoperative Treatment

The preoperative treatment of diabetes did not affect early mortality (group OT, 18/596 [3.0%]; group IT, 7/171 [4.1%]). Five-year survival was also similar (94.64% ± 1.8% in group IT vs 92.0% ± 1.3% in group OT, $P =$

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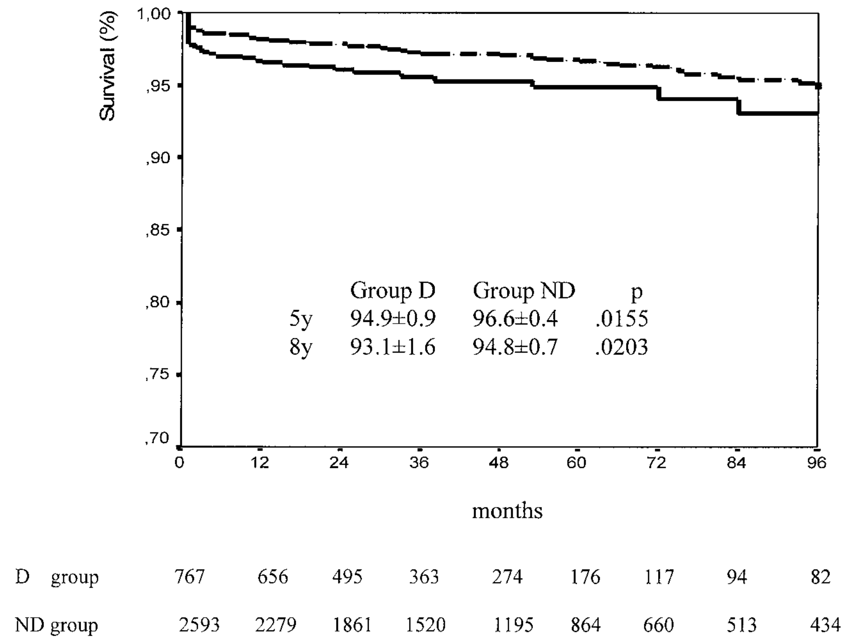


Figure 2. Five-year freedom from cardiac death (first month included): group D *(solid line)* versus group ND *(dashed line)*.

TABLE 5. Cox analysis: Independent risk factors for increased mortality, any death, and cardiac deaths

	Any death				Cardiac deaths			
Variable	All patients, HR (95%CL)		Group D, HR (95%CL)	Group ND, HR (95%CL)	All patients, HR (95%CL)		Group D, HR (95%CL)	Group ND, HR (95%CL)
Age	1.0 (1.01-1.04)	$P = .0003$	1.0 (0.97-1.04)	1.04 (1.01-1.06)	1.0 (1.0-1.05)	$P = .0061$	1.0 (0.97-1.06)	1.03 (1.01-1.06)
EF ≤35%	2.3 (1.5-3.5)	$P = .0001$	1.8 (0.8-3.9)	2.6 (1.6-4.3)	2.3 (1.3-4.0)	$P = .0025$	1.7 (0.6-4.7)	2.3 (1.2-4.5)
Previous AMI	1.4 (1.1-1.9)	$P = .0138$	1.2 (0.7-2.2)	1.5 (1.1-2.1)	1.2 (0.8-1.8)	$P = .2448$	1.4 (0.7-2.8)	1.2 (0.8-1.8)
CHF	2.1 (1.2-3.8)	$P = .0095$	4.5 (1.9-10.5)	1.6 (0.7-3.5)	1.9 (0.8-4.1)	$P = .1192$	1.6 (0.4-7.1)	2.1 (0.8-5.4)
CRF (cr > 2.0 mg/dL)	3.9 (2.1-7.2)	$P < .0001$	1.0 (0.1-1.3)	5.6 (2.9-10.8)	5.8 (2.8-12.0)	$P < .0001$	1.7 (0.2-13.4)	7.8 (3.5-17.4)
Urgent	1.4 (1.1-1.9)	$P = .0158$	2.1 (1.2-3.5)	1.3 (0.9-1.8)	1.6 (1.1-2.3)	$P = .0132$	2.4 (1.3-4.6)	1.4 (0.9-2.2)
Peripheral vasculopathy	1.6 (1.1-2.3)	$P = .0153$	1.9 (1.0-3.6)	1.4 (0.8-2.3)	1.2 (0.9-2.0)	$P = .5909$	1.1 (0.5-2.8)	1.2 (0.6-2.3)
SVG to LAD	1.4 (0.9-2.0)	$P = .0868$	1.8 (0.9-3.4)	1.3 (0.8-2.0)	2.0 (1.3-3.2)	$P = .0021$	1.9 (0.8-4.7)	2.0 (1.2-3.4)
Diabetes	1.3 (0.9-1.7)	$P = .1166$	–	–	1.6 (1.1-2.3)	$P = .0180$	–	–

HR, Hazard ratio; *CL,* confidence limit; *EF,* ejection fraction; *AMI,* acute myocardial infarction; *CHF,* chronic heart failure; *CRF,* chornic renal failure.

.1850), as was freedom from cardiac death after 5 years (97.1% ± 1.3% in group IT vs 94.4% ± 1.1% in group OT, $P = .1225$).

Analyzing the patients who survived 30 days, 5-year survival was not significantly better in group IT (98.6% ± 1.0%) than in group OT (94.8% ± 1.1%), even if Cox analysis did not confirm this hypothesis. Freedom from cardiac-related death was not different in either group (99.4% ± 0.6% in group IT vs 96.7% ± 0.9% in group OT).

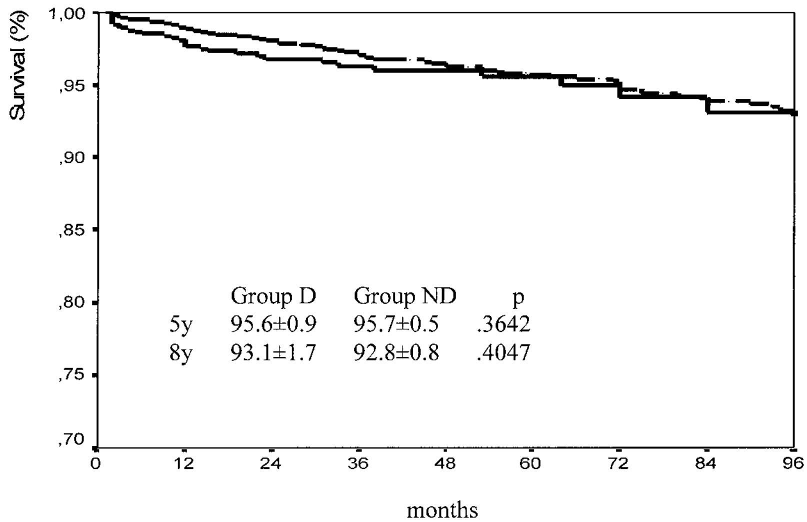
There were no statistically significant differences in short- or long-term mortality for diabetic patients treated perioperatively with insulin versus those who were not.

Results According to Perioperative Surgical Strategy

Tables 7 and 8 show 10-year survival and 10-year freedom from cardiac death according to some technical variables used during the procedure. Even if there is an evident benefit at the univariate analysis in using extensive arterial grafting, the Cox analysis failed to confirm this hypothesis. Only the use of SVG on LAD was a risk factor for increased incidence of cardiac deaths with and without the exclusion of the first month (Tables 5 and 6).

Discussion

Because morbidity and mortality caused by ketoacidosis and infections have a low incidence, coronary artery disease



D group	742	656	495	363	274	176	117	94	82
ND group	2544	2279	1861	1520	1195	864	660	513	434

Figure 3. Five-year actuarial survival (first month excluded): group D *(solid line)* versus group ND *(dashed line)*.

TABLE 6. Cox analysis: Independent risk factors for increased late mortality (first month excluded), all causes and cardiac causes

	Any death			Cardiac deaths		
Variable	All patients, HR (95%CL)	Group D, HR (95%CL)	Group ND, HR (95%CL)	All patients, HR (95%CL)	Group D, HR (95%CL)	Group ND, HR (95%CL)
Age	1.03 (1.01-1.05) $P = .0025$	1.0 (0.96-1.04)	1.04 (1.01-1.06)	1.02 (0.9-1.1) $P = .0581$	1.0 (0.94-1.05)	1.03 (0.98-1.07)
EF ≤35%	2.7 (1.6-4.5) $P = .0001$	2.9 (1.1-7.7)	2.7 (1.5-5.0)	2.8 (1.4-5.8) $P = .0033$	2.9 (0.8-10.6)	2.6 (1.1-6.1)
Previous AMI	1.5 (1.0-2.1) $P = .0327$	1.1 (0.5-2.4)	1.6 (1.1-2.5)	1.4 (0.8-2.3) $P = .1982$	1.7 (0.6-4.8)	1.2 (0.7-2.3)
CRF > 2.0 mg/dL	5.9 (2.8-12.3) $P = .0001$	3.7 (0.5-28.4)	6.9 (3.1-15.3)	11.1 (4.7-26.1) $P < .0001$	3.9 (0.8-5.5)	13.2 (5.0-34.3)
Peripheral vasculopathy	1.7 (1.1-2.8) $P = .0226$	3.0 (1.4-6.5)	1.3 (0.7-2.4)	–	2.0 (0.7-6.2)	0.9 (0.3-2.4)
SVG-LAD	1.1 (0.7-1.8) $P = .5786$	1.1 (0.4-3.2)	1.1 (0.7-1.9)	1.8 (1.0-3.1) $P = .0484$	1.3 (0.4-4.3)	1.9 (1.0-3.7)

HR, Hazard ratio; *CL,* confidence limit; *EF,* ejection fraction; *AMI,* acute myocardial infarction; *CRF,* chronic renal failure.

assumes a larger responsibility as a cause of death in diabetic patients.[28,29] The overall prevalence of coronary disease is as high as 55% among adult diabetic patients compared with 2% to 4% for the general population.[30] In a large autopsy study 91% of the patients with adult diabetes and no known coronary artery disease had severe narrowing of at least one major coronary artery, and 83% had severe 2- or 3-vessel involvement.[31] The relative risk of myocardial infarction is 50% greater in diabetic men and 150% greater in diabetic women. Similarly, diabetic men have sudden death 50% more often and diabetic women 300% more often than do their age-matched nondiabetic counterparts.[32] The mortality for myocardial infarction is higher than in nondiabetic patients[33,34] with[35] or without[36,37] thrombolytic therapy. Furthermore, the presence of diabetes mellitus is an independent predictor of cardiac mortality, which ranges from 26% to 62% in the first year after myocardial infarction and can reach 79% by 5 years.[38,39]

Diabetic patients with multivessel coronary disease who undergo myocardial revascularization, both surgical and interventional, are considered at high risk for early and late death.[1-11] Because other reports were not in agreement with these findings,[15-22] we tried to find a personal answer to this problem by analyzing our database, which included patients operated on during 12 years.

The analysis of 30-day mortality showed that diabetes is a univariate risk factor for higher early mortality, but multivariable analysis rejected this hypothesis. Analysis of a large cohort of patients in a New York State database found that diabetes was a risk factor in 2 different periods: 1992 to 1995 and 1996.[11,12] This finding was confirmed by others.[7,8]

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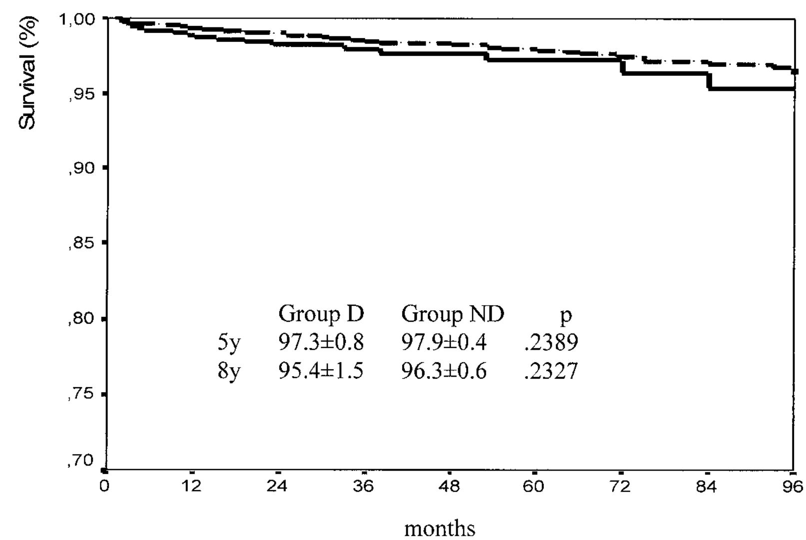

D group	742	656	495	363	274	176	117	94	82
ND group	2544	2279	1861	1520	1195	864	660	513	434

Figure 4. Five-year freedom from cardiac death (first month excluded): group D *(solid line)* versus group ND *(dashed line)*.

TABLE 7. Ten-year (first month included) survival according to same surgical aspects (univariate analysis)

	All patients			Group D			Group ND		
	N	Survival	*P* value	N	Survival	*P* value	N	Survival	*P* value
ITA to LAD*	2973	88.8 ± 1.4	.0927	690	87.5 ± 3.3	.1821	2283	89.3 ± 1.5	.1968
SVG to LAD	283	84.9 ± 2.3		53	79.0 ± 6.6		230	86.1 ± 2.4	
LITA ± SVG (s)	667	88.8 ± 1.8		171	90.9 ± 3.6		496	88.7 ± 2.0	
BITA ± SVG (s)	1137	94.7 ± 0.8	.1999†	276	93.3 ± 1.7	.9345	861	95.2 ± 0.9	.3166
TAMR	1401	92.5 ± 1.2	.5093†	308	85.5 ± 5.6	.6879	1093	93.9 ± 0.9	.3462
2ACs ± SVG (s)	1855	92.6 ± 1.0	.5635†	420	86.4 ± 4.9	.6587	1435	93.8 ± 0.8	.3537
CPB‡									
With	1275	93.2 ± 0.9	.9924	343	91.1 ± 2.0	.7640	932	93.9 ± 1.0	.9341
Without	1214	94.1 ± 0.9		293	93.1 ± 1.6		914	94.4 ± 1.0	
CPL§									
Crystalloid	269	91.1 ± 1.7		40	90.0 ± 4.7		229	90.4 ± 1.9	
Cold blood	288	92.3 ± 1.6	.7790‖	48	95.7 ± 2.9	.8058	240	91.6 ± 1.8	.8564
Warm blood	1617	92.2 ± 0.9	.7261‖	394	89.7 ± 2.2	.9055	1223	93.0 ± 0.9	.8716

All intermittent antegrade; no statistical difference was present when comparing groups. *ITA,* Internal thoracic artery; *BITA,* bilateral internal thoracic artery; *TAMR,* total arterial myocardial revascularization; *CPL,* cardioplegia.
*With or without SVG, other arterial conducts, or both.
†*P* value versus LITA ± SVG(s).
‡Five-year survival.
§Eight-year survival.
‖*P* value versus crystalloid.

However, other reports failed to identify diabetes as a risk factor in the general population[18-20,22] or in the elderly.[21]

In our opinion 30-day mortality is influenced by technical details more than by the disease itself. Even if no surgical aspect was able to influence the 30-day outcome in diabetic patients, some aspects allowed a reduction of mortality more in group D than in group ND. Use of SVG on LAD in group D was related to high mortality (4/53 [7.5%]); on the contrary, when the left internal thoracic artery was used, the mortality showed a 2.6-fold reduction (21/714 [2.9%]). The same aspect allowed a minor reduction in group ND (from 3.0% to 1.8%, 1.7-fold). The huge

TABLE 8. Ten-year (first month included) freedom from cardiac death according to same surgical aspects (univariate analysis)

	All patients			Group D			Group ND		
	N	Survival	*P* value	N	Survival	*P* value	N	Survival	*P* value
ITA to LAD*	2973	93.8 ± 1.0	.0041	690	90.5 ± 3.3	.1954	2283	94.6 ± 1.0	.0072
SVG to LAD	283	88.3 ± 2.1		53	82.3 ± 6.5		230	89.5 ± 2.1	
LITA ± SVG	667	93.7 ± 1.3		171	93.1 ± 3.5		496	93.9 ± 1.5	
BITA ± SVG	1137	97.6 ± 0.5	.0642†	276	95.3 ± 1.5	.5616	861	98.3 ± 0.5	.0155
TAMR	1401	93.7 ± 2.3	.1640†	308	90.2 ± 5.6	.5898	1093	94.4 ± 0.9	.1077
2 ACs ± SVG	1855	94.2 ± 1.5	.8697†	420	91.1 ± 3.6	.7140	1435	95.0 ± 2.7	.1092
CPB‡									
With	1275	96.2 ± 0.7	.3171	343	93.9 ± 1.8	.2766	932	97.1 ± 0.7	.1937
Without	1214	95.8 ± 0.9		293	95.3 ± 1.4		921	96.0 ± 1.0	
CPL§									
Crystalloid	269	93.2 ± 1.5		40	90.0 ± 4.7		229	94.7 ± 1.3	
Cold blood	288	94.7 ± 1.3	.5298‖	48	97.8 ± 2.2	.5543‖	240	94.1 ± 1.5	.6785‖
Warm blood	1617	95.1 ± 1.1	.5588‖	394	94.0 ± 1.5	.4097‖	1223	95.6 ± 1.2	.7456‖

All intermittent antegrade; no statistical difference was present when comparing groups. *ITA,* Internal thoracic artery; *BITA,* bilateral internal thoracic artery; *TAMR,* total arterial myocardial revascularization; *CPB,* cardiopulmonary bypass; *CPL,* cardioplegia.
*±SVG, other arterial conducts, or both.
†*P* value versus LITA ± SVG(s).
‡Five-year survival.
§Eight-year survival.
‖*P* value versus crystalloid.

application of the non-CPB strategy reduced the early mortality from 4.0% to 2.0% in group D (2-fold) and from 2.1% to 1.5% in group ND (1.4-fold). Cumulating all these small and apparently not influential improvements, diabetic patients are no longer at higher risk for 30-day mortality.

However, if only cardiac mortality in considered, diabetes appears to have a significant influence on early outcome because the relative incidence of cardiac deaths is higher in group D than in group ND. The anatomic aspect of the disease (diffuse coronary disease, small vessels, and diffuse calcifications) can explain a higher cardiac mortality.

Late survival, including 30-day mortality, showed, at univariate analysis, that diabetes was a risk factor, but the Cox analysis did not confirm this finding. Excluding 30-day mortality, diabetes was not a risk factor at either univariable or multivariable analysis.

When only cardiac deaths were considered, diabetes was a risk factor both at the univariable and multivariable analysis for increased early cardiac mortality and for reduced life expectancy as a result of cardiac death. However, when the analysis included only the patients who survived 30 days, diabetes disappeared as a risk factor both at univariable and multivariable analysis, showing that the influence of diabetes on survival without cardiac death is mainly expressed during the first postoperative month.

Other reports show clearly that diabetes is an important risk factor for late survival. Herlitz and colleagues[6] showed that real 2-year survival was 86.1% in diabetic and 93.5% in nondiabetic patients ($P < .0001$). At the multivariable analysis, diabetes had a relative risk of 1.7. Morris and coworkers[40] reported a 5-year survival of 80% in diabetic patients and 91% in nondiabetic patients and an 8-year survival of 66% and 84%, respectively ($P < .0001$). Diabetes was an independent risk factor with a *P* value of .0001. Smith and associates[41] showed a 15-year survival of 40% in diabetic and 60% in nondiabetic patients. Diabetes was a strong independent risk factor ($P = .0001$) but only in the late phase (>1 year after the operation). The same findings were confirmed by other studies.[8-10] Diabetes was rarely not recognized as an independent risk factor for late survival, often only in subgroups of patients.[19] When freedom from cardiac death was considered, diabetes was again a risk factor. Pick and colleagues[9] found that diabetes was an independent risk factor both for 10-year overall (risk hazard ratio, 2.94) and cardiac (hazard ratio, 1.73) mortality. Globally, diabetes was a risk factor in the late period, starting the first year after the procedure.

Our findings are in contrast with those in many of the published studies on this topic. Logically, if diabetic patients in the general population have higher mortality than nondiabetic patients as a result of cardiac causes, it is reasonable that a diabetic patient who undergoes myocardial revascularization has a life expectancy better than that of a nonoperated patient and similar to that of a nondiabetic patient. Even if diabetes was a risk factor for higher cardiac 5-year mortality, this finding was the consequence of a higher early cardiac mortality (2.2% in group D vs 1.1% in group ND, $P = .016$) and not of a late higher mortality.

In fact, survival from surgical intervention was not found to be different for diabetic versus nondiabetic patients who survived to 1 month. The preoperative treatment of diabetic patients did not influence the outcome. Surprisingly, insulin-treated patients showed a high long-term survival (94.6% by 5 years).

Perhaps long-term treatment with insulin, because antidiabetic centers are widely diffused, can better control hyperglycemia, lowering the complication rate in the long term. However, the sample size is small, and definitive conclusions can not be drawn.

Our analysis was not able to show improvement related to any technical aspect during the operation. Early and late outcomes of diabetic patients were not influenced by use of SVG on LAD. Conversely, nondiabetic patients were influenced by use of SVG on LAD only in the analysis of freedom from cardiac death, both early and late, with or without the inclusion of the first month.

This is in contrast with other reports[9,15,42] that show a better outcome in diabetic patients if a single or a double internal thoracic artery is used. We were not able to find any benefit with the use of bilateral internal thoracic arteries in nondiabetic patients, and the use of left internal thoracic arteries to LAD demonstrated an advantage only for cardiac deaths. This is not easy to explain. We think that the patency rate of the SVG in the 1990s is perhaps better than the patency rate of the SVG in the 1980s. Worldwide use of antiplatelet agents, as well as statins, can contribute to this theoretic benefit. Moreover, the mean follow-up in our series is shorter than in other reports,[9,42] and some authors[40] did not use a multivariable analysis to demonstrate their hypothesis.

The similar late outcome in diabetic and nondiabetic patients after a mean follow-up of 50 months suggests that the effect of surgical intervention in diabetic patients is striking. The huge cardiovascular mortality is highly reduced after myocardial revascularization, and the risks of myocardial infarction with the related mortality are also reduced. However, the incidence of cardiac deaths remains higher than that in nondiabetic patients, although this finding is limited to the first 30 days after the operation. The price to pay for diabetes seems today smaller than in the past.

One must take care with interpretations of subgroup analyses. Lack of statistical significance might simply be a lack of statistical power because of the reduced sample size. Statistical significance might be due to spurious results, which are expected with multiple comparisons.

In multivariable models one must remember that not only the factors in the model but the factors in the univariable analyses were considered. Therefore any borderline statistical result should be considered especially exploratory.

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See appendix on page 154.

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APPENDIX. List and definition of variables

Preoperative	
Age	Continuous (y)
Age ≥75 y	Dichotomous
Sex	Dichotomous
Body weight	Kilograms
History of hypertension	Need of medical treatment (Ca^{2+} blockers, β-blockers, angiotensin-converting enzyme inhibitors)
History of smoking	More than 10 cigarettes a day smoked at least for 10 y
Hypercholesterolemia	Historical or at-present cholesterol value >200 mg/dL
Chronic renal failure	Creatinine value >2.0 mg/dL
Chronic hepatic failure	Bilirubin value >2.0 mg/dL
Chronic obstructive pulmonary disease	FEV_1 less than 75% of predicted value, air Po_2 lower than 60 mm Hg or chronic medical treatment
Unstable angina	Presence of angina at rest, stable angina with worsening pattern, or de novo angina.
Chronic heart failure	Heart failure in the history or at the present admission without angina
Acute myocardial infarction <24 h	Acute myocardial infarction 24 hours before surgical intervention
Preoperative intra-aortic balloon pump	Use of intra-aortic balloon pump to stabilize unstable angina
Previous atrial fibrillation	Dichotomous
Not elective operation	Any condition (eg, unstable angina, cardiogenic shock, critic left main stenosis) that avoids discharge from the hospital
Diabetes	Medical treatment for hyperglycemia at rest
Insulin treatment	Insulin-dependent diabetes
Oral treatment	Diabetes on oral treatment
Ventricular arrhythmia	In history or requiring medical treatment at this admission
Peripheral vasculopathy	Symptoms or angiographic or echocardiographic evidence of dilation or reduction of flow (stenosis or occlusion) of any artery, with the exclusion of carotid arteries
Carotid disease	Presence of a fibrocalcific plaque with a stenosis ≥50% or of a soft plaque conditioning any degree of stenosis
Previous CVA	History of previous CVA with or without persistent neurologic defect
Previous acute myocardial infarction	Electrocardiographic sign of myocardial infarction or documented non-Q infarction
Left main stem lesion	Stenosis ≥50%
Ejection fraction	Continuous
Ejection fraction ≤35%	Dichotomous
Nitroglycerin e.v.	Need of nitroglycerin e.v. at the admission in operating room
Perioperative	
Use of CPB	Dichotomous
Normothermic perfusion	Perfusion temperature ≥34°C
Use of SVG on LAD	Dichotomous
Use of bicaval internal thoracic artery	Dichotomous
Use of only arteries	Dichotomous
Simultaneous carotid surgery	Dichotomous
Untouchable ascending aorta	Severe atherosclerotic or calcified aortic wall not eligible for clamping or manipulation detected before the operation or when the chest was open