Long-Term Impact of Diabetes and Its Comorbidities in Patients Undergoing Isolated Primary Coronary Artery Bypass Graft Surgery

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Background—The objective of this study was to identify the impact of diabetes and related comorbidities, namely chronic renal failure, peripheral vascular disease, and low ejection fraction (<35%), on long-term survival of patients undergoing coronary artery bypass graft surgery.

Methods and Results—A unicenter study was conducted on 9125 survivors of isolated coronary artery bypass graft surgery between 1992 and 2002. There were 6581 nondiabetic patients and 2544 diabetics, including 1809 patients with noninsulin-dependent diabetes mellitus and 735 patients with insulin-dependent diabetes mellitus. Cardiac-specific survival at 5 and 10 years was lower in insulin-dependent diabetes mellitus compared with both nondiabetic mellitus patients and patients with noninsulin-dependent diabetes mellitus (P<0.0001). However, freedom from cardiac-related death was similar for patients with noninsulin-dependent diabetes mellitus and nondiabetes mellitus patients up to 6 years (P=0.08) after surgery and was significantly lower thereafter (P=0.004). Cardiac-specific survival after coronary artery bypass graft surgery in patients with one or more comorbidities was comparable (P=0.4) for both nondiabetes mellitus patients and patients with noninsulin-dependent diabetes mellitus, but was significantly lower for those requiring insulin therapy (P<0.0001). Noninsulin-dependent diabetes mellitus was not an independent predictor of long-term cardiac death (hazard ratio: 1.09, P=0.41); however, insulin-dependent diabetes mellitus, chronic renal failure, peripheral vascular disease, and low ejection fraction were all independent risk factors for late cardiac death (all P<0.0001). The impact of comorbidities on the long-term risk of cardiac death was similar for the 3 groups.

Conclusions—Noninsulin-dependent diabetes is not an independent predictor of late cardiac death after coronary artery bypass graft surgery, because cardiac-related survival is similar to that of nondiabetic patients for 6 years after surgery. In diabetic and nondiabetic patients, cardiac survival is adversely affected by the need for insulin therapy and/or the presence and number of comorbidities such as chronic renal failure, peripheral vascular disease, and low ejection fraction. (Circulation. 2007;116[suppl I]:I-220–I-225.)

Key Words: coronary disease ■ diabetes mellitus ■ revascularization ■ surgery ■ survival

Diabetes and its related complications and comorbidities are powerful risk factors for cardiovascular disease. The incidence of diabetes is increasing markedly and the World Health Organization estimates that by 2025, there will be 300 million patients with diabetes (5.4% of the world population). Patients with diabetes constitute a high-risk group for early cardiovascular surgical morbidity and mortality. They also account for up to 38% of patients undergoing cardiac procedures, especially coronary revascularization. There is considerable information on perioperative morbidity and mortality in patients with diabetes after coronary artery bypass grafting (CABG) in which poor early outcome and higher in-hospital morbidity and mortality have been demonstrated compared with nondiabetic patients. Frequently related comorbidities associated with diabetes, including chronic renal failure (CRF), peripheral vascular disease (PVD), and low ejection fraction (LEF), can also impact on short-term survival in the patient undergoing CABG, whether diabetic or not. However, the impact of diabetes and diabetes-related complications on long-term mortality in patients surviving CABG surgery has not been extensively evaluated. We hypothesized that patients with diabetes with attendant comorbidities and insulin requirement are at greater risk of death after CABG surgery. Therefore, the goal of the present study was to evaluate the impact of diabetes and related comorbidities, namely CRF, PVD, and LEF, and the
role of insulin dependence on long-term survival of patients surviving CABG surgery.

Methods

Study Population

Patient and operative information was reviewed from the computerized cardiac surgical database that was collected prospectively for all patients. We retrospectively analyzed data for all (n=9125) patients with diabetes and nondiabetic patients who survived primary isolated CABG surgery and were discharged from the hospital between January 1992 and December 2002 at the “Quebec Heart Institute,” Quebec City, Canada. Patients with diabetes were identified as those requiring treatment with nutritional modification, oral medications, and/or insulin at the time of surgery. Patients with no preoperative diagnosis in whom diabetes was discovered and treated during and after hospitalization were included in the diabetic group. Patients with no history of diabetes who received insulin postoperatively for temporary high blood glucose level, but who did not require specific treatment for diabetes after hospital discharge, were placed in the nondiabetic group. Comorbid conditions were identified from medical records obtained at the time of hospitalization for CABG surgery and included the following: PVD, which was defined as nontraumatic carotid intervention or stenoses >80% (by history, Doppler ultrasonography, or bruit), nontraumatic lower extremity vascular surgery (amputation, or bypass surgery), or disease (claudication, absence of pedal pulses, and/or ischemic ulcers); CRF, which was defined by preoperative serum creatinine ≥150 μmol/L, and LEF, which was defined as an ejection fraction of ≤35%. For the purpose of the present study, patients were stratified into 3 main groups: nondiabetic (non-DM), noninsulin-dependent diabetic (NIDDM), and insulin-dependent diabetic patients (IDDM). The latter group represents patients who were given insulin as part of their treatment, and not exclusively type I diabetics. Several subgroups were identified on the basis of none, one, or more of the aforementioned comorbidities to facilitate separate statistical analyses. Cardiac-specific survival and Cox regression analyses were performed to assess long-term survival and overall impact of diabetes and comorbidities on cardiac-related death. Cardiac death was defined as any cardiac-related, sudden, or unknown death. Stroke was considered as cardiac death. The date and cause of death were obtained from the Quebec Statistical Institute. All patients without a Quebec provincial health insurance number, for whom the long-term follow-up data might have been incomplete (n=500 [5.1%]), were excluded from the study. Follow-up for 9125 patients enrolled was 100% complete as of December 2005 (ie, 7.1±3.2 years).

Statistical Analysis

Results are expressed as mean±SD or percentage for continuous and categorical variables, respectively. Patients were censored at the time of last complete information collection (December 2005). Patients with noncardiac death were censored at the time of death. Continuous and dichotomous variables were analyzed using one-way analysis of variance or χ² test, respectively. Survival function was obtained from the Nelson-Aalen estimator of the cumulative hazard rate. The Cox regression model estimates the hazard ratio of each independent variable on cardiac-specific survival over the entire length of follow-up. These independent variables were age, gender, CRF, PVD, LEF, chronic obstructive pulmonary disease, previous myocardial infarction, triple-vessel disease, hypercholesterolemia, previous cerebrovascular accident, hypertension, use of internal thoracic artery, and obesity (body mass index ≥30 m²). All parameters were initially analyzed using univariate Cox regression models. Variables with a probability value <0.25 were candidates for the multivariate Cox regression model building. Selection variables were performed using 2 statistical approaches. Selection variables with interaction terms were performed using a forward approach. More detailed analyses were performed in patients with CRF, PVD, and LEF attributable to the frequent presence of these comorbidities in patients with diabetes. Akaike’s information criteria and Schwarz’ Bayesian criteria were used to compare candidate models. The same approach was performed to include interaction terms in the Cox model. Martingales residuals were used to examine the functional form of the continuous variable age and to determine that no transformation was necessary. After model building, adequacy of the proportional hazards assumption was checked. To check the proportionality assumption, first the graphical representation of the logarithm cumulative hazard rates versus time was used to assess parallelism and constant separation among the different values of nominal variables, whereas the continuous variable age was stratified into 4 disjointed strata. Second, an artificially time-dependent covariate was added to the model to test the proportionality assumption. For all variables in the final model, proportional hazards assumptions were not rejected, because local tests linked to the time-dependent covariates were not significant and scatterplots were roughly constant over time. The graphical representations of Martingale and deviance residuals versus risk scores did not suggest any potential outliers. Significance was ascribed with probability values <0.05. To test survival rates at various intervals throughout follow-

**TABLE 1. Perioperative Data of Non-DM, NIDDM, and IDDM patients**

<table>
<thead>
<tr>
<th></th>
<th>Non-DM (n=6581; 72.1%)</th>
<th>NIDDM (n=1809; 19.8%)</th>
<th>IDDM (n=735; 8.1%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (mean±SD), years</td>
<td>62.6±10.3</td>
<td>64.5±9.3</td>
<td>63.5±9.7</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Women</td>
<td>1442 (21.6%)</td>
<td>488 (27.0%)</td>
<td>274 (37.3%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Chronic pulmonary disease</td>
<td>1097 (16.7%)</td>
<td>303 (16.7%)</td>
<td>138 (18.8%)</td>
<td>0.42</td>
</tr>
<tr>
<td>Previous myocardial infarction</td>
<td>2920 (44.4%)</td>
<td>767 (42.5%)</td>
<td>267 (36.3%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Cerebrovascular accident</td>
<td>91 (1.4%)</td>
<td>36 (2.0%)</td>
<td>27 (3.7%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Hypercholesteremia</td>
<td>5857 (89.2%)</td>
<td>1578 (87.3%)</td>
<td>629 (85.6%)</td>
<td>0.02</td>
</tr>
<tr>
<td>Hypertension</td>
<td>3435 (52.2%)</td>
<td>1225 (67.7%)</td>
<td>531 (72.3%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Urgent/emergent operation</td>
<td>903 (13.7%)</td>
<td>244 (13.5%)</td>
<td>136 (18.5%)</td>
<td>0.001</td>
</tr>
<tr>
<td>No. of diseased vessel</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>1-vessel</td>
<td>489 (7.3%)</td>
<td>94 (5.2%)</td>
<td>36 (4.9%)</td>
<td></td>
</tr>
<tr>
<td>2-vessel</td>
<td>1994 (30.3%)</td>
<td>459 (25.4%)</td>
<td>180 (24.5%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>3-vessel</td>
<td>4099 (62.3%)</td>
<td>1254 (69.3%)</td>
<td>517 (70.4%)</td>
<td></td>
</tr>
<tr>
<td>Vessel bypassed (mean±SD)</td>
<td>3.2±1.1</td>
<td>3.4±1.1</td>
<td>3.4±1.1</td>
<td>0.24</td>
</tr>
<tr>
<td>Left internal thoracic use (≥1)</td>
<td>5772 (87.8%)</td>
<td>1559 (86.2%)</td>
<td>619 (84.2%)</td>
<td>0.01</td>
</tr>
</tbody>
</table>
up, the survival curves were visually assessed to determine probable points of separation. Log-rank tests were performed at these identified intervals, for accordingly censored data, to obtain specific respective probability values. Analyses were performed using the statistical software version package of SAS 9.1.3 (SAS Institute Inc, Cary, NC).

Statement of Responsibility
Authors had full access to all data and take responsibility for the integrity of data. All authors have read and agree with the contents of the article as written.

Results
Among our study patients (n=9125) who underwent isolated primary CABG surgery and survived to hospital discharge at our institution between 1992 and 2002, 6581 (72.1%) had no diabetes, whereas diabetes was found in 2544 (27.9%) patients. In the latter group, 1809 (19.8%) patients were classified in the NIDDM and 735 (8.1%) patients in the IDDM group, respectively. Perioperative characteristics for patients in the 3 main study groups are listed in Table 1. The prevalence of all aforementioned comorbidities and their combinations (≥2 comorbidities) was significantly higher in IDDM patients compared with both NIDDM and non-DM patients (Table 2).

Overall mean duration of follow-up was 7.1±3.2 years (range, 0.1 to 14 years). During follow-up, there were a total of 1659 deaths in our cohort of patients; 1053 in the non-DM, 387 in the NIDDM, and 219 in the IDDM groups of patients, respectively. The total number of cardiac deaths, established at the last follow-up, was 451, 152, and 98 in non-DM, NIDDM, and IDDM patients, respectively.

Survival Analysis
Cardiac-specific survival rates at 5, 7, and 10 years after CABG surgery in patients with one or more comorbidities (Figure 3) were similar for non-DM (91.5%, 87.3%, and 78.6%) and NIDDM (92.0%, 86.2%, and 78.1%) patients (P=0.4). IDDM patients with one or more comorbidities displayed cardiac-specific survival rates that were comparable to the other groups only during the first 2 years after CABG surgery (P=0.3); survival was significantly lowered during the remaining follow-up period (P<0.0001). In patients with each comorbidity, cardiac-specific survival rates were compared separately for the 3 groups but showed no significant differences during follow-up (Figures 4, 5, and 6). Ten-year cardiac-specific survival rates were 77.9% in non-DM, 80.2% in NIDDM, and 67.9 in IDDM patients with CRF (P<0.3). In patients with PVD, it was 86.5% in non-DM, 84.6% in NIDDM, and 79.6% in IDDM group (P<0.4). It was 75.3% in non-DM patients, 73.4% in NIDDM, and 45.9% in IDDM patients with LEF, respectively (P<0.3). The overall impact of combined comorbidities was a significant decline in cardiac-specific survival rate at 5, 7, and 10 years compared with patients presenting with a single comorbidities for each group.

Cox Multivariate Analysis
Cox multivariate proportional hazards analysis was performed to control for confounding variables. Independent survival rates at 5, 7, and 10 years after CABG surgery in patients with one or more comorbidities (Figure 3) were similar for non-DM (91.5%, 87.3%, and 78.6%) and NIDDM (92.0%, 86.2%, and 78.1%) patients (P=0.4). IDDM patients with one or more comorbidities displayed cardiac-specific survival rates that were comparable to the other groups only during the first 2 years after CABG surgery (P=0.3); survival was significantly lowered during the remaining follow-up period (P<0.0001). In patients with each comorbidity, cardiac-specific survival rates were compared separately for the 3 groups but showed no significant differences during follow-up (Figures 4, 5, and 6). Ten-year cardiac-specific survival rates were 77.9% in non-DM, 80.2% in NIDDM, and 67.9 in IDDM patients with CRF (P<0.3). In patients with PVD, it was 86.5% in non-DM, 84.6% in NIDDM, and 79.6% in IDDM group (P<0.4). It was 75.3% in non-DM patients, 73.4% in NIDDM, and 45.9% in IDDM patients with LEF, respectively (P<0.3). The overall impact of combined comorbidities was a significant decline in cardiac-specific survival rate at 5, 7, and 10 years compared with patients presenting with a single comorbidities for each group.

Cox Multivariate Analysis
Cox multivariate proportional hazards analysis was performed to control for confounding variables. Independent

Table 2. Risk of Cardiac Death Expressed by Hazard Ratio for Each Comorbidity Among Non-DM, NIDDM, and IDDM Patients

<table>
<thead>
<tr>
<th>Comorbidity</th>
<th>Non-DM (n=6581; 72.1%)</th>
<th>NIDDM (n=1809; 19.8%)</th>
<th>IDDM (n=735; 8.1%)</th>
<th>P Value</th>
</tr>
</thead>
<tbody>
<tr>
<td>CRF</td>
<td>557 (8.5%)</td>
<td>222 (12.3%)</td>
<td>156 (21.2%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>LEF</td>
<td>311 (4.7%)</td>
<td>127 (7.0%)</td>
<td>61 (8.3%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>PVD</td>
<td>872 (13.3%)</td>
<td>351 (19.4%)</td>
<td>201 (27.4%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CRF+PVD</td>
<td>126 (1.9%)</td>
<td>70 (3.9%)</td>
<td>63 (8.6%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CRF+LEF</td>
<td>69 (1.1%)</td>
<td>24 (1.3%)</td>
<td>18 (2.4%)</td>
<td>0.004</td>
</tr>
<tr>
<td>PVD+LEF</td>
<td>56 (0.8%)</td>
<td>29 (1.6%)</td>
<td>19 (2.6%)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>CRF+PVD+LEF</td>
<td>16 (0.2%)</td>
<td>9 (0.05%)</td>
<td>8 (1.1%)</td>
<td>0.001</td>
</tr>
</tbody>
</table>

Figure 1. Cardiac-specific survival analysis in non-DM, NIDDM, and IDDM patients.
predictors of late cardiac-related death based on this analysis are indicated in Table 3. NIDDM was not an independent risk factor for cardiac-related death (hazard ratio: 1.09, 95% CI: 0.88 to 1.34; \( P = 0.4 \)); however, IDDM, CRF, PVD, and LEF all had a negative impact on cardiac-related survival.

**Discussion**

Cardiovascular disease progresses more rapidly in adults with diabetes compared with nondiabetic patients. As the prevalence and incidence of diabetes mellitus has increased worldwide over the past decade, healthcare challenges of these individuals are magnified. Diabetes is a major independent risk factor for cardiovascular disease even after adjustment for its related comorbidities. Coronary artery disease is a frequent event and CABG appears to be a preferred revascularization strategy in patients with diabetes. Because prevalence of diabetes increases with age, these patients are often affected by senile cardiovascular diseases such as calcified aortic stenosis. The latter along with CABG constitute the main pathologies requiring surgical treatment in this population. As such, patients with diabetes undergoing cardiac surgery represent a large and complex population.

The impact of diabetes on reduced short-term survival in patients undergoing cardiac surgery has been demonstrated. Specific molecular mechanisms involved in the diabetic response to cardiac surgery and cardiopulmonary bypass have been identified by gene expression profiling. However, long-term survival of patients with diabetes after cardiac surgery has been less extensively studied and remains controversial. In the present study, a large, unicenter regional database with 100% follow-up was used to examine long-term cardiac-specific survival, because cardiac death is the most frequent cause of death in patients with diabetes undergoing CABG surgery.

Our findings reveal that NIDDM is not an independent risk factor for long-term cardiac-related mortality. Long-term cardiac-specific survival of NIDDM patients was excellent...
and similar to that observed for nondiabetic patients up to 6 years after CABG. In NIDDM patients with none of the indicated comorbidities, cardiac-specific survival was comparable to that observed 10 years postoperatively. In contrast, all IDDM patients, with or without comorbidities, showed higher cardiac mortality compared with the other study groups with a divergence of the risk curve occurring as early as 2 years after surgery. Thus, IDDM is an independent risk factor for long-term cardiac-related death. Indeed, long-term cardiac-specific survival was most negatively influenced by the requirement for insulin therapy and presence of diabetic-related comorbidities.

Several studies have documented that diabetes is an independent determinant of delayed mortality; however, most studies have not focused on specific subgroups of patients such as IDDM patients or those with frequent comorbidities related to atherosclerosis and diabetes, who may be at greater risk of late mortality. Studies in which these parameters have been considered have provided controversial results that included: no unfavorable effect of diabetes on intermediate-term mortality,16,20,21 significant negative effect of insulin requirement on long-term survival,17,21,22 or identification of specific factors such as CRF, LEF, and PVD that are independently associated with delayed mortality.15,18,20 The present study documents that insulin-treated diabetes and the presence of associated comorbidities have a strong negative impact on long-term cardiac-specific survival compared with that observed for non-DM and NIDDM patients without comorbidities. However, in contrast to previously reported findings, a late divergence of the cardiac death risk curve in favor of non-DM patients was observed in our cohort of patients (Figures 1 and 2) that could be related to factors such as the recency of comorbidity apparition or insulin requirement associated with the longer mean duration of follow-up in our patients compared with other studies. This may explain, in part, why no divergence was observed in survival curves for NIDDM and non-DM patients who presented with at least one comorbidity at the time of surgery (Figure 3).

The presence of single or combined comorbidities increased the risk of cardiac death in diabetic and non-DM patients during follow-up. However, the impact of these comorbidities was similar for NIDDM and non-DM patients. The different natural evolution of these comorbidities in diabetic and non-DM patients and the more regular clinical follow-up of patients with diabetes may explain the differences. The UK Prospective Diabetes Study demonstrated that strict control of glycemia reduced microvascular complications and acute cardiac events. In addition, the Post Coronary Artery Bypass Graft Trial reported that aggressive reduction of plasma lipids significantly reduced ischemic complications and improved permeability of aortocoronary grafts.

The cardiac-specific survival of all patients could be negatively affected by the presence of comorbidities. The Cox multivariate hazard ratio model showed that each comorbidity could influence long-term cardiac-specific survival separately in these 3 groups of patients. However, the strong negative impact of comorbidities may overshadow the detrimental effects of NIDDM on cardiac death risk in patients undergoing CABG surgery. The latter has been expressed by a nonsignificantly different hazard ratio for cardiac death in NIDDM compared with non-DM patients. We compared cardiac-specific survival rates separately in patients with each comorbidity (CRF, PVD, and LEF) and showed no significant differences. However, the absence of a statistically significant differences with CRF and LEF (Figures 4 and 5) is likely attributable to low statistical power because fewer patients were available for these subgroup analyses during the last several years of follow-up. Cardiac-specific survival rates for each group were reversely and similarly affected by the combined presence of these comorbidities.

**Study Limitations**

Several limitations exist in this study. First, the development of comorbidities during follow-up was not identified. Second, development of diabetes in patients without diabetes at the time of surgery, and progression to insulin therapy in previously NIDDM patients, was not determined during follow-up. Third, treatment of diabetes and associated comorbidities evolved during follow-up, but long-term effect of these changes were not evaluated. Fourth, the duration of diabetes...
before CABG surgery was unknown and was not considered in the long-term results.

***Conclusion***

The long-term implications of diabetes were studied in 9125 consecutive patients who underwent primary isolated CABG surgery at the Quebec Heart Institute. NIDDM and IDDM were present in 19.8% and 8.1% of the patient population studied. Noninsulin-dependent diabetes was not an independent risk factor for long-term cardiac-related death. Long-term survival of NIDDM subjects in the absence of comorbidities after CABG was excellent. Cardiac-specific survival for NIDDM patients was similar to that observed for non-DM patients in the first 6 years after operation, and even up to 10 years for NIDDM patients without comorbidities. IDDM patients had a poorer cardiac-specific survival rate compared with NIDDM patients. In diabetic and non-DM patients, 10-year survival was adversely affected by the need for insulin therapy and/or presence and number of comorbidities such as CRF, PVD, and LEF.

***Acknowledgments***

We acknowledge the assistance of Ms Brigitte Dionne, Ms Stephanie Dion, and Mr Serge Simard in the data analysis for this publication.

***Disclosure***

None.

***References***

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doi: 10.1161/CIRCULATIONAHA.106.681320
Circulation is published by the American Heart Association, 7272 Greenville Avenue, Dallas, TX 75231
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Print ISSN: 0009-7322. Online ISSN: 1524-4539

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