ORIGINAL ARTICLE

Glycemic Control and Excess Mortality in Type 1 Diabetes

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ABSTRACT

BACKGROUND

The excess risk of death from any cause and of death from cardiovascular causes is unknown among patients with type 1 diabetes and various levels of glycemic control. We conducted a registry-based observational study to determine the excess risk of death according to the level of glycemic control in a Swedish population of patients with diabetes.

METHODS

We included in our study patients with type 1 diabetes registered in the Swedish National Diabetes Register after January 1, 1998. For each patient, five controls were randomly selected from the general population and matched according to age, sex, and county. Patients and controls were followed until December 31, 2011, through the Swedish Register for Cause-Specific Mortality.

RESULTS

The mean age of the patients with diabetes and the controls at baseline was 35.8 and 35.7 years, respectively, and 45.1% of the participants in each group were women. The mean follow-up in the diabetes and control groups was 8.0 and 8.3 years, respectively. Overall, 2701 of 33,915 patients with diabetes (8.0%) died, as compared with 4835 of 169,249 controls (2.9%) (adjusted hazard ratio, 3.52; 95% confidence interval [CI], 3.06 to 4.04); the corresponding rates of death from cardiovascular causes were 2.7% and 0.9% (adjusted hazard ratio, 4.60; 95% CI, 3.47 to 6.10). The multivariable-adjusted hazard ratios for death from any cause according to the glycated hemoglobin level for patients with diabetes as compared with controls were 2.36 (95% CI, 1.97 to 2.83) for a glycated hemoglobin level of 6.9% or lower (≤52 mmol per mole), 2.38 (95% CI, 2.02 to 2.80) for a level of 7.0 to 7.8% (53 to 62 mmol per mole), 3.11 (95% CI, 2.66 to 3.62) for a level of 7.9 to 8.7% (63 to 72 mmol per mole), 3.65 (95% CI, 3.11 to 4.30) for a level of 8.8 to 9.6% (73 to 82 mmol per mole), and 8.51 (95% CI, 7.24 to 10.01) for a level of 9.7% or higher (≥83 mmol per mole). Corresponding hazard ratios for death from cardiovascular causes were 2.92 (95% CI, 2.07 to 4.13), 3.39 (95% CI, 2.49 to 4.61), 4.44 (95% CI, 3.32 to 5.96), 5.35 (95% CI, 3.94 to 7.26), and 10.46 (95% CI, 7.62 to 14.37).

CONCLUSIONS

In our registry-based observational study, patients with type 1 diabetes and a glycated hemoglobin level of 6.9% or lower had a risk of death from any cause or from cardiovascular causes that was twice as high as the risk for matched controls. (Funded by the Swedish Society of Medicine and others.)

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Type 1 diabetes is associated with a substantially increased risk of premature death as compared with that in the general population.[1-8] Among persons with diabetes who are younger than 30 years of age, excess mortality is largely explained by acute complications of diabetes, including diabetic ketoacidosis and hypoglycemia[7-9]; cardiovascular disease is the main cause of death later in life.[7-9]

Improving glycemic control in patients with type 1 diabetes substantially reduces their risk of microvascular complications and cardiovascular disease.[10,11] Accordingly, diabetes treatment guidelines emphasize good glycemic control,[12-15] which is indicated by the glycated hemoglobin level, a measure of the mean glycemic level recorded during the preceding 2 to 3 months.[16] Although a target level of less than 7.0% (53 mmol per mole) is generally recommended[12-15] and is considered to be associated with a lower risk of diabetic complications, as compared with higher levels, in two national registries, only 13 to 15% of patients with type 1 diabetes met this target, whereas more than 20% had very poor glycemic control (i.e., a glycated hemoglobin level >8.8%, or ≥73 mmol per mole).[1,17] The excess risks of death from any cause and from cardiovascular causes in patients with diabetes who have varying degrees of glycemic control, as compared with the risks in the general population, have not been evaluated. We undertook this evaluation using the Swedish National Diabetes Register, which includes information on glycemic control for most adults with type 1 diabetes in Sweden.

Methods

Study Design and Oversight

This study was approved by the ethics committee of the University of Gothenburg, Sweden. There was no commercial sponsorship.

The National Diabetes Register, initiated in 1996, has been described previously[18,19]; it includes information on risk factors, complications of diabetes, and medications in patients 18 years of age or older. Informed consent for inclusion in the register is obtained from each patient, and virtually all patients in Sweden with type 1 diabetes are included. The register defines type 1 diabetes on the basis of epidemiologic data: treatment with insulin and a diagnosis at the age of 30 years or younger; this definition has been validated as accurate in 97% of the cases listed in the register.[19] Patients with at least one listing in the National Diabetes Register between January 1, 1998, and December 31, 2011, were included in the study. For the first registration of each patient with type 1 diabetes, five unregistered controls matched with the patient for age, sex, and county were randomly selected from the general population in Sweden, a method that has been used in previous studies.[20,21]

Information on coexisting conditions and causes of death was retrieved by linking personal identification numbers from patients and controls to the Swedish Inpatient Register and the Cause of Death Register. Information on education and country of birth was retrieved from the Longitudinal Integration Database for Health Insurance and Labor Market Studies.[20,21] Education was categorized as low (compulsory only), intermediate, or high (university level or similar). Country of birth was categorized as Sweden or other. Information on prescribed drugs was retrieved from the Swedish Prescribed Drug Register, which includes this information for the entire Swedish population dating from July 2005.[22]

Patients and controls were followed from baseline until death or December 31, 2011. In all, 0.2% of patients with type 1 diabetes (74 of 33,989) and 0.3% of matched controls (576 of 169,825) were excluded because of inconsistent data on vital status, leaving 33,915 patients with type 1 diabetes and 169,249 controls.

The Inpatient Registry includes all inpatient admissions nationwide from 1987 onward. Codes from the *International Classification of Diseases* (ICD), 9th and 10th Revisions, were used to define acute myocardial infarction, coronary heart disease, hospitalization for heart failure, atrial fibrillation, stroke, cancer diagnoses, renal dialysis, and transplantation from 1987 onward. (For ICD codes, see the Supplementary Appendix, available with the full text of this article at NEJM.org.) ICD codes do not differentiate hypoglycemic comas from hyperglycemic comas. Dates and diagnoses for death from cardiovascular disease, death from cancer, diabetes-related death, and external and all other causes of death were retrieved from the Cause of Death Register.

Microalbuminuria was defined as two positive results for three urine samples obtained within 1 year, with positivity defined as an albumin: creatinine ratio of 3 to 30 mg per millimole (approximately 30 to 300 mg per gram) or a urinary albumin clearance of 20 to 200 μg per minute

(20 to 300 mg per liter). Macroalbuminuria was defined as an albumin:creatinine ratio of more than 30 mg per millimole (close to 300 or more mg per gram) or a urinary albumin clearance of more than 200 μg per minute (>300 mg per liter). The estimated glomerular filtration rate (eGFR) was calculated by means of the Modification of Diet in Renal Disease equation.[23] Stage 5 chronic kidney disease was defined as the need for renal dialysis or renal transplantation or as an eGFR of less than 15 ml per minute.

All-cause and cardiovascular mortality were assessed across categories of updated mean glycated hemoglobin level[24] to compare mortality among patients with type 1 diabetes with mortality in matched controls according to levels of glycemic control. (The updated mean is the mean value calculated at a certain point in time [e.g., if three values exist for glycated hemoglobin level until that point, then the updated mean is the mean level of those values].) Corresponding analyses of mortality between patients and controls were performed for two renal variables, with the first categorized as normoalbuminuria, microalbuminuria, macroalbuminuria, or stage 5 chronic kidney disease, and the second categorized as an eGFR level of 15 to less than 60 ml per minute, 60 to 120 ml per minute, or more than 120 ml per minute.

STATISTICAL ANALYSIS

Crude mortality rates were described as events per 1000 patient-years; exact Poisson confidence intervals of 95% were used. Survival analyses were performed with the use of Cox regression and stratified in matched groups according to age and sex in model 1; adjusted for time-updated age (the value recorded closest to the time preceding each event), duration of diabetes, and sex in model 2; and further adjusted for level of education, birth in Sweden or elsewhere, and status before baseline with respect to a history of conditions other than diabetes (i.e., coronary heart disease, atrial fibrillation, heart failure, acute myocardial infarction, stroke, and cancer) in model 3. The third model was the main model used to evaluate the association between different categories of glycated hemoglobin level and outcomes in patients with type 1 diabetes as compared with the reference population. Analysis of the gathered data showed that the proportional-hazards assumption was fulfilled.

A Cox regression model was used in sensitivity analyses to evaluate the association between various levels of glycemic control and outcomes in patients with type 1 diabetes. Model A was adjusted for time-updated age and sex, as were models B and C, with model B also adjusted for time-updated diabetes duration and model C also adjusted for educational category, birth in Sweden or elsewhere, and status with respect to a history of conditions other than diabetes before baseline. In addition, time-updated mean systolic blood pressure, time-updated mean body-mass index, and time-updated smoking status were added to model D, time-updated mean levels of high-density and low-density lipoprotein cholesterol and time-updated status with respect to treatment with lipid-lowering drugs to model E, and time-updated status with respect to renal impairment (normoalbuminuria, microalbuminuria, macroalbuminuria, or stage 5 chronic kidney disease) to model F. All tests were two-tailed and conducted at a significance level of 0.05. Analyses of mortality according to renal disease status among patients with type 1 diabetes versus controls and within the diabetes group were performed in accordance with the methods used to determine the effect of time-updated mean glycated hemoglobin level. All analyses were performed with the use of SAS Software, version 9.2 (SAS Institute).

RESULTS

STUDY POPULATION

The baseline characteristics of the two study groups are shown in Table 1. Among the 33,915 patients with type 1 diabetes and 169,249 controls, the proportion of women, the age distribution, and educational levels were similar, but a greater proportion of the patients with diabetes were born in Sweden. All cardiovascular conditions, with the exception of atrial fibrillation, were more common among patients with diabetes than among controls. The mean glycated hemoglobin level at baseline was 8.2% (65.8 mmol per mole) in patients with type 1 diabetes, and the mean duration of diabetes was 20.4 years.

MORTALITY

Table 2 shows rates of death from any cause, from cardiovascular causes, from cancer, from external causes, and from diabetes-related causes among patients with type 1 diabetes and controls. These

Table 1. Baseline Characteristics of Patients with Type 1 Diabetes and Controls.*

Characteristic	Controls (N=169,249)	Patients with Type 1 Diabetes (N=33,915)						
			Glycated Hemoglobin Level†					
		Total (N=33,915)	≤6.9% (N=6142)	7.0–7.8% (N=7759)	7.9–8.7% (N=8951)	8.8–9.6% (N=5442)	≥9.7% (N=4000)	Missing Data (N=1621)
Female sex — no. (%)	76,382 (45.1)	15,302 (45.1)	2711 (44.1)	3470 (44.7)	3984 (44.5)	2451 (45.0)	1942 (48.6)	744 (45.9)
Age — yr	35.7±14.6	35.8±14.6	33.9±14.2	37.2±15.1	37.5±14.8	36.1±14.2	32.8±13.4	32.6±14.5
Born in Sweden — no. (%)	146,353 (86.5)	31,838 (93.9)	5732 (93.3)	7333 (94.5)	8462 (94.5)	5110 (93.9)	3728 (93.2)	1473 (90.9)
Educational level — no. (%)								
Low	31,238 (18.7)	6503 (19.3)	859 (14.1)	1372 (17.8)	1704 (19.2)	1181 (21.9)	1028 (25.9)	359 (22.4)
Middle	80,436 (48.1)	16,890 (50.2)	2729 (44.8)	3688 (48.0)	4557 (51.2)	2926 (54.2)	2204 (55.6)	786 (49.1)
High	55,547 (33.2)	10,249 (30.5)	2507 (41.1)	2627 (34.2)	2631 (29.6)	1293 (23.9)	734 (18.5)	457 (28.5)
Information from National Diabetes Register								
Glycated hemoglobin — mmol/mol		65.8±15.8	45.6±5.5	57.3±2.6	67.2±2.8	76.9±2.8	94.9±11.3	
Diabetes duration — yr		20.4±14.8	16.4±15.9	22.0±15.0	22.8±14.3	21.5±13.6	18.3±12.9	16.8±14.8
BMI		25.1±4.0	24.6±4.0	25.0±3.8	25.3±3.8	25.4±4.1	25.0±4.7	24.7±5.0
LDL cholesterol — mmol/liter		2.66±0.83	2.53±0.76	2.60±0.79	2.68±0.83	2.74±0.86	2.87±0.95	2.59±0.81
Blood pressure — mm Hg								
Systolic		126.9±17.0	124.4±15.9	126.8±16.6	128.4±17.1	127.8±17.2	127.0±18.1	123.7±16.6
Diastolic		73.6±9.2	72.2±8.9	73.0±8.9	73.8±9.0	74.4±9.3	75.1±9.6	72.9±9.4
Smoking — no. (%)		4277 (13.6)	515 (8.9)	770 (10.5)	1121 (13.3)	859 (16.9)	855 (23.4)	157 (13.1)
Information from Inpatient Register before baseline — no. (%)‡								
Acute myocardial infarction, ICD code I21	967 (0.6)	745 (2.2)	78 (1.3)	181 (2.3)	221 (2.5)	140 (2.6)	95 (2.4)	30 (1.9)
Coronary heart disease, ICD codes I20–I25	1826 (1.1)	1459 (4.3)	173 (2.8)	349 (4.5)	433 (4.8)	262 (4.8)	180 (4.5)	62 (3.8)
Atrial fibrillation, ICD code I48	938 (0.6)	242 (0.7)	46 (0.7)	58 (0.7)	72 (0.8)	31 (0.6)	25 (0.6)	10 (0.6)
Heart failure, ICD code I50	515 (0.3)	513 (1.5)	62 (1.0)	100 (1.3)	159 (1.8)	82 (1.5)	76 (1.9)	34 (2.1)
Stroke, ICD codes I61–I64	728 (0.4)	501 (1.5)	67 (1.1)	117 (1.5)	140 (1.6)	82 (1.5)	68 (1.7)	27 (1.7)
Cancer, ICD codes C00–C97	2506 (1.5)	607 (1.8)	105 (1.7)	155 (2.0)	170 (1.9)	90 (1.7)	53 (1.3)	34 (2.1)

* Plus–minus values are means ±SD. Percentages for glycated hemoglobin level are based on values from the National Glycohemoglobin Standardization Program, and concentrations are based on values from the International Federation of Clinical Chemistry. *International Classification of Diseases* (ICD) codes from the 10th revision were used. BMI denotes body-mass index, the weight in kilograms divided by the square of the height in meters and LDL low-density lipoprotein.

† Molar equivalents for glycated hemoglobin level are as follows: 6.9% or lower, 52 mmol per mole or lower; 7.0 to 7.8%, 53 to 62 mmol per mole; 7.9 to 8.7%, 63 to 72 mmol per mole; 8.8 to 9.6%, 73 to 82 mmol per mole; 9.7% or higher, 83 mmol per mole or higher.

‡ Diagnostic codes for the conditions listed are from the ICD, 10th Revision.

rates of death are also shown in relation to baseline glycated hemoglobin level for patients with diabetes. The death rate for patients with type 1 diabetes was 9.97 per 1000 observation-years (2701 patients died, or 8.0%) and the rate for controls was 3.45 per 1000 observation-years (4835 controls died, or 2.9%). Excess mortality among patients with diabetes was mainly due to cardiovascular disease and diabetes-related causes of death. The between-group difference for cancer-related deaths was not significant, whereas deaths from external causes and from a composite of other causes were more common among patients with type 1 diabetes.

Death rates and hazard ratios for deaths from all causes and deaths from cardiovascular causes are shown in Figure 1 according to age and sex. Hazard ratios for death from any cause and for death from cardiovascular causes among patients with type 1 diabetes versus controls were 3.52 (95% confidence interval [CI], 3.06 to 4.04) and 4.60 (95% CI, 3.47 to 6.10), respectively, after adjustment for time-updated age, sex, time-updated diabetes duration, birth in Sweden or elsewhere, educational level, and time-updated status with respect to previous coronary heart disease, acute myocardial infarction, stroke, heart failure, atrial fibrillation, and cancer. There was an interaction between diabetes and sex, with women having higher hazard ratios for death from cardiovascular causes ($P<0.001$) but not for death from any cause ($P=0.31$). Hazard ratios for patients with diabetes versus controls did not differ significantly between the first 7 calendar years of follow-up (1998 through 2004) and the final 7 years of follow-up (2005 through 2011), for either death from any cause (3.62 [95% CI, 3.11 to 4.21] and 3.45 [95% CI, 2.98 to 4.00], respectively; $P=0.41$ for interaction) or death from cardiovascular causes (4.90 [95% CI, 3.63 to 6.63] and 4.38 [95% CI, 3.26 to 5.89], respectively; $P=0.25$ for interaction).

RISK OF DEATH

There was a significant excess risk of death from any cause and from cardiovascular causes among patients with type 1 diabetes who had an updated mean glycated hemoglobin level of 6.9% or lower (≤52 mmol per mole), as compared with controls, with the risk gradually increasing at higher levels (see Table 3 for model 3, and Table S1 in the Supplementary Appendix for models 1 and 2). In the final model (model 3), the hazard ratio for death from any cause among patients with diabetes was 2.36 (95% CI, 1.97 to 2.83) at an updated mean glycated hemoglobin level of 6.9% or lower and increased to 8.51 (95% CI, 7.24 to 10.01) for a level of 9.7% or higher (≥83 mmol per mole). For death from cardiovascular causes, the corresponding hazard ratios ranged from 2.92 (95% CI, 2.07 to 4.13) to 10.46 (95% CI, 7.62 to 14.37).

Analyses of outcomes within the group of patients with diabetes showed that the risk of death from any cause and the risk of death from cardiovascular causes increased incrementally with higher updated mean glycated hemoglobin levels (see Table 4 for models C through F, and Table S2 in the Supplementary Appendix for models A and B). Findings were stable over all categories of updated mean glycated hemoglobin level in models that were adjusted for other risk factors. Adjustment for time-updated status with respect to renal disease yielded risk estimates for both death from any cause and death from cardiovascular causes that were virtually unchanged for patients with glycated hemoglobin levels ranging from 7.0 to 7.8% (53 to 62 mmol per mole) versus glycated hemoglobin levels of 6.9% or lower, and the hazard ratios were moderately attenuated but remained significant for other categories of glycated hemoglobin level. When the updated mean glycated hemoglobin level was analyzed as a continuous variable, an increase of 1.0% (10 mmol per mole) was associated with a hazard ratio of 1.30 (95% CI, 1.27 to 1.34) for death from any cause and 1.26 (95% CI, 1.19 to 1.32) for death from cardiovascular causes (model C), but with adjustment for time-updated renal disease, the hazard ratios fell to 1.20 (95% CI, 1.16 to 1.24) and 1.14 (95% CI, 1.07 to 1.21), respectively.

Among patients with type 1 diabetes and normoalbuminuria, the risk of death from any cause was 2.76 (95% CI, 2.33 to 3.27) and the risk of death from cardiovascular disease was 3.64 (95% CI, 2.61 to 5.06), as compared with the risks in the general population (Table 3). Among patients with type 1 diabetes and stage 5 chronic kidney disease, the excess hazard ratio increased to 28.09 (95% CI, 22.95 to 34.39) and 38.98 (95% CI, 26.90 to 56.47), respectively. There was a monotonic increase in risk with more advanced kidney disease that was not affected after adjustment for other variables (Table 4). The correspond-

ing hazard ratios for death from any cause and death from cardiovascular causes according to time-updated eGFR categories are shown in Tables 3 and 4.

DEATHS RELATED TO DIABETES

There were 912 patients in whom the cause of death was related to diabetes. The primary cause was reported as diabetic ketoacidosis or hypoglycemia for 132 patients (14.5%), renal complications for 84 patients (9.2%), vascular complications for 82 patients (9.0%), and eye complications for 1 patient (0.1%); multiple or unspecified complications were reported for 613 patients (67.2%). Diabetic ketoacidosis or coma was the primary cause of death for 22 of 70 patients (31.4%) younger than 30 years of age, 29 of 176 patients (16.5%) between 30 and 40 years of age, and 81 of 2455 patients (3.3%) older than 40 years of age. Among patients for whom there was an unspecified diagnosis of diabetes-related death, 359 deaths (91.3%) occurred outside the hospital.

MEDICATIONS

According to the Prescribed Drug Register, 43.1% of patients with type 1 diabetes received a prescription for a statin medication at any time after 2005, as compared with 9.0% of controls. Renin–angiotensin–aldosterone system inhibitors were prescribed for 39.7% of patients with type 1 diabetes as compared with 10.7% of controls.

DISCUSSION

This nationwide Swedish study of 33,915 patients with type 1 diabetes and 169,249 controls matched for age and sex shows that for patients with type 1 diabetes who had on-target glycemic control, the risk of death from any cause and the risk of death from cardiovascular causes were still more than twice the risks in the general population. For patients with diabetes who had very poor glycemic control, the risks of death from any cause and of death from cardiovascular causes were 8 and 10 times as high, respectively, as those in the general population. The excess risks of death among patients with type 1 diabetes were almost entirely accounted for by cardiovascular disease and diabetes, whereas cancer-related deaths were no more common among patients with type 1 diabetes than among con-

Table 2. Mortality among Patients with Type 1 Diabetes as Compared with Controls According to Baseline Level of Glycated Hemoglobin.*

Variable	Controls (N=169,249)	Patients with Type 1 Diabetes (N=33,915)					
			Glycated Hemoglobin Level				
		Total (N=33,915)	≤6.9% (N=6142)	7.0–7.8% (N=7759)	7.9–8.7% (N=8951)	8.8–9.6% (N=5442)	≥9.7% (N=4000)
Death from any cause — no. (%)	4835 (2.9)	2701 (8.0)	333 (5.4)	553 (7.1)	757 (8.5)	473 (8.7)	478 (12.0)
No./1000 patient-yr (95% CI)	3.45 (3.36–3.55)	9.97 (9.59–10.35)	7.01 (6.28–7.80)	8.73 (8.01–9.49)	10.14 (9.43–10.89)	10.54 (9.61–11.53)	16.25 (14.83–17.78)
Death from cardiovascular disease — no. (%)	1444 (0.9)	927 (2.7)	102 (1.7)	201 (2.6)	280 (3.1)	164 (3.0)	139 (3.5)
No./1000 patient-yr (95% CI)	1.03 (0.98–1.09)	3.42 (3.20–3.65)	2.15 (1.75–2.61)	3.17 (2.75–3.64)	3.75 (3.32–4.22)	3.65 (3.12–4.26)	4.73 (3.97–5.58)
Cancer-related death — no. (%)	1671 (1.0)	349 (1.0)	61 (1.0)	77 (1.0)	121 (1.4)	51 (0.9)	34 (0.9)
No./1000 patient-yr (95% CI)	1.19 (1.14–1.25)	1.29 (1.16–1.43)	1.28 (0.98–1.65)	1.22 (0.96–1.52)	1.62 (1.34–1.94)	1.14 (0.85–1.49)	1.16 (0.80–1.62)
Diabetes-related death — no. (%)	110 (0.1)	912 (2.7)	91 (1.5)	166 (2.1)	238 (2.7)	168 (3.1)	214 (5.4)
No./1000 patient-yr (95% CI)	0.08 (0.06–0.09)	3.37 (3.15–3.59)	1.92 (1.54–2.35)	2.62 (2.24–3.05)	3.19 (2.80–3.62)	3.74 (3.20–4.35)	7.28 (6.33–8.32)
External cause of death — no. (%)	558 (0.3)	163 (0.5)	20 (0.3)	42 (0.5)	37 (0.4)	22 (0.4)	33 (0.8)
No./1000 patient-yr (95% CI)	0.40 (0.37–0.43)	0.60 (0.51–0.70)	0.42 (0.26–0.65)	0.66 (0.48–0.90)	0.50 (0.35–0.68)	0.49 (0.31–0.74)	1.12 (0.77–1.58)
Other cause of death — no. (%)	1052 (0.6)	350 (1.0)	59 (1.0)	67 (0.9)	81 (0.9)	68 (1.2)	58 (1.5)
No./1000 patient-yr (95% CI)	0.75 (0.71–0.80)	1.29 (1.16–1.43)	1.24 (0.95–1.60)	1.06 (0.82–1.34)	1.09 (0.86–1.35)	1.51 (1.18–1.92)	1.97 (1.50–2.55)

* Mortality rates were calculated as events per 1000 patient-years; exact Poisson confidence intervals (CIs) of 95% were used.

Subgroup	Type 1 Diabetes	Reference	Hazard Ratio (95% CI)	P Value
	no. of events (%)			
Death from any cause				
Male				
18–34 yr	160 (1.6)	283 (0.6)	2.84 (2.34–3.45)	<0.001
35–49 yr	428 (8.9)	524 (2.2)	4.26 (3.75–4.84)	<0.001
50–64 yr	631 (21.6)	1217 (8.4)	2.86 (2.60–3.15)	<0.001
≥65 yr	367 (50.3)	1046 (29.2)	2.20 (1.96–2.48)	<0.001
Female				
18–34 yr	90 (1.1)	110 (0.3)	4.11 (3.11–5.43)	<0.001
35–49 yr	239 (6.2)	280 (1.4)	4.39 (3.70–5.22)	<0.001
50–64 yr	482 (19.6)	638 (5.2)	4.17 (3.70–4.69)	<0.001
≥65 yr	304 (43.4)	737 (21.3)	2.62 (2.29–3.00)	<0.001
Death from cardiovascular causes				
Male				
18–34 yr	18 (0.2)	26 (0.1)	3.49 (1.91–6.36)	<0.001
35–49 yr	144 (3.0)	140 (0.6)	5.36 (4.25–6.77)	<0.001
50–64 yr	238 (8.2)	414 (2.9)	3.17 (2.70–3.72)	<0.001
≥65 yr	149 (20.4)	416 (11.6)	2.25 (1.87–2.72)	<0.001
Female				
18–34 yr	11 (0.1)	8 (0.0)	6.94 (2.79–17.25)	<0.001
35–49 yr	67 (1.7)	46 (0.2)	7.50 (5.16–10.92)	<0.001
50–64 yr	161 (6.5)	112 (0.9)	7.92 (6.22–10.08)	<0.001
≥65 yr	139 (19.8)	282 (8.1)	3.12 (2.55–3.83)	<0.001

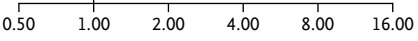

Figure 1. Hazard Ratios for Death from Any Cause and for Death from Cardiovascular Causes According to Age and Sex among Patients with Type 1 Diabetes versus Controls.

Hazard ratios were estimated by means of Cox regression.

trols. As compared with men, women with type 1 diabetes had a significantly greater excess risk of death from cardiovascular disease but not of death from any cause. The excess risk of death associated with diabetes did not diminish over time, with increases during the last 7 calendar years of the study (2005 through 2011) that were similar to those during the first 7 years (1998 through 2004).

Some previous studies have evaluated the relationship between glycemic control and all-cause mortality among persons with type 1 diabetes, and some of these studies[25,26] (but not all[19,27,28]) have shown an association between the level of glycemic control and all-cause mortality. A novel aspect of the current study is the strong and monotonic increase in the risk of death from any cause with higher mean glycated hemoglobin levels, which may be explained by the use of an updated mean glycated hemoglobin level in our analyses, which is known to provide a more accurate estimate of glycemic control[24] than measurement of the glycated hemoglobin level at a single time point, an approach often used in other studies.[25-28]

Unlike patients with type 2 diabetes, those with type 1 diabetes generally do not have excess rates of obesity, hypertension, or hypercholesterolemia[1]; thus, the increased risks of death from any cause and of death from cardiovascular causes among patients with type 1 diabetes who have good glycemic control is unexplained. It is possible that a history of poor glycemic control is associated with increased cardiovascular risk[11]; however, the mean follow-up period for each patient in our study was fairly long (approximately 8 years), and patients who have good glycemic control over time generally have better control earlier than those who do not have good control over time.[29]

The excess risk of death from any cause or from cardiovascular disease did not decrease over time in the present study. In a recent large study from Canada and the United Kingdom that did not distinguish types of diabetes, the excess risk of death declined substantially over time, albeit

Table 3. Adjusted Hazard Ratios for Death from Any Cause and Death from Cardiovascular Causes among Patients with Type 1 Diabetes versus Controls, According to Time-Updated Mean Glycated Hemoglobin Level and Renal Disease Status, Model 3.*

Variable	Hazard Ratio	
	Death from Any Cause	Death from Cardiovascular Disease
Time-updated mean glycated hemoglobin level — no. of events/total no.	7386/200,539	2326/200,539
Reference group (controls)	1.00	1.00
≤6.9%	2.36 (1.97–2.83)	2.92 (2.07–4.13)
7.0–7.8%	2.38 (2.02–2.80)	3.39 (2.49–4.61)
7.9–8.7%	3.11 (2.66–3.62)	4.44 (3.32–5.96)
8.8–9.6%	3.65 (3.11–4.30)	5.35 (3.94–7.26)
≥9.7%	8.51 (7.24–10.01)	10.46 (7.62–14.37)
Time-updated renal disease — no. of events/total no.	6673/197,786	2091/197,786
Reference group (controls)	1.00	1.00
Normoalbuminuria	2.76 (2.33–3.27)	3.64 (2.61–5.06)
Microalbuminuria	4.87 (4.00–5.92)	6.35 (4.41–9.16)
Macroalbuminuria	9.82 (8.11–11.89)	13.10 (9.19–18.67)
Stage 5 chronic kidney disease	28.09 (22.95–34.39)	38.98 (26.90–56.47)
Time-updated eGFR and stage 5 chronic kidney disease — no. of events/total no.	6711/198,632	2108/198,632
Reference group (controls)	1.00	1.00
eGFR		
>120 ml/min	4.41 (3.53–5.50)	4.65 (2.91–7.42)
60 to 120 ml/min	3.24 (2.74–3.84)	4.56 (3.30–6.31)
15 to <60 ml/min	7.64 (6.26–9.32)	10.42 (7.25–14.98)
Stage 5 chronic kidney disease	29.01 (23.68–35.54)	41.32 (28.52–59.86)

* The analysis, based on Cox regression, was adjusted for time-updated age, sex, time-updated duration of diabetes, birth in Sweden or elsewhere, educational level, and status with respect to a history of conditions other than diabetes at baseline, in accordance with model 3 of the survival analysis (see the Supplementary Appendix for details). The term "time-updated" refers to the value recorded closest to the time of each event. Numbers in parentheses are 95% CIs. P<0.001 for all comparisons.

not among patients younger than 40 years of age.[30] It is possible that a large proportion of patients in this age group had type 1 diabetes. In our study, beginning with the year 2005, patients with type 1 diabetes were four to five times as likely as controls to receive a prescription for statins or renin–angiotensin–aldosterone system inhibitors. Thus, the omission of currently recommended cardioprotective treatment cannot explain the remaining excess risk of death; determination of the underlying reasons will require further research.

The results of this study contrast with those of earlier published studies[26,31] in that the risk of death was greater among patients with type 1 diabetes and normoalbuminuria than among controls, a finding that may be due to our population-based design, which included more extensive adjustments for risk factors. Furthermore, the risk of death for patients with type 1 diabetes and stage 5 chronic kidney disease was 30 times as high as that among controls; however, an increased glycated hemoglobin level remained a powerful risk factor for death after adjustment for renal complications, indicating the presence of a substantial residual risk associated with poor glycemic control. In this context, renal disease should be viewed as a media-

Table 4. Adjusted Hazard Ratios for Death from Any Cause and for Death from Cardiovascular Causes among Patients with Type 1 Diabetes According to Time-Updated Mean Glycated Hemoglobin Level and Renal Disease Status, Models C through F.

Variable	Hazard Ratio for Death from Any Cause				Hazard Ratio for Death from Cardiovascular Disease			
	Model C*	Model D†	Model E‡	Model F§	Model C*	Model D†	Model E‡	Model F§
Time-updated mean glycated hemoglobin level — no. events/total no.	2648/33,432	2432/31,996	1659/29,238	1928/30,649	912/33,432	844/31,996	572/29,238	677/30,649
≤6.9%	1.00	1.00	1.00	1,00	1.00	1.00	1.00	1.00
7.0–7.8%	1.01 (0.88–1.15)	1.05 (0.91–1.22)	1.05 (0.88–1.25)	0.99 (0.84–1.16)	1.17 (0.92–1.49)	1.21 (0.94–1.56)	1.13 (0.84–1.51)	1.19 (0.90–1.57)
P value	0.93	0.50	0.57	0.87	0.19	0.13	0.42	0.21
7.9–8.7%	1.31 (1.15–1.50)	1.37 (1.19–1.57)	1.42 (1.20–1.68)	1.22 (1.04–1.42)	1.54 (1.22–1.95)	1.60 (1.25–2.04)	1.45 (1.09–1.94)	1.41 (1.08–1.85)
P value	<0.001	<0.001	<0.001	0.01	<0.001	<0.001	0.01	0.01
8.8–9.6%	1.53 (1.32–1.77)	1.56 (1.33–1.82)	1.67 (1.38–2.02)	1.36 (1.14–1.61)	1.82 (1.41–2.36)	1.84 (1.40–2.42)	1.68 (1.21–2.33)	1.56 (1.15–2.11)
P value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	0.002	0.004
≥9.7%	3.49 (2.99–4.06)	3.43 (2.91–4.04)	3.96 (3.21–4.87)	2.52 (2.09–3.04)	3.48 (2.64–4.60)	3.54 (2.62–4.77)	3.68 (2.54–5.34)	2.43 (1.73–3.41)
P value	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001	<0.001
Time-updated renal disease — no. of events/total no.	1935/30,679	1821/29,778	1593/28,451		677/30,679	641/29,778	553/28,451	
Normoalbuminuria	1.00	1.00	1.00		1.00	1.00	1.00	
Microalbuminuria	1.87 (1.65–2.11)	1.83 (1.62–2.07)	1.94 (1.70–2.21)		1.91 (1.56–2.35)	1.85 (1.50–2.28)	1.97 (1.58–2.46)	
P value	<0.001	<0.001	<0.001		<0.001	<0.001	<0.001	
Macroalbuminuria	3.81 (3.39–4.29)	3.79 (3.35–4.28)	3.82 (3.34–4.36)		4.01 (3.29–4.89)	4.05 (3.30–4.98)	3.98 (3.18–4.98)	
P value	<0.001	<0.001	<0.001		<0.001	<0.001	<0.001	
Stage 5 chronic kidney disease	10.50 (9.11–12.11)	10.41 (8.92–12.15)	11.19 (9.47–13.22)		10.77 (8.43–13.76)	10.28 (7.88–13.42)	11.81 (8.91–15.66)	
P value	<0.001	<0.001	<0.001		<0.001	<0.001	<0.001	
Time-updated eGFR and stage 5 chronic kidney disease — no. of events/total no.	1973/31,525	1842/30,406	1619/29,045		694/31,525	653/30,406	561/29,045	
eGFR								
>120 ml/min	1.00	1.00	1.00		1.00	1.00	1.00	
60 to 120 ml/min	0.76 (0.63–0.93)	0.79 (0.65–0.96)	0.76 (0.62–0.94)		1.04 (0.70–1.56)	1.03 (0.69–1.55)	1.04 (0.67–1.64)	
P value	0.006	0.02	0.01		0.84	0.87	0.85	
15 to <60 ml/min	1.90 (1.55–2.34)	1.96 (1.58–2.43)	1.83 (1.46–2.30)		2.54 (1.66–3.87)	2.50 (1.64–3.82)	2.44 (1.52–3.90)	
P value	<0.001	<0.001	<0.001		<0.001	<0.001	<0.001	
Stage 5 chronic kidney disease	6.81 (5.47–8.47)	6.88 (5.46–8.67)	7.10 (5.55–9.09)		8.98 (5.77–13.96)	8.36 (5.30–13.17)	9.82 (5.96–16.16)	
P value	<0.001	<0.001	<0.001		<0.001	<0.001	<0.001	

* Model C was adjusted for time-updated age, sex, time-updated duration of diabetes, birth in Sweden or elsewhere, educational level, and status with respect to a history of conditions other than diabetes at baseline.

† Model D includes the adjustments in model C and was also adjusted for time-updated mean systolic blood pressure, time-updated mean body-mass index, and time-updated smoking status.

‡ Model E includes the adjustments in model C and was also adjusted for time-updated mean level of high-density lipoprotein cholesterol, time-updated mean level of low-density lipoprotein cholesterol, and time-updated lipid-lowering medication.

§ Model F includes the adjustments in model C and was also adjusted for time-updated normoalbuminuria, microalbuminuria, macroalbuminuria, and stage 5 chronic kidney disease.

tor of the relationship between poor glycemic control and adverse events (since hyperglycemia is a prerequisite for the development of diabetic nephropathy) rather than as a risk factor that is independent of the glycated hemoglobin level.[32] Diabetic ketoacidosis and hypoglycemia were common causes of death in younger persons (accounting for 31.4% of deaths in adults younger than 30 years of age) but were less frequent causes in older persons. Furthermore, the higher excess risk of death from cardiovascular disease among women than among men was also observed in a large cohort followed until the year 2000 in the United Kingdom.[5]

The present study has several strengths. All patients in Sweden with type 1 diabetes who received the diagnosis before they reached 30 years of age were, in principle, included. At least one measurement of the glycated hemoglobin level was available for all patients, as was information on educational level, coexisting conditions, and other risk factors.

The present study has several limitations. First, the history of glycated hemoglobin levels was not complete for many patients; thus, we could not conclude that patients who have consistently good glycemic control from the time of diagnosis onward still have an excess risk of death. Second, in order to accurately represent the general population, we did not expressly exclude patients with type 2 diabetes from the control group. Although the prevalence of type 1 diabetes in Sweden is high,[33] the prevalence of type 2 diabetes is only approximately 4%.[15,33] Thus, excluding patients with type 2 diabetes would probably have resulted in only marginal increases in the estimated hazard ratios. Third, although the associations between glycated hemoglobin level and risk of death are robust, the observational nature of the study does not allow us to definitively exclude the possibility of residual confounding. Fourth, we could have underestimated diabetic coma as a cause of death, since the majority of unspecified diabetes-related deaths occurred outside the hospital. Hypoglycemia is difficult to document in real-life studies, since patients with hypoglycemic symptoms do not always measure glucose levels. Therefore, data on hypoglycemia were incomplete. Finally, the two 7-year study periods may be of insufficient duration to detect significant temporal changes in mortality.

In conclusion, our data show that among patients with type 1 diabetes who have a glycated hemoglobin level of 6.9% or lower, the risks of death from any cause and from cardiovascular causes are twice as high as those in the general population and that the risks are several times as high among patients with poor glycemic control.

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