Mortality and Morbidity in Diabetic and Nondiabetic Patients During a 2-Year Period After Coronary Artery Bypass Grafting

JOHAN HERLITZ, MD
GUNNAR BRANDRUP WOGNSEN, MD
HÅKAN EMANUELSSON, MD
MARIA HAGLID, RA
BJÖRN W. KARLSON, MD
THOMAS KARLSSON, MSC
PER ALBERTSSON, MD
STAFFAN WESTBERG, MD

OBJECTIVE — To describe mortality and morbidity during a 2-year period after coronary artery bypass grafting (CABG) among diabetic and nondiabetic patients.

RESEARCH DESIGN AND METHODS — All the patients in western Sweden in whom CABG was undertaken between June 1988 and June 1991 and in whom concomitant procedures were not performed were registered prospectively. The study was a prospective follow-up.

RESULTS — Diabetic patients (n = 268) differed from nondiabetic patients (n = 1,859) in that more women were included, and the patients more frequently had a previous history of myocardial infarction (MI), hypertension, congestive heart failure, intermittent claudication, and obesity. Diabetic patients more frequently required reoperation and had a higher incidence of peri- and postoperative neurological complications. Mortality during the 30 days after CABG was 6.7% in diabetic patients versus 3.0% in nondiabetic patients ($P < 0.01$). Mortality between day 30 and 2 years was 7.8 and 3.6%, respectively ($P < 0.01$). During 2 years of follow-up, a history of diabetes appeared to be a significant independent predictor of death. Whereas the development of MI after discharge from the hospital did not significantly differ between the two groups; 6.3% of diabetic patients developed stroke versus 2.5% in nondiabetic patients ($P < 0.001$).

CONCLUSIONS — Diabetic patients have a mortality rate during the 2-year period after CABG that is about twice that of nondiabetic patients during both the early and late phase after the operation.

An increasing proportion of high-risk patients are offered revascularization because of signs and symptoms of ischemic heart disease (1,2). Patients with a history of diabetes constitute one such high-risk group. Diabetic patients developing symptoms of ischemic heart disease and acute myocardial infarction (AMI) in particular have a very high mortality rate (3–5).

This study aims to describe the prognosis during 2 years after coronary artery bypass grafting (CABG) in diabetic and nondiabetic patients. The following aspects of the prognosis will be evaluated: *1*) mortality over 2 years and during the early and late phases, *2*) place and mode of death, *3*) postoperative complications, *4*) development of myocardial infarction (MI) during a 2-year period, *5*) development of stroke during a 2-year period, and *6*) need for hospitalization during a 2-year period.

From the Division of Cardiology, Sahlgrenska University Hospital, Göteborg, Sweden.
Address correspondence and reprint requests to Johan Herlitz, MD, Division of Cardiology, Sahlgrenska University Hospital, S-413 45 Göteborg, Sweden.
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AMI, acute myocardial infarction; BARI, Bypass Angioplasty Revascularization Investigation; CABG, coronary artery bypass grafting; C_{cr}, creatinine clearance; MI, myocardial infarction; OR, odds ratio; P_{cr}, serum creatine; PTCA, percutaneous transluminal coronary angioplasty.

RESEARCH DESIGN AND METHODS

Patient population
Between June 1988 and June 1991, all the patients from western Sweden in whom CABG was performed without concomitant procedures at the Department of Thoracic and Cardiovascular Surgery at Sahlgrenska Hospital and at the Scandinavian Heart Center in Göteborg were registered prospectively. At the time, these two hospitals performed all CABG in the western health care region of Sweden. The region serves a population of ~1,600,000.

Operative technique
All the operations were performed using cardiopulmonary bypass and, with few exceptions, moderate hypothermia. Anesthesia was induced with thiopentane, followed by pancuronium, and continued with a combination of fentanyl and nitrous oxide and intermittent administration of a volatile anesthetic.

Myocardial preservation was achieved with a hypercalcemic hypothermic crystalloid solution (modified St. Thomas). Myocardial temperature was usually monitored and kept under 15°C. In the arrested heart, the distal anastomoses were performed first using a continuous running suture technique, and the aortic anastomoses were performed over a partial occluding clamp during reperfusion of the heart and while rewarming the patient.

Renal function
The formula that estimates creatinine clearance (C_{cr}) to describe renal function was adapted from Cockcroft and Gault (30): $C_{cr} = (140 - \text{age}) \cdot \text{wt}/(P_{cr} \cdot 72)$ for men and $C_{cr} = (140 - \text{age}) \cdot \text{wt}/(P_{cr} \cdot 85)$ for women. C_{cr} is given in milliliters per minute, age is given in years, weight is given in kilograms, and serum creatinine (P_{cr}) is given in milligrams per deciliter.

Renal dysfunction was defined as C_{cr} <60.

Obesity

Obesity was defined as a BMI >30. The BMI was obtained by dividing body weight by the square of the height (wt/[height]^2).

Data analysis

All the initial clinical, laboratory, angiographic, and surgical data were obtained prospectively and were registered and stored in a computerized database.

History

All patients were interviewed by a member of the research team before the operation. Information about their previous history was collected from this interview and from data from the hospital medical records. A history of diabetes was based on information from the patient and from data from hospital medical records, not from actual laboratory values. In principle, all case histories of diabetes were confirmed both via medical records and patient information. Measurements for blood glucose were not routinely made before operation, and when such measurements were made, the information was not collected in our data bank.

Follow-up

All patients still living were sent a questionnaire 3 months, 1 year, and 2 years after the operation. They were asked whether they had been rehospitalized after the operation and at which hospital. The medical records of the referring hospital were checked for all patients during the 2-year follow-up period.

Morbidity during follow-up

The following definitions were used for AMI and stroke. For AMI, two of the following criteria had to be filled: *1*) pain suggesting AMI of at least 15 min in duration, *2*) elevated serum enzyme activity indicating AMI (mainly elevated creatine kinase MB), and *3*) development of Q-waves in at least 2 leads on a 12-lead standard electrocardiogram. Death <28 days after date of AMI was classified as fatal AMI. Perioperative infarctions were not included. When stroke occurred, there was a development of neurological deficit with a duration of >24 h. Death <28 days after stroke was classified as a fatal stroke. In the description of fatal and nonfatal AMI and stroke, only the first episode is included in the analyses.

Deaths during the 2 years after the operation were obtained from the Swedish National Registry of Deaths. From this registry, information about all deaths in Sweden is available within 2 weeks after the date of death. For the patients who died in a hospital, we used their case record forms, including findings at autopsy, for information about mode of death. For the patients who died outside a hospital, we used information from death certificates, autopsy findings, and sometimes police investigations. The cause of death was defined as cardiac death, other vascular death, other defined death, or uncertain cause. Cardiac death included death caused by confirmed or possible MI and death in which any of the following were described in relation to the time of death: symptoms of congestive heart failure or cardiogenic shock, ventricular fibrillation, electromechanical dissociation,

Table 1—*Baseline characteristics*

	No diabetes	Diabetes	*P*
n	1,859	268	
Sex (male)	1,524 (82)	201 (75)	<0.01
Previous history			
MI (1/0)*	1,114 (60)	183 (68)	<0.01
Angina pectoris (0/0)	1,808 (97)	266 (99)	—
Congestive heart failure (1/0)	261 (14)	63 (24)	<0.001
Hypertension (3/0)	644 (35)	133 (50)	<0.0001
Renal dysfunction (5/0)	507 (27)	83 (31)	—
Cerebrovascular disease (0/0)	148 (8)	30 (11)	—
Intermittent claudication (1/1)	199 (11)	61 (23)	<0.0001
Obesity (0/0)	216 (12)	48 (18)	<0.01
Height (cm, mean, median)	173 (173)	172 (172)	—
Weight (kg, mean, median)	78 (77)	79 (79)	—
Smoking (9/2)	245 (13)	32 (12)	—
PTCA (0/0)	95 (5)	15 (6)	—
CABG (0/0)	92 (5)	24 (9)	<0.05
Three-vessel disease (77/18)	1,156 (65)	179 (72)	<0.05
Ejection fraction <40% (137/30)	152 (9)	26 (11)	—
Age (years, mean, median)	62.6 (64)	62.6 (64)	—

Data are *n* (%). Number of patients with missing information. *P* value denoted if $P < 0.05$.

Table 2—*Surgical values and postoperative complications*

	No diabetes	Diabetes	*P*
n	1,859	268	
Surgical values			
Aortic cross-clamp time (mean, minutes) (4/1)*	53.1	56.4	<0.05
No. of grafts (mean) (4/1)	3.7	3.9	<0.05
Internal mammary artery (4/0)	1,465 (79)	197 (74)	<0.05
Thrombendarterectomy (9/2)	138 (7)	18 (7)	—
Postoperative complications			
Reoperation (6/1)	118 (6)	29 (11)	<0.01
Neurological complications (10/2)	60 (3)	22 (8)	<0.001
Pneumo/hydrothorax (10/2)	101 (5)	17 (6)	—
Supraventricular arrhythmias (10/2)	521 (28)	67 (25)	—
Inotropic drugs (7/2)	332 (18)	61 (23)	—
Prolonged reperfusion in heart lung machine (9/2)	32 (2)	6 (2)	—
Assistance device (8/2)	47 (3)	11 (4)	—
S-ASAT max >2.0 (27/5)	494 (27)	77 (29)	—

Data are *n* (%). *Number of patients with missing information. *P* value denoted if $P < 0.05$. S-ASAT, aspartate aminotransferase in serum.

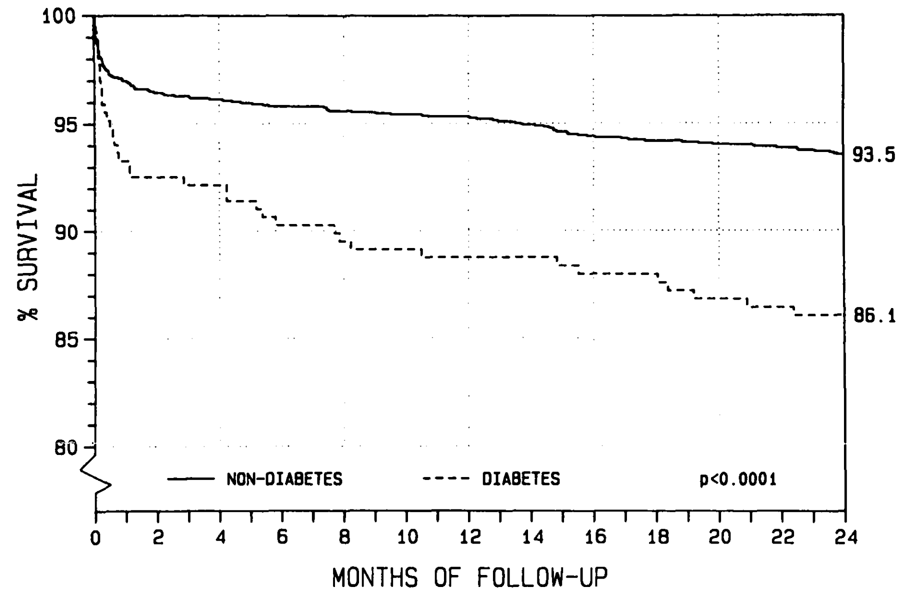

Figure 1—*Cumulative mortality during 2 years after CABG in diabetic and nondiabetic patients.*

primary asystole, cardiac tamponade, ventricular septal rupture, papillary muscle rupture, or death related to the time of CABG or percutaneous transluminal angioplasty (PTCA). Other vascular death included deaths not related to cardiac disease that were related to a vascular catastrophe, the most common being stroke, ruptured aortic aneurysm, and pulmonary embolism. A classification system was developed for this record review.

Statistical analysis

Fisher's permutation test was used to test for differences between patients with and without diabetes, with the exception of mortality, development of AMI and stroke, where the log rank test was used. Cox's proportional hazards model was used for multivariate analysis of mortality and development of stroke and logistic regression for development of neurological complication and rehospitalization.

All *P* values are two-sided and have not been corrected for multiple comparisons. SAS software, version 6.10, was used. For *P* value calculation using the Fisher's permutation test, the Edgeworth expansion was used (6).

RESULTS— In all, 2,129 patients were operated on. Information on history of diabetes was missing in two of these patients (0.1%). Of the remaining 2,127 patients, 268 (13%) had a history of diabetes. Of these patients, 31% were on insulin treatment, 44% were on oral medication, and 25% were on diet only.

Baseline characteristics

Patients with a history of diabetes were more frequently female and more frequently had a history of previous AMI, congestive heart failure, hypertension, intermittent claudication, obesity, previous CABG, and three-vessel disease (Table 1).

Factors at operation

The degree of urgency of the operation did not differ between diabetic and nondiabetic patients. The aortic cross-clamp time was longer, and more peripheral grafts were used among diabetic patients. Furthermore, an internal mammary artery graft was more frequently used among nondiabetic patients (Table 2).

Postoperative complications

Diabetic patients more frequently required reoperation and more frequently developed neurological complications. In a multivariate analysis considering all factors listed in Table 1, a history of diabetes appeared as an independent predictor for development of neurological complications ($P < 0.01$) (Table 2). Inotropic treatment was used more often in diabetic patients than in nondiabetic patients.

Mortality

During the first 30 days after the operation, 6.7% of the diabetic patients died versus 3.0% of the nondiabetic patients ($P < 0.01$). Even late mortality was higher among diabetic patients, as was the total 2-year mortality (Table 3). In Table 4, early, late, and total 2-year mortality in diabetic and nondiabetic patients, first, excluding patients with diet-controlled diabetes, and second, excluding very sick patients (defined as ejection fraction <40%), is shown. In both analyses, results appeared similar as compared with the total series of patients. Among diabetic patients, the 2-year mortality rate among those on insulin treatment was 18%, among those on oral antidiabetic medication 11%, and among those on diet 14% (NS). In Table 3, factors in the clinical history being associated with death in univariate analysis are shown.

In a multivariate analysis considering these factors, the following appeared as significant independent predictors of mortality during a 2-year period after CABG: *1*) a history of congestive heart failure, *2*) renal dysfunction, *3*) age,

Table 3—*Factors in clinical history associated with 2-year mortality in univariate analysis*

	2-year mortality	*P*
Age (years) (≥65/<65)	10.9/4.5	<0.0001
Sex (M/F)	6.5/11.8	<0.001
History		
Myocardial infarction (yes/no)	8.4/6.0	<0.05
Congestive heart failure (yes/no)	15.5/6.0	<0.0001
Hypertension (yes/no)	9.7/6.1	<0.01
Renal dysfunction (yes/no)	12.9/5.3	<0.0001
Cerebrovascular disease (yes/no)	12.4/7.0	<0.05
Intermittent claudication (yes/no)	13.9/6.5	<0.0001
Previous CABG (yes/no)	16.4/7.0	<0.0001
Three-vessel disease (yes/no)	8.2/4.8	<0.01
Ejection fraction <40 (yes/no)	12.4/6.3	<0.01

Data are %.

Table 4—*Mortality during 2 years of follow-up*

	No diabetes	Diabetes	*P*
All patients			
n	1,859	268	
Mortality			
<30 days	56 (3.0)	18 (6.7)	<0.01
30 days to 2 years	64 (3.6)	19 (7.8)	<0.01
2 years (total)	120 (6.5)	37 (13.9)	<0.0001
Patients with diet-controlled diabetes excluded			
n	1,859	201	
Mortality			
<30 days	56 (3.0)	15 (7.5)	<0.01
30 days to 2 years	64 (3.6)	13 (7.1)	<0.05
2 years (total)	120 (6.5)	28 (14.0)	<0.0001
Patients with ejection fraction <40% excluded			
n	1,707	242	
Mortality			
<30 days	51 (3.0)	14 (5.8)	<0.05
30 days to 2 years	54 (3.3)	16 (7.2)	<0.01
2 years (total)	105 (6.2)	30 (12.5)	<0.001

Data are *n* (%). *P* value denoted if $P < 0.05$.

4) a history of diabetes, and 5) a history of intermittent claudication (Table 5). A history of diabetes was a significant independent predictor for death between day 30 and 2 years, but not between day 0 and day 30.

The overall death rate in terms of cardiac death was 9.9% in diabetic patients and 4.6% in nondiabetic patients ($P < 0.001$). The corresponding values for other vascular deaths were 1.6 and 1.1%, respectively ($P > 0.2$); for other defined causes of death, including cancer, 1.7 and 0.5%, respectively ($P < 0.05$); and for uncertain causes of death, 1.2 and 0.4%, respectively ($P = 0.09$). The place and mode of death were similar in diabetic and nondiabetic patients.

Morbidity

The proportion of diabetic patients who developed AMI after CABG (perioperative AMI not included) was 4.2% as compared with 2.1% for nondiabetic patients ($P = 0.06$). The corresponding values for fatal AMI were 0.4 and 0.5%, respectively ($P > 0.2$) and for nonfatal AMI, 3.7 and 1.6%, respectively ($P < 0.05$).

The proportion of diabetic patients who developed stroke was 6.3% as compared with 2.5% for nondiabetic patients ($P < 0.001$). The corresponding values for fatal stroke were 1.2 and 0.6%, respectively ($P > 0.2$) and for nonfatal stroke, 5.2 and 1.9%, respectively ($P < 0.001$). In a multivariate analysis considering all factors listed in Table 1, a history of diabetes was an independent significant predictor of stroke ($P < 0.01$).

Medication at discharge

Prescription of various medications at discharge was similar in diabetic and nondiabetic patients with the exception of antidiabetic treatment and other treatment for heart failure being more frequently prescribed to diabetic patients and lipid-lowering drugs being more frequently prescribed to nondiabetic patients (Table 6). In 0.4% of patients classified as nondiabetic, antidiabetic medication was prescribed at discharge. Whether this was caused by misclassification on admission or diabetes discovered in the hospital is not known.

Rehospitalization

Among diabetic patients, the proportion who were rehospitalized during 2 years was 55% versus 41% among nondiabetic patients ($P < 0.0001$). In a multivariate analysis considering all factors listed in Table 1, a history of diabetes was an independent predictor for rehospitalization ($P < 0.01$; odds ratio [OR] 1.59).

The proportion of diabetic patients who were rehospitalized because of cardiovascular reasons was 41% versus 31% for nondiabetic patients ($P < 0.001$). In a multivariate analysis, a history of diabetes appeared as an independent predictor for rehospitalization for cardiovascular reasons ($P < 0.01$; OR 1.47).

Table 5—*Independent predictors of death during 2 years of follow-up*

	β	Relative risk	*P*
Congestive heart failure	0.622 ± 0.205	1.86 (1.25–2.78)	<0.01
Renal dysfunction	0.595 ± 0.203	1.81 (1.22–2.70)	<0.01
Age ≥65 years	0.581 ± 0.214	1.79 (1.17–2.72)	<0.01
Diabetes	0.574 ± 0.224	1.78 (1.14–2.76)	<0.05
Intermittent claudication	0.506 ± 0.222	1.66 (1.07–2.56)	<0.05

Data are means ± SE or relative risk (95% CI).

CONCLUSIONS— In this study, which was prospective in design, we found that 13% of the patients had a history of diabetes. The study might be unique because it represents all patients having CABG in a well-defined area. In previous studies, the proportion of diabetic patients among patients in whom CABG was undertaken has been reported as varying between 6 and 54% (7–10). Among all patients in the study, 40% were randomized on days 5–21 to 2 years with treatment with either metoprolol or placebo. However, outcome in terms of mortality or ischemic events were similar in the two treatment groups (11), and the intervention study, thus, cannot be regarded as a disturbing factor for the total analysis of our data.

Diabetic patients had a different pattern of risk indicators. Similar observations have been made in other studies, both among CABG populations (9,12–14) and among patients suffering from AMI (3–5,15,16). It was, however, surprising that the occurrence of renal dysfunction was similar in patients with and without a history of diabetes. This observation suggested a high degree of selection among diabetic patients for CABG regarding renal function.

In terms of surgical values, there were some minor differences between di-

Table 6—*Medication at discharge*

	No diabetes	Diabetes	*P*
n	1,859	268	
β-blockers (93/18)	51	52	—
Calcium antagonists (72/13)	8	8	—
Long-acting nitrates (72/13)	1	0.8	—
Diuretics for heart failure (68/14)	22	26	—
Digitalis (70/13)	33	35	—
Other treatment for heart failure (77/13)	3	6	<0.05
Other antihypertensives (72/13)	4	7	—
Other antiarrhythmics (73/13)	9	9	—
Antidiabetics (72/13)	0.4	70	<0.0001
Aspirin (64/13)	90	87	—
Dipyridamol (70/13)	84	83	—
Apeccumarol (71/13)	7	6	—
Psychopharmaceuticals (71/13)	3	4	—
Lipid-lowering drugs (72/14)	5	0.8	<0.01
Other medication (72/14)	39	41	—

Data are %. *P* value denoted if $P < 0.05$. Data in parentheses represent number of patients with missing information.

abetic and nondiabetic patients. In previous studies, Fietsam et al. (17) reported that the bypass time and occlusion time were similar in diabetic and nondiabetic patients (17). Lawrie et al. (18) found that the number of grafts was similar in diabetic and nondiabetic patients, whereas on the other hand, Morris et al. (19) reported that diabetic patients received more grafts.

The majority of postoperative complications occurred with a similar frequency in diabetic and nondiabetic patients. In previous studies, experience has varied. Fietsam et al. (17) found an increase in morbidity among diabetic patients (18.5 vs. 8.3%) caused by more infections, respiratory insufficiencies, arrhythmias, and the need for assistance devices. However, they did not find any increase in the occurrence of reoperation, stroke, or perioperative MI.

Kuan et al. (20) reported that diabetic patients ran an increased risk of stroke, hemorrhage, and perioperative MI (20). In another study, however, morbidity was reported to be similar in diabetic and nondiabetic patients (21).

The mortality was about twice as high during both the early and the late phase in diabetic patients as compared with nondiabetic patients. Our study confirms that diabetes per se conforms an increased long-term mortality risk after CABG. Similar findings have been made in previous studies, both among patients having undergone CABG (12–14,22,23) and among patients with other manifestations of ischemic heart disease (3–5).

To try to explain the higher mortality among diabetic patients, we also explored the place and mode of death. There was no indication that the pattern of death was particularly different among diabetic patients. However, the number of patients who died was relatively small.

In previous postinfarction studies, it has been shown that diabetic patients run a higher risk of reinfarction than nondiabetic patients (5,15). In the present study, we found only borderline significance ($P = 0.06$) for the difference in the development of a new AMI during 2-year period after hospital discharge, although the AMI rate was almost twice as high for diabetic patients.

On the other hand, we found that stroke developed much more frequently among diabetic patients. The risk of thromboembolic complications in patients with ischemic heart disease has not previously been shown to be associated with a history of diabetes.

Although diabetic patients remain a high-risk group after CABG, there is no indication that the impact of CABG on survival is less marked among patients with such a history compared with those without (21). However, in the largest overview of the impact of CABG on long-term survival, the outcome in diabetic patients was not mentioned (24).

Data from the National Heart, Lung and Blood Institute (NHLBI)-funded Bypass Angioplasty Revascularization Investigation (BARI) have recently become public, although not published in any journal, because of important observations among diabetic patients (25). This is a multicenter international randomized trial studying patients who need their first revascularization because of severe ischemia with obstructions in two or more major coronary arteries. Over 5 years, patients with diabetes who were on drug therapy had a significantly lower ($P = 0.001$) mortality rate if treated with CABG (19%) compared with those patients treated with PTCA (35%). The 2-year mortality rate among patients randomized to CABG in the BARI was lower than that in the present study (K.M. Detre, personal communication). This might be explained by less complicated disease in the BARI, since those patients had to be eligible for revascularization by PTCA.

The mechanisms behind the higher mortality in diabetic patients can only be speculated upon. Those patients often suffer from a more extensive coronary artery disease (26) and a more compromised myocardial function (26,27). However, in a multivariate analysis considering the occurrence of three-vessel disease as well as ejection fraction, diabetes still appeared as an independent predictor of mortality.

Autonomic dysfunction has also been proposed as a plausible mechanism behind the increased mortality among diabetic patients (28). However, instantaneous death was not particularly increased among the diabetic patients in the present study.

Limitations

Although this study includes >2,000 patients who underwent CABG, there were only 268 patients with a history of diabetes. With an even larger sample size, it is possible that comparisons that reached borderline significance in the present analysis would have reached significance levels.

The diagnosis of diabetes was based on information from patient interviews and hospital record forms and not on laboratory tests. Consequently, the possibility of a slight underestimation of the occurrence of diabetes cannot be excluded (29).

We do believe that there is some

underreporting of the development of AMI and stroke, particularly fatal occurrences, since only about half of the patients who died were autopsied.

Implications

This study confirms that, even after CABG, diabetic patients with ischemic heart disease remain a high-risk group with a mortality rate during both the early and late phase that is twice as high as that of nondiabetic patients. Diabetes per se conforms an increased long-term mortality risk after CABG.

Further steps should be taken to try to diminish this difference. One approach might be to more aggressively normalize their metabolic status before as well as after the operation. However, only prospective randomized trials will clarify the value of such an approach.

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