ABSTRACT

BACKGROUND Patients with diabetes mellitus (DM) have an increased risk of adverse outcomes after coronary artery bypass grafting (CABG). Previous studies have reported prognosis in relation to treatment with or without insulin, and not to the type of diabetes.

OBJECTIVES This study investigated long-term survival in patients with type 1 DM (T1DM) and type 2 DM (T2DM) following CABG.

METHODS We included all patients from the SWEDHEART (Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies) register who underwent primary isolated CABG in Sweden during 2003 through 2013. We identified patients with T1DM or T2DM in the Swedish National Diabetes Register. We calculated hazard ratios (HRs) with 95% confidence intervals (CIs) for all-cause mortality in patients with T1DM or T2DM.

RESULTS In total, 39,235 patients were included, of whom 725 (1.8%) had T1DM and 8,208 (21%) had T2DM. Patients with T1DM were younger (59 vs. 67 years), had reduced kidney function (31% vs. 24%), and had peripheral vascular disease (21% vs. 11%) more often than patients with T2DM or no diabetes. During a mean follow-up of 5.9 ± 3.2 years (230,085 person-years), 6,765 (17%) patients died. Among patients with T1DM, 152 (21%) died, and among patients with T2DM, 1,549 (19%) died. Adjusted hazard ratio (95% confidence interval) for death in patients with T1DM and T2DM, compared with patients without diabetes, were 2.04 (1.72 to 2.42), and 1.11 (1.05 to 1.18), respectively.

CONCLUSIONS Patients with T1DM had more than double the long-term risk of death after CABG compared with patients without diabetes. The long-term risk of death in patients with T2DM was only slightly increased.

The prevalence of diabetes mellitus (DM) is increasing worldwide, with an estimated doubling of cases within the next 20 years (1). Patients with DM have an increased risk of cardiovascular disease and death compared with those without DM. In the general population of patients with type 1 diabetes mellitus (T1DM), the excess risk of death is 4-fold in men and 8-fold in women relative to those without DM (2,3). In the general population of patients with type 2 diabetes mellitus (T2DM),
there is a doubling of the age-adjusted prevalence of coronary heart disease, and the risk of death is between 2 and 4 times higher than in those without DM (4,5). Approximately 25% of all U.S. patients who undergo multivessel coronary revascularization have DM (6).

**METHODS**

This observational, nationwide population-based cohort study database was created by cross-linking several national Swedish health data registers. The unique personal identity number assigned to every Swedish citizen was used as the identifier in the records linkage procedure at the Swedish National Board of Health and Welfare. The database was then anonymized according to regulations. The personal identity number and national registers are described in the Online Appendix.

In brief, all patients who underwent primary isolated nonemergency CABG in Sweden between 2003 and 2013 were included. The study population and baseline characteristics were obtained from the SWEDHEART (Swedish Web-System for Enhancement and Development of Evidence-Based Care in Heart Disease Evaluated According to Recommended Therapies) register, and further expanded with information from the National Patient Register, the Swedish Renal Register, and socioeconomic data from Statistics Sweden (a government agency) (15). Data sources are described in detail in the Online Appendix. The regional Human Research Ethics Committee, Stockholm, Sweden, approved the study.

**DEFINITIONS OF DM.** The type of DM (1 or 2) was obtained from the Swedish National Diabetes Register (Online Appendix). All patients who were not included in the Swedish National Diabetes Register were considered as being nondiabetic. The epidemiological definition of T1DM was onset of DM at age <30 years and treatment with insulin only (16). T2DM was defined as DM treated with diet or oral hypoglycemic agents alone, or age >40 years at onset and treated with insulin alone or in combination with oral hypoglycemic agents (17).

**OUTCOMES.** We obtained the date and cause of death from the national Cause of Death Register. Causes of death were categorized as cardiovascular or noncardiovascular. Rehospitalization for MI, heart failure, stroke, or repeat revascularization (percutaneous coronary intervention [PCI] or CABG) data were obtained from the National Patient Register. A major adverse coronary event (MACE) was defined as hospital stay for MI, stroke, heart failure, or revascularization. International Classification of Diseases codes for the outcome measures are shown in the Online Appendix.

**MISSING DATA.** Missing data (renal function [4.5%], ejection fraction [2.6%], body mass index [7.6%], education [2.5%], number of bypass grafts [14%]) were managed by multiple imputation (Online Appendix).

**STATISTICAL METHODS.** Patient characteristics were described using frequencies and percents for
categorical variables, and means and standard deviations for continuous variables. The primary outcome measure was death from any cause. Patients contributed person-time in days from the date of surgery until the date of death from any cause or the end of follow-up (March 24, 2014). Secondary outcome measures included cardiovascular death, and a combination of hospital stay for MI, heart failure, stroke, or repeat revascularization. Information regarding cause of death and hospital stay was available until December 31, 2012; therefore, the follow-up period for the secondary outcome measures ended on December 31, 2012. As a result, patients who underwent surgery during 2013 (n = 2,473) were excluded from the secondary outcome analyses.

We used Cox regression to estimate the risk of all-cause mortality or a combined endpoint (all-cause mortality or hospital stay for MI, heart failure, stroke, or repeat revascularization) in patients with T1DM or T2DM in a comparison with reference patients without diabetes. We calculated crude and multivariable adjusted hazard ratios (HRs) and 95% confidence intervals (CIs). We included all the variables listed in Table 1 as covariates in the final multivariable model.

We investigated differences in each cause of mortality (cardiovascular death or other causes) by competing risk regression based on the Fine-Gray proportional subhazards model (18), and calculated subdistribution HR and 95% CI. Data management and statistical analyses were performed using Stata 13.1 (Stata Corp, College Station, Texas) and R version 3.1.1 (R Foundation for Statistical Computing, Vienna, Austria).

RESULTS

Patient characteristics are presented in Table 1. A total of 39,235 patients with a mean age of 67 years were included, of whom 21% (8,170 of 39,235) were women. In total, there were 23% (8,933 of 39,235) patients with DM, of whom 1.8% (725 of 39,235) had T1DM and 21% (8,208 of 39,235) had T2DM. Patients with T1DM were more likely to be younger, female, and have chronic kidney disease, peripheral vascular disease, and heart failure in comparison with patients with no DM or T2DM.

During a mean follow-up time of 5.9 ± 3.2 years (230,085 person-years), in total, 17% (6,765 of 39,235) patients died: 17% (5,064 of 30,302) with no DM, 21% (1,549 of 8,208) with T1DM, and 19% (1,549 of 8,208) with T2DM. The unadjusted Kaplan-Meier estimated survival curve is shown in Figure 1, and the age-adjusted survival curve is shown in Figure 2. The crude incidence rate of death in patients with no DM, T1DM, and T2DM was 28% (95% CI: 27 to 29), 39% (95% CI: 33 to 45), and 33% (95% CI: 31 to 35) per 1,000 person-years, respectively. After 1 year of surgery, survival was 97%, 96%, and 97% in patients with no DM, T1DM, and T2DM, respectively. The corresponding figures after 5 years were 89%, 85%, and 89%, respectively. After multivariable adjustment, the HR (95% CI) for death was 2.04 (1.72 to 2.42) in patients with T1DM and 1.11 (1.05 to 1.18) in patients with T2DM, compared with no DM. Furthermore, we categorized causes of death into cardiovascular death or noncardiovascular death. The point estimates indicated a stronger association between T1DM and noncardiovascular death than with cardiovascular death. The association between T2DM and cardiovascular death was not significant (HR: 1.08, 95% CI: 0.95 to 1.19).

When we analyzed death and MACE as a composite outcome, the associations found were similar to those for death alone, with nearly a doubling of risk in patients with T1DM and only a small increase in risk in patients with T2DM (Central Illustration).

In a subset of patients with T1DM and T2DM (n = 8,933), we found that there was a significantly higher risk for all-cause mortality in T1DM compared with T2DM (adjusted HR: 1.70 [95% CI: 1.40 to 2.06]). In 99.6% (8,899 of 8,933) of these patients, information regarding preoperative glycated hemoglobin (HbA
1c
) and diabetes duration was available. When HbA
1c
 and duration of disease were added to the multivariable model, the risk for all-cause mortality in T1DM compared with T2DM was slightly attenuated (adjusted HR: 1.44 [95% CI: 1.14 to 1.80]).

RELATIONSHIP BETWEEN TYPE OF DM, DURATION OF DISEASE, AND GLYCEMIC CONTROL. Patients with T1DM had a longer duration of disease than patients with T2DM (mean 40.8 vs. 9.6 years) (Table 2). In patients with T1DM, 94% had a longer duration of disease than 20 years, compared with 10% in patients with T2DM. Furthermore, patients with T1DM had, in general, higher HbA
1c
 levels than patients with T2DM.

RELATIONSHIP BETWEEN T1DM, T2DM, AND DEATH ACCORDING TO SEX. In men with T1DM, 19% (79 of 420) died during follow-up compared with 24% (73 of 305) among women with T1DM. The adjusted risk of death was similar among men and women with T1DM: HR: 1.83 (95% CI: 1.45 to 2.30) and HR: 2.17 (95% CI: 1.66 to 2.84), respectively (Table 3). The absolute risk
of death in women with T2DM was higher than that in men with T2DM (22% vs. 18%). However, after adjustment for confounders, the relative risks were similar for both men and women with T2DM (Table 3).

Similar sex-specific associations between types of diabetes were also found for death and MACE combined as outcome (Table 3).

**DISCUSSION**

In a large nationwide cohort of patients who underwent a first isolated CABG during an 11-year period in Sweden, we found that patients with T1DM had a risk of death after CABG double that of patients without DM. There was a small, but statistically significant,
increase in the risk of death in patients with T2DM when compared with those without DM (Central Illustration). In addition, there was no difference in relative risks for death or cardiovascular events between women and men, neither in those with T1DM or T2DM.

A number of either population-based or randomized trials have reported on the association between DM and the risk of cardiovascular disease (14). However, most of these studies have either only included patients with T2DM or have not made any distinction between T1DM and T2DM, and thus have analyzed patients as being merely diabetic or nondiabetic. This also holds true for previous studies on the importance of DM for prognosis after CABG, which may explain the conflicting results found in previous studies (7–11). To the best of our knowledge, only 1 previous study has investigated the association between T1DM and T2DM and outcomes after CABG (11), wherein both subtypes of DM were associated with the combined outcome of death or MI. That study included only 50 patients with T1DM, and the inclusion period was 1980 to 1995. Thus, considering the recent rather steep decline in cardiovascular events and death associated with DM (19–22), and the small number of events reported in that study, we believe that the findings may not be applicable to contemporary cohorts of CABG patients.

The 2 main findings in our study were that T1DM was associated with a doubling of mortality, but also that patients with T2DM had only a minimally increased risk of death in comparison with nondiabetic patients (Central Illustration). Furthermore, patients with T1DM were more likely than patients with T2DM or without diabetes to have comorbidities, such as chronic kidney disease, end-stage renal disease, peripheral vascular disease, or heart failure, which all have been associated with a worse prognosis in diabetic patients who undergo CABG (9,10). However, even after adjustment for these risk factors, the association between T1DM and adverse outcome was significant. One of the main differences between the 2 subtypes of diabetes is the duration of the disease. In the present study, the difference in mean duration of disease between patients with T1DM and T2DM was >30 years. This fact may help explain the differences seen in prognosis between the 2 subtypes of diabetes, because the duration of exposure to risk factors and comorbidities was considerably longer in patients with T1DM than in those with T2DM. In addition, HbA1c levels were higher in patients with T1DM than in those with T2DM, revealing poorer glycemic control in patients with T1DM. The association between glycemic control and micro- and macroangiopathy seems to be more significant in T1DM than in T2DM (16,22). Although we do not have any data on microvascular complications, the increase in HbA1c levels together with the longer duration of diabetes seen in T1DM might explain our findings. Interestingly, in a recently published study, HbA1c levels in patients with insulin-treated DM who underwent PCI were not related to mortality (23). In the
same study, patients with DM without insulin treatment were more likely to benefit from better glycemic control. However, the investigators were unable to subtype their patients into T1DM or T2DM, but only into treatment groups with or without insulin. Furthermore, in a recently published study from the same register where our T1DM patients were retrieved, even those T1DM patients who had a HbA1c level below 7.0% had a more than doubled risk of death as compared with the general population (24). This indicates that even with optimal glycemic control T1DM patients are at high risk of premature death.

We found only a small increase in the risk of death in patients with T2DM when compared with those without DM. This finding may have several explanations. First, previous studies have suggested that a large proportion of patients with MI have either glucose intolerance or established T2DM, which has gone undetected until they are admitted for an acute coronary syndrome (24). Thus, if a large proportion of patients were categorized as non-DM patients and truly had either glucose intolerance or established T2DM, and this was related to outcome, this may have diluted the associations seen between both T2DM and T1DM and the outcome measures. However, studies that have investigated the prognostic importance of glucose intolerance in patients with MI have failed to show any convincing associations with adverse outcomes (25). Second, because all patients with T2DM already had established coronary artery disease, and as a consequence a very high risk of recurrent cardiovascular events, they may have been treated with optimal medications and measures to reduce their risk of future cardiovascular events (26). Their treatment may even have been better
than that for patients without DM, thus diluting the differences in risk between those with T2DM and those without DM.

It is generally thought that women with DM have a higher relative risk of cardiovascular events than men with DM (12,27,28). However, recent studies have challenged this statement and have found similar risks in men and women (19). In the present study, we found no sex differences in relative risks between outcomes and both T1DM and T2DM cohorts.

By using the National Diabetes Register, we were able to classify all patients according to the type of DM, and thus investigate the importance of the 2 subtypes for prognosis. The information used for categorization into T1DM and T2DM has been shown to have high validity (16). To the best of our knowledge, this was the first study of a contemporary cohort of patients undergoing CABG where the association between subtypes of DM and prognosis were investigated. Moreover, we also had information on the characteristics that distinguish T1DM from T2DM in general, that is, duration of diabetes and glycemic control, which allowed us to speculate to some extent on potential mechanisms responsible for the differences seen in prognosis among patients with T1DM and T2DM. The nationwide population-based design allowed for a large study population, and the rather long follow-up led to a large number of events, which gave us the opportunity to analyze additional clinically relevant outcomes, such as cause-specific mortality and need for repeat revascularization. The high-quality Swedish national registers from which we derived the study population and retrieved patient characteristics and outcomes have been found to have high validity in previous studies (15,29,30).

Furthermore, as the coverage of these registers is virtually complete and countrywide, the risk of misclassification of disease or outcome was small, and there was no loss to follow-up. In addition, considering the nationwide design of our study and the recent study period, reflecting current standard of care, we believe that our results have a high external validity and are applicable to other patients with DM undergoing CABG in countries with a similar level of healthcare.

### TABLE 3 Absolute and Relative Risks of Death or MACE: Death After Primary Isolated CABG in Patients With T1DM or T2DM Compared With Patients Without DM Stratified by Sex

<table>
<thead>
<tr>
<th>No DM</th>
<th>T1DM n = 725</th>
<th>T2DM n = 8,208</th>
</tr>
</thead>
<tbody>
<tr>
<td><strong>Death</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>3,918/24,329 (16.1)</td>
<td>79/420 (18.8)</td>
</tr>
<tr>
<td>Crude rate per 1,000 person-yrs</td>
<td>27.3 (26.5-28.2)</td>
<td>34.1 (27.3-42.5)</td>
</tr>
<tr>
<td>Crude HR</td>
<td>1.00</td>
<td>1.28 (1.02-1.60)</td>
</tr>
<tr>
<td>Adjusted HR</td>
<td>1.00</td>
<td>1.45 (1.20-2.30)</td>
</tr>
<tr>
<td>Women</td>
<td>1,146/5,973 (19.2)</td>
<td>73/305 (23.9)</td>
</tr>
<tr>
<td>Crude rate per 1,000 person-yrs</td>
<td>31.8 (30.0-33.7)</td>
<td>45.4 (36.1-57.1)</td>
</tr>
<tr>
<td>Crude HR</td>
<td>1.00</td>
<td>1.46 (1.15-1.85)</td>
</tr>
<tr>
<td>Adjusted HR</td>
<td>1.00</td>
<td>2.17 (1.66-2.84)</td>
</tr>
<tr>
<td><strong>MACE: death</strong></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Men</td>
<td>6,070/22,777 (26.7)</td>
<td>123/391 (31.5)</td>
</tr>
<tr>
<td>Crude rate per 1,000 person-yrs</td>
<td>57.6 (56.2-59.1)</td>
<td>75.4 (63.2-90.0)</td>
</tr>
<tr>
<td>Crude HR</td>
<td>1.00</td>
<td>1.30 (1.08-1.55)</td>
</tr>
<tr>
<td>Adjusted HR</td>
<td>1.00</td>
<td>1.52 (1.26-1.82)</td>
</tr>
<tr>
<td>Women</td>
<td>1,761/5,635 (31.2)</td>
<td>116/282 (41.1)</td>
</tr>
<tr>
<td>Crude rate per 1,000 person-years</td>
<td>67.6 (64.6-70.9)</td>
<td>106 (88.1-127)</td>
</tr>
<tr>
<td>Crude HR</td>
<td>1.00</td>
<td>1.51 (1.25-1.82)</td>
</tr>
<tr>
<td>Adjusted HR</td>
<td>1.00</td>
<td>1.75 (1.42-2.16)</td>
</tr>
</tbody>
</table>

Values are n events/n patients (%) or HR (95% CI). All variables listed in Table 1 were included as covariates in the final multivariable model. *MACE: death is defined as a combined endpoint of death, or readmission for myocardial infarction, heart failure, or stroke, or repeat revascularization.

CI = confidence interval; HR = hazard ratio; MACE = major adverse cardiac event(s); other abbreviations as in Table 1.
a potential limitation because it has been shown that a large proportion of patients with acute coronary syndromes have undetected T2DM or glucose intolerance (24).

CONCLUSIONS

We found that patients with T1DM had a doubling of the risk of death, whereas patients with T2DM had almost a similar risk of death as patients without diabetes in a nationwide cohort of 39,235 patients who underwent CABG. Our data indicate that patients with T1DM are at high risk for adverse outcome after CABG and should be closely followed up, and that all possible measures to mitigate their risk of death or recurrent cardiovascular events should be instituted.

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REFERENCES


KEY WORDS isolated CABG, major adverse coronary event, prognosis, revascularization

APPENDIX For supplemental tables and an expanded Methods section, please see the online version of this article.