Severe Hypoglycemia and Mortality After Cardiovascular Events for Type 1 Diabetic Patients in Sweden

Tom W.C. Lung,[1] Dennis Petrie,[1] William H. Herman,[2] Andrew J. Palmer,[3] Ann-Marie Svensson,[4] Bjorn Eliasson,[4] and Philip M. Clarke[1]

Diabetes Care 2014;37:2974–2981 | DOI: 10.2337/dc14-0405

OBJECTIVE

To examine whether previous severe hypoglycemic events were associated with the risk of all-cause mortality after major cardiovascular events (myocardial infarction [MI] or stroke) in patients with type 1 diabetes.

RESEARCH DESIGN AND METHODS

This study is based on data from the Swedish National Diabetes Register linked to patient-level hospital records, prescription data, and death records. We selected patients with type 1 diabetes who visited a clinic during 2002–2010 and experienced a major cardiovascular complication after their clinic visit. We estimated a two-part model for all-cause mortality after a major cardiovascular event: logistic regression for death within the first month and a Cox proportional hazards model conditional on 1-month survival. At age 60 years, 5-year cumulative mortality risk was estimated from the models for patients with and without prior diabetes complications.

RESULTS

A total of 1,839 patients experienced major cardiovascular events, of whom 403 had previously experienced severe hypoglycemic events and 703 died within our study period. A prior hypoglycemic event was associated with a significant increase in mortality after a cardiovascular event, with hazard ratios estimated at 1.79 (95% CI 1.37–2.35) within the first month and 1.25 (95% CI 1.02–1.53) after 1 month. Patients with prior hypoglycemia had an estimated 5-year cumulative mortality risk of 52.4% (95% CI 45.3–59.5) and 39.8% (95% CI 33.4–46.3) for MI and stroke, respectively.

CONCLUSIONS

We have found evidence that patients with type 1 diabetes in Sweden with prior severe hypoglycemic events have increased risk of mortality after a cardiovascular event.

This study examines factors associated with all-cause mortality after cardiovascular complications (myocardial infarction [MI] and stroke) in patients with type 1 diabetes. In particular, we aim to determine whether a previous history of severe hypoglycemia is associated with increased mortality after a cardiovascular event in type 1 diabetic patients.

Hypoglycemia is the most common and dangerous acute complication of type 1 diabetes and can be life threatening if not promptly treated (1). The average

[1]Centre for Health Policy, School of Population and Global Health, University of Melbourne, Melbourne, Australia
[2]Department of Internal Medicine, University of Michigan, Ann Arbor, MI
[3]Menzies Research Institute Tasmania, University of Tasmania, Hobart, Australia
[4]Institute of Medicine, Sahlgrenska University Hospital, University of Gothenburg, Gothenburg, Sweden

Corresponding author: Tom W.C. Lung, tom.lung@unimelb.edu.au.

Received 13 February 2014 and accepted 7 July 2014.

This article contains Supplementary Data online at http://care.diabetesjournals.org/lookup/suppl/doi:10.2337/dc14-0405/-/DC1.

A slide set summarizing this article is available online.

individual with type 1 diabetes experiences about two episodes of symptomatic hypoglycemia per week, with an annual prevalence of 30–40% for hypoglycemic episodes requiring assistance for recovery (2). We define severe hypoglycemia to be an episode of hypoglycemia that requires hospitalization in this study.

The evidence surrounding the impact that severe hypoglycemia has on cardiovascular events and mortality in patients with diabetes is limited. In studies of type 2 diabetes, two trials found higher mortality in patients with severe hypoglycemia than those without hypoglycemia (3,4), while the Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) trial showed that severe hypoglycemia was associated with a significant increase in the adjusted risks of major micro- and macrovascular events, cardiovascular death, and all-cause death (5). Patients with type 1 diabetes are more susceptible to hypoglycemia than those with type 2 diabetes, and therefore it is potentially of greater relevance if severe hypoglycemia is associated with mortality (6). In type 1 diabetes, the Diabetes Control and Complications Trial (DCCT) compared the effects of standard blood glucose control versus intensive control on the complications of diabetes (7). The DCCT demonstrated a threefold increased risk for severe hypoglycemia in the intensive treatment group compared with the conventional group (6). The low incidence of cardiovascular disease (CVD) events in the DCCT meant there was a lack of statistical power to investigate whether severe hypoglycemia was associated with mortality after major cardiovascular events (6); therefore, there is a need to explore this issue elsewhere.

We derive equations for all-cause mortality risk after a major cardiovascular complication in type 1 diabetes and use these to estimate 5-year cumulative mortality risk for people with particular characteristics. These estimates quantify how the impact of prior severe hypoglycemic events on mortality after a major cardiovascular complication compares with the impact of important clinical risk factors, such as, BMI, HbA_{1c}, and other comorbidities.

RESEARCH DESIGN AND METHODS

Data

This study uses a large linked data set comprising health records from the Swedish National Diabetes Register (NDR), which were linked to administrative records on hospitalization, prescriptions, and national death records. Initiated in 1996 as a tool for quality assurance in diabetes care, reporting to the NDR is not mandatory, but all hospital diabetes outpatient clinics and primary health care centers are encouraged to do so. All included patients have agreed to be registered before inclusion. Today, 100% of hospital outpatient clinics and 95% of primary health care centers participate. In Sweden, almost all patients with type 1 diabetes receive their treatment at hospital outpatient clinics, with an estimated 90% of adult patients with type 1 diabetes reporting to the NDR in 2011. Demographic data, diabetes duration, and treatment modalities, as well as various risk factors and diabetes complications, are recorded (7).

This study is based on data from four sources: *1*) risk factor data from the Swedish NDR (1 January 1987–31 December 2010), *2*) hospital records of inpatient episodes from the National Inpatients Register (IPR) (1 January 1987–31 December 2011), *3*) death records (1 January 2002–31 December 2012), and *4*) prescription data records (1 July 2005–31 December 2011).

The data were confidentially linked at the patient level by the NDR. The regional ethics committee at the University of Gothenburg approved the study. Inpatient episodes refer to all recorded admissions at Swedish hospitals for patients with type 1 diabetes registered with the NDR. The IPR was established in 1964, and diagnoses are coded according to the Swedish ICD system. A study comparing registered diagnoses in the IPR with information in medical records found positive predictive values of IPR diagnoses were 85–95% for most diagnoses (8). In terms of NDR coverage, a recent study found that 91% of those aged 18–34 years and with type 1 diabetes in the Prescribed Drug Register could be matched with those in the NDR for 2007–2009 (9).

The outcome of the study was all-cause mortality after a major cardiovascular complication (MI or stroke). Our sample for analysis included patients with type 1 diabetes who visited a clinic after 2002 and experienced a major cardiovascular complication after this clinic visit. Only the next major cardiovascular complication recorded after their clinic visit was included. This may or may not have been the individuals' first major CVD event but was the next event that occurred after they entered the observation period. We define type 1 diabetes as diabetes diagnosed under the age of 30 years, being reported as being treated with insulin only at some clinic visit, and when alive, having had at least one prescription for insulin filled per year between 2006 and 2010 (the full calendar years for which prescription data were available), and not having filled a prescription for metformin at any point between July 2005 and December 2010 (under the assumption that metformin users were more likely to be type 2 diabetes patients).

A severe hypoglycemic event was defined as one that required hospitalization, identified through ICD hospitalization codes recorded in the Supplementary Data. Type 2 diabetes ICD codes were also included, as it was assumed these were reporting errors in the hospital admission codes and that these patients were actually patients with type 1 diabetes based on their NDR identification. Only the first and second hospitalization codes were used to identify events. Potential severe hypoglycemia events were further examined to exclude those where other conditions (i.e., insulinoma, severe liver disease, encephalitis, meningitis, and sepsis) were reported in the primary or secondary hospitalization diagnosis codes and may have caused the event. A list of the ICD codes that warranted exclusion is provided in the Supplementary Data. MI and stroke events that were recorded on the same day were included as MIs, given the elevated mortality risk in the first month post event for MIs compared with strokes.

Other major complications were defined from hospital and death records using ICD-9 and ICD-10 codes for the following: fatal and nonfatal MI, fatal or nonfatal stroke, heart failure, amputation, peripheral vascular disease (PVD), hyperglycemia, end-stage renal disease (ESRD), ischemic heart disease (IHD) and unstable angina, atrial fibrillation (AF), percutaneous coronary intervention (PCI), coronary artery bypass graft (CABG), and hypoglycemia. Full lists of the ICD-9 and ICD-10 codes are recorded in the Supplementary Data.

In addition to prior hospitalizations for comorbidities, additional risk factors at time of CVD event were considered. The last available measure prior to their CVD event was used in our analysis. Physicians and nurses in hospital clinics report to the NDR measures of HbA_{1c}, blood pressure, BMI, LDL cholesterol, HDL cholesterol, and total cholesterol at least annually via the Internet or via direct transfer of data from medical record databases. All HbA_{1c} values were converted to National Glycohemoglobin Standardization Program standard levels (10). In addition to the current HbA_{1c}, a weighted average HbA_{1c} variable was also included to capture previous control of HbA_{1c} (metabolic memory) (11). Estimated glomerular filtration rate was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (12). Formulae are provided in the Supplementary Data. Microalbuminuria was defined as urinary albumin excretion $>$20 μg/min but $<$200 μg/min and macroalbuminuria as $>$200 μg/min in two out of three consecutive tests. Patients with macroalbuminuria were recorded as also having microalbuminuria.

Statistical Analysis

All analyses were undertaken using STATA (Stata Statistical Software, release 12.1; StataCorp, College Station, TX). Summary statistics were calculated at baseline (time at major CVD event) for patients and stratified by CVD event (MI or stroke) and prior hypoglycemic event. The Mann-Whitney test was used to test for statistical differences (at the 5% level) between patients with and without prior severe hypoglycemic events. Kaplan-Meier survival curves were estimated for patients stratified by prior severe hypoglycemic events. We conducted a log-rank test for the equality of survivor functions for the Kaplan-Meier survival curves.

Time at risk was calculated from the time of the patients' complication to either their date of death or censoring by reaching the end of the study period (31 December 2012). As MI and stroke and the impact of different risk factors were associated with changing mortality risk over time (13), a two-part model was used that included a logistic regression for survival within the first month, followed by a Cox model conditional on surviving 1 month.

Explanatory variables included in both models were type of complication (MI or stroke), age at complication, duration of diabetes, sex, smoking status, HbA_{1c}, BMI, systolic blood pressure, diastolic blood pressure, chronic kidney disease status based on estimated glomerular filtration rate, microalbuminuria and macroalbuminuria status, HDL, LDL, total–to–HDL cholesterol ratio, triglycerides, lipid medication status, clinic visits within the year prior to the CVD event, and prior hospitalization events: hypoglycemia, hyperglycemia, MI, stroke, heart failure, AF, amputation, PVD, ESRD, IHD/unstable angina, PCI, and CABG.

The last known value for each clinical risk factor, prior to the cardiovascular complication, was used for analysis. Patients with missing values prior to their major CVD complication had their values imputed using chained equations (14,15), with five imputed data sets generated.

Initially, all explanatory variables were included and excluded if the variable was not statistically significant at a 5% level ($P < 0.05$) via stepwise backward elimination. We tested the proportional hazards assumption in the Cox model and did not find evidence to reject proportional hazards. A univariate analysis was also conducted using only prior hypoglycemic event in both logistic and Cox models to explore whether the impact of a prior hypoglycemic event may in part act through mediating other factors that impact on mortality.

For both logistic and Cox models, we tested the heterogeneity of the impact of a prior severe hypoglycemic event on all-cause mortality. One by one, we included and tested an interaction variable of severe hypoglycemia with *1*) patients who had a stroke versus an MI, *2*) patients experiencing their first CVD event versus patients who had prior CVD events, and *3*) patients who experienced a hypoglycemic event within 5 years of the CVD event versus patients who experienced a hypoglycemic event $>$5 years before their CVD event.

In order to explore possible mechanisms through which severe hypoglycemia events might increase all-cause mortality, we also used the same sample to conduct another multivariate analysis (Cox model), which examined whether risk factors, in particular a history of severe hypoglycemia, predicted time to subsequent CVD events.

The logistic and Cox models were used to estimate the cumulative 5-year mortality risk after a cardiovascular event by using the baseline hazard from our sample. To calculate the first year of survival after a CVD event, we used the logistic model to calculate the probability of death for the first month after a CVD event and used the Cox model to calculate the probability of death for the remaining 11 months. Mortality each year thereafter was calculated using the Cox model only.

Our reference patient had mean baseline characteristics at the time of CVD event (and no prior complications). We estimated the impact on 5-year mortality for changes in important factors while holding all other things equal in a few hypothetical scenarios: patients with no complications, patients with prior hospitalization for hypoglycemia, patients with prior hospitalization for stroke, patients with prior hospitalization for heart failure, patients with macroalbuminuria, and patients with CKD stage 3 or above.

For determination of 95% CIs, 1,000 bootstrapped samples were used. Comparable estimates of mortality risk from the general population were obtained from Swedish life tables (16) and multiplied with the relative risk of mortality from a large type 1 diabetes population (17) to put any increased mortality after a cardiovascular event into perspective.

RESULTS

Summary Statistics

We identified 27,087 patients who had an NDR clinic visit between 1 January 2002 and 31 December 2010. We excluded 168 patients (0.62%), as they did not have any records of an insulin prescription for all years of the prescription data (2005–2011) and had not been recorded as dead. Of 7,509 (0.51%) patients, 38 had possible episodes of severe hypoglycemia, which were excluded, as they may have been caused by other conditions. There were 1,839 patients with an NDR clinic visit and a subsequent cardiovascular complication (MI or stroke) between 1 January 2002 and 31 December 2011. Of these patients, 16 (0.87%) had at least one hospital code that referred to them as having type 2

diabetes, of whom 10 (62.5%) had a prior hypoglycemic event, while 6 (37.5%) did not.

Baseline characteristics are summarized in Table 1, along with the percentage missing for each variable. A total of 1,224 patients had an MI (of whom 24 had a stroke on the same day), and 615 had a stroke as their first recorded major cardiovascular complication after their NDR clinic visit; 935 (50.8%) MI events and 435 (23.7%) stroke events were recorded as their first CVD event. There were 359 deaths within the first month of the major cardiovascular event. We used the hospitalization database (from 1987 to 2010) to determine that 403 (21.9%) patients were recorded as having had prior hospitalizations for hypoglycemia before their CVD event (2002–2010), of whom 164 (40.7%) experienced a hospitalization for hypoglycemia within 5 years of their major CVD event.

After testing for significant differences using the Mann-Whitney test, patients with previous hypoglycemic hospitalizations were ~1.5 years older, had 2 additional years of diabetes duration, slightly lower BMI, and proportionately higher incidence of prior hospitalization events (stroke, hyperglycemia, PVD, amputation, and ESRD).

The Kaplan-Meier graphs in Fig. 1 depict a possible dose-response relationship between survival after a CVD event and previous episodes of severe hypoglycemia with those having had two or more events having higher mortality than those having had one prior event and those having had one prior event having higher mortality than those who have had no prior events. The log-rank test for Fig. 1 returned a χ^2 value of 39.22 ($P < 0.01$) for mortality after a CVD event and previous episodes of severe hypoglycemia, which rejects the null hypothesis that the two curves are the same at the 1% significance level. Additional Kaplan-Meier graphs in the Supplementary Data show survival by CVD event type and that the possible dose-response relationship still exists when the sample is stratified by age and sex.

Table 2 presents the significant variables and their estimated hazard ratios (HRs) for the logistic and Cox models when using backward stepwise regression ($P < 0.05$) and the univariate analysis

Table 1—Baseline (at time of CVD event) patient characteristics stratified by CVD (MI and stroke) and prior hypoglycemic events in our sample

	Missing in overall (%)	Overall	MI	Stroke	No prior hypoglycemic event	Prior hypoglycemic event
n in sample		1,839	1,224	615	1,436	403
Age at event (years)*	0	59.46 (11.76)	60.27 (11.58)	57.84 (11.95)	59.13 (11.49)	60.64 (12.61)
Diabetes duration (years)*	0	44.25 (12.45)	45.24 (12.22)	42.30 (12.68)	43.86 (12.38)	45.68 (12.62)
HbA_{1c} (%)	0.49	8.27 (1.27)	8.26 (1.26)	8.28 (1.28)	8.28 (1.24)	8.23 (1.36)
HbA_{1c} (mmol/mol)	0.49	66.89 (13.87)	66.81 (13.79)	67.06 (14.03)	67.00 (13.56)	66.50 (14.89)
BMI (kg/m^2)*	4.35	25.72 (4.31)	25.93 (4.32)	25.32 (4.28)	25.97 (4.30)	24.85 (4.23)
Total–to–HDL cholesterol ratio	14.14	3.39 (1.22)	3.44 (1.26)	3.29 (1.12)	3.41 (1.25)	3.32 (1.12)
HDL (mmol/L)	13.97	1.57 (0.50)	1.55 (0.50)	1.61 (0.50)	1.57 (0.50)	1.58 (0.50)
LDL (mmol/L)	13.87	2.72 (0.92)	2.73 (0.91)	2.71 (0.94)	2.73 (0.93)	2.70 (0.91)
Triglycerides (mmol/L)	12.29	1.41 (0.90)	1.43 (0.96)	1.35 (0.78)	1.41 (0.91)	1.39 (0.89)
Systolic blood pressure (mmHg)	0.76	139.07 (19.99)	138.32 (19.75)	140.57 (20.37)	139.44 (19.68)	137.77 (21.01)
Diastolic blood pressure (mmHg)	0.76	72.60 (10.57)	71.47 (10.43)	74.84 (10.48)	72.63 (10.51)	72.47 (10.78)
eGFR ($mL/min/1.73\ m^2$)	7.18	65.97 (29.69)	64.75 (29.44)	68.43 (30.06)	66.17 (29.29)	65.26 (31.08)
Sex (male = 1), *n* (%)*	0	1,015 (55)	644 (53)	371 (60)	775 (54)	240 (60)
Lipid medication, *n* (%)	8.21	1,080 (58)	745 (61)	335 (55)	852 (54)	228 (63)
Smoking, *n* (%)	1.25	275 (15)	182 (15)	93 (15)	217 (15)	58 (15)
Microalbuminuria, *n* (%)	0	944 (51)	630 (51)	314 (51)	732 (51)	212 (53)
Macroalbuminuria, *n* (%)	0	526 (29)	345 (28)	181 (29)	411 (29)	115 (29)
Prior MI, *n* (%)	0	289 (16)	230 (19)	59 (10)	218 (15)	71 (18)
Prior stroke, *n* (%)*	0	180 (10)	94 (8)	86 (14)	128 (9)	52 (13)
Prior heart failure, *n* (%)	0	227 (12)	177 (14)	50 (8)	176 (12)	51 (13)
Prior hyperglycemia, *n* (%)*	0	264 (14)	157 (13)	107 (17)	183 (13)	81 (20)
Prior PVD, *n* (%)*	0	496 (27)	344 (28)	152 (25)	358 (25)	138 (34)
Prior amputation, *n* (%)*	0	109 (6)	71 (6)	38 (6)	74 (5)	35 (9)
Prior ESRD, *n* (%)*	0	176 (10)	106 (9)	70 (11)	122 (8)	54 (13)
Prior unstable angina/IHD, *n* (%)	0	629 (34)	478 (39)	151 (25)	481 (33)	148 (37)
Prior AF, *n* (%)	0	75 (4)	53 (4)	22 (4)	55 (4)	20 (5)
Prior PCI, *n* (%)	0	164 (9)	131 (11)	33 (5)	126 (9)	38 (9)
Prior CABG, *n* (%)	0	280 (15)	210 (17)	70 (11)	215 (15)	65 (16)

Data are means (SD) unless otherwise indicated. *With use of the Mann-Whitney test, variables are statistically significant at the 5% level for differences between patients with no prior hypoglycemic event versus patients with a prior hypoglycemic event.

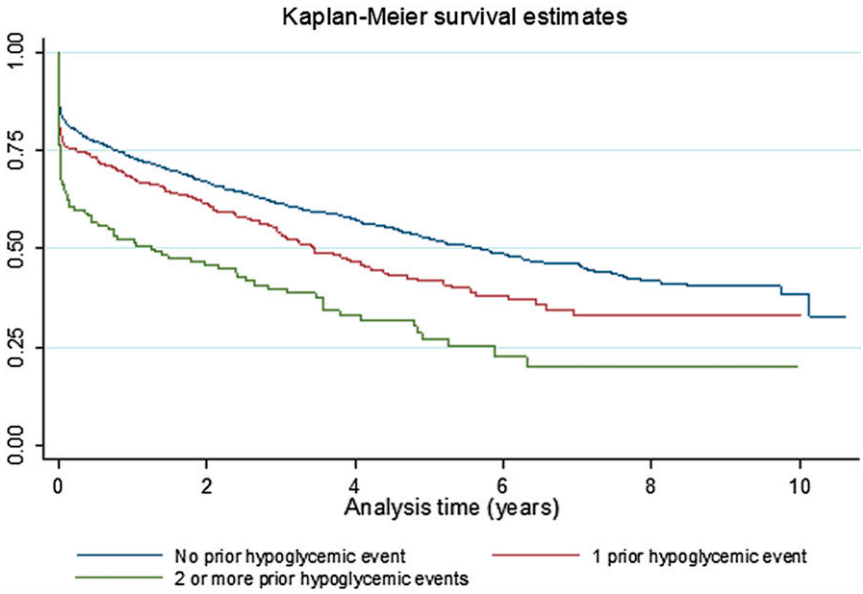

Figure 1—Survival after a CVD event, stratified by prior hypoglycemic events.

with only prior hypoglycemic events. Patients who had prior hypoglycemic events had an estimated HR for mortality of 1.79 (95% CI 1.37–2.35) in the first 28 days after a CVD event and an estimated HR of 1.25 (95% CI 1.02–1.53) of mortality after 28 days post CVD event in the backward regression model. The univariate analysis showed a similar result compared with the backward regression model, with prior hypoglycemic events having an estimated HR for mortality of 1.79 (95% CI 1.38–2.32) and 1.35 (95% CI 1.11–1.65) in the logistic and Cox regressions, respectively. Even when all explanatory factors were included in the models (see Supplementary Data), the mortality increase associated with a prior severe hypoglycemic event was still significant, and the *P* values and SE are similar when compared with the backward stepwise regression. Similarly, when explanatory factors were included individually, the mortality increase associated with a prior severe hypoglycemic event was also still significant.

When testing for possible heterogeneity of the relative impact of having had a prior severe hypoglycemic event for patients who had a stroke versus an MI for both logistic and Cox models, the null hypothesis of no difference could not be rejected at the 5% level (P = 0.853 logistic, P = 0.443 Cox). Similarly, we found no differences between patients with their first CVD event compared with subsequent CVD events (P = 0.842 logistic, P = 0.409 Cox) and patients who experienced a prior hypoglycemic event within 5 years of their CVD event compared with >5 years of their CVD event (P = 0.432 logistic, P = 0.346 Cox). The results of the Cox model, which examined whether the increase in all-cause mortality associated with prior severe hypoglycemia may have been driven by an increase in subsequent CVD events, are included in the Supplementary Data. Of those patients who survived their CVD event, 521 had a subsequent CVD event, and there was no evidence of a significant relationship between a history of severe hypoglycemia and subsequent CVD event (HR 0.95 [95% CI 0.72–1.25]).

The estimated 5-year cumulative mortality risk after a CVD event at age 60

Table 2—Univariate analysis and manual backward stepwise logistic regression for death within 28 days from event using multiple imputed data sets (n = 1,839) and a Cox model for time to death after 28 days since first major cardiovascular event since the first clinic visit after 2002 (n = 1,613), conditional on 28-day survival (with imputation)

	Logistic regression: univariate analysis			Cox regression: univariate analysis	
Variable	Odds ratio (95% CI)	*P*	Variable	HR (95% CI)	*P*
Prior hypoglycemia	1.79 (1.38–2.32)	<0.001	Prior hypoglycemia	1.35 (1.11–1.65)	0.003
	Manual backward stepwise regression			Manual backward stepwise regression	
Variable	Odds ratio (95% CI)	*P*	Variable	HR (95% CI)	*P*
Prior hypoglycemia	1.79 (1.37–2.35)	<0.001	Prior hypoglycemia	1.25 (1.02–1.53)	0.033
Stroke event*	0.44 (0.33–0.59)	<0.001	Log weighted HbA_{1c} (%)	2.57 (1.29–5.09)	<0.001
Age at event	1.03 (1.02–1.04)	<0.001	Age at event	1.06 (1.05–1.07)	<0.001
Systolic blood pressure (mmHg)	0.99 (0.98–1.00)	0.001	BMI (kg/m^2)	0.98 (0.96–1.00)	0.041
Lipid medication	0.63 (0.49–0.82)	<0.001	Triglycerides (mmol/L)	1.12 (1.02–1.23)	0.019
Macroalbuminuria	1.90 (1.45–2.48)	<0.001	Macroalbuminuria	1.48 (1.20–1.83)	<0.001
Prior heart failure	1.91 (1.38–2.64)	<0.001	Prior heart failure	1.48 (1.18–1.86)	<0.001
Clinic visits within 1 year	0.63 (0.48–0.81)	<0.001	CKD stage 3 and above	1.87 (1.52–2.29)	<0.001
Constant**	0.31 (0.11–0.91)	0.033	Year of event	0.94 (0.91–0.98)	<0.001
			Prior stroke	1.32 (1.04–1.67)	0.023
			Prior PVD	1.47 (1.23–1.76)	<0.001
			Prior ESRD	1.39 (1.03–1.88)	0.032

*Complication reference group is MI. **Constant value is not an odds ratio.

years is presented in Fig. 2. The 5-year cumulative estimated mortality risk for those without complications after MI and stroke were 40.1% (95% CI 35.2–45.1) and 30.4% (95% CI 26.3–34.6), respectively. Patients with prior heart failure were at the highest estimated 5-year cumulative mortality risk, with those who suffered an MI and stroke having a 56.0% (95% CI 47.5–64.5) and 44.0% (95% CI 35.8–52.2) 5-year cumulative mortality risk, respectively. Patients who had a prior severe hypoglycemic event and suffered an MI had an estimated 5-year cumulative mortality risk at age 60 years of 52.4% (95% CI 45.3–59.5), and those who suffered a stroke had a 5-year cumulative mortality risk of 39.8% (95% CI 33.4–46.3). Patients at age 60 years who suffer a major CVD complication have over twofold risk of 5-year mortality compared with the general type 1 diabetic Swedish population, who had an estimated 5-year mortality risk of 13.8% (95% CI 12.0–16.1).

CONCLUSIONS

This is the first study that estimated risk equations for survival after major cardiovascular complications (MI and stroke) in patients with type 1 diabetes. We found evidence that prior severe hypoglycemia is associated with reduced survival after a major CVD event but no evidence that prior severe hypoglycemia is associated with an increased risk of a subsequent CVD event.

Compared with the general type 1 diabetic Swedish population, a major CVD complication increased 5-year mortality risk at age 60 years by >25% and 15% in patients with an MI and stroke, respectively. Patients with a history of a hypoglycemic event had an even higher mortality after a major CVD event, with approximately an additional 10% being dead at the 5-year mark. This risk was comparable with that in those with late-stage kidney disease. This information is useful in determining the prognosis of patients after a major cardiovascular event and highlights the need to include this as a risk factor in simulation models (18) that are used to improve decision making (19).

A strength of this study was the use of the NDR data, a large diabetes register that has been linked to hospital, prescription, and death data. The NDR includes a significant proportion of the type 1 diabetic population in Sweden and thus contains many more events compared with other large type 1 diabetes trials. The DCCT/ Epidemiology of Diabetes Interventions and Complications (EDIC) study identified 144 CVD events during the mean 17 years of follow-up in the trial (11), while the EURODIAB Prospective Complications Study identified 176 patients with incident CVD (20) during 7 years of follow-up. In comparison, the NDR identified 1,839 CVD events over a maximum of 10 years of follow-up. Another key strength of the data is the wide range of prospectively collected clinical risk factors, which has enabled us to identify important risk factors and allows estimates of survival durations to be refined.

A recent systematic review of cardiac implications of hypoglycemia in patients with diabetes identified only one study of type 2 diabetic patients (ADVANCE) that could determine a clear association between prior severe hypoglycemia and increased risk of death from any cause (HR 2.69 [95% CI 1.97–3.67]) (21). We have estimated a lower association in type 1 diabetes, with an HR of 1.79 (95% CI 1.37–2.35) in the first 28 days after a CVD event and an HR of 1.25 (95% CI 1.02–1.53) after 28 days post CVD event. Our other analysis suggests that having a prior hypoglycemic event

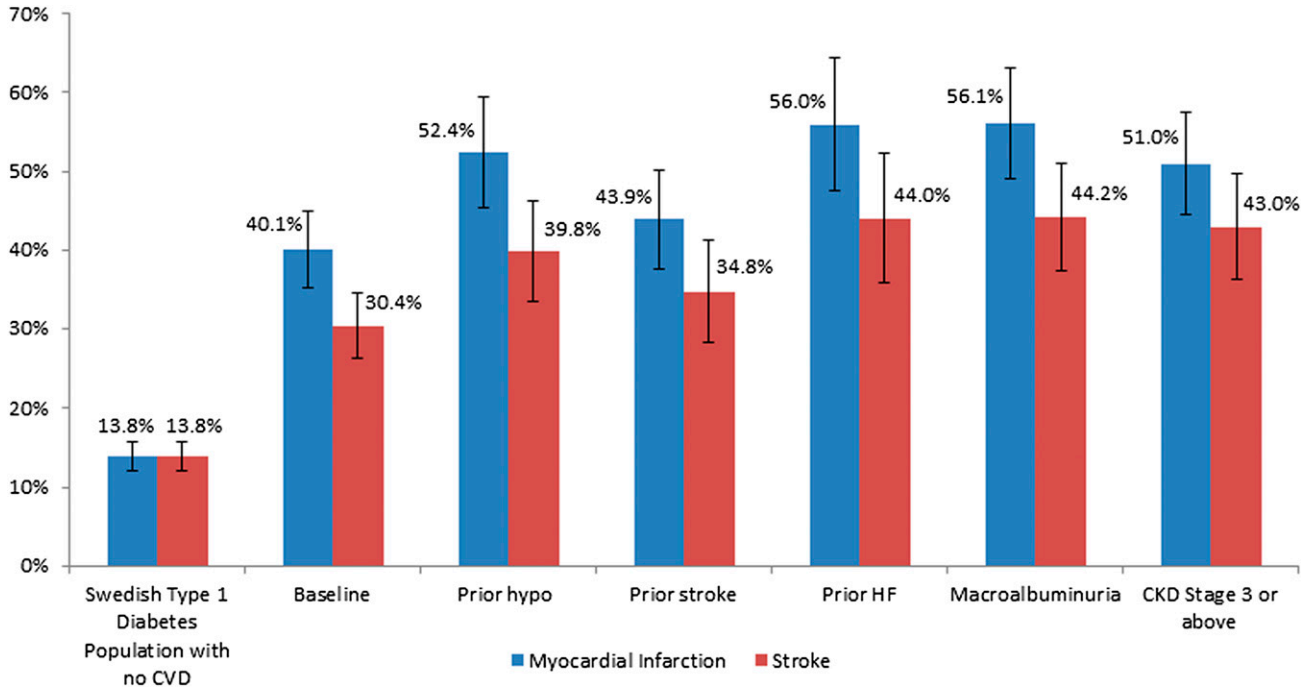

Figure 2—Estimated 5-year mortality risk after CVD events for 60-year-old patients with particular characteristics. Combined mortality from logistic and Cox regressions for baseline patient (without prior diabetes complications) and patients having had a prior hypoglycemic (hypo) event, a prior stroke event, a prior heart failure (HF) event, macroalbuminuria, CKD stage 3 or above, and the Swedish type 1 diabetic population for patients experiencing *1*) an MI at age 60 years or *2*) a stroke at age 60 years.

does not impact on having a subsequent CVD event. We can infer from this that it is more likely that a history of severe hypoglycemia modifies the response to a CVD event rather than increasing the likelihood of additional CVD events.

This is the first study that has found some evidence of a dose-response relationship, where patients who experienced two or more severe hypoglycemic events had higher mortality after a cardiovascular event compared with those who experienced one severe hypoglycemic event. A lack of statistical power prevented us from investigating this further when we tried to stratify by number of prior severe hypoglycemic events in our regression models. There was no evidence of a dose-response relationship between repeated episodes of severe hypoglycemia and vascular outcomes or death in previous type 2 diabetes studies (5). Our definition of a severe hypoglycemic event as a hospitalization was more restrictive than that used in the ADVANCE study (5), where severe hypoglycemia was self-reported and defined as hypoglycemia requiring help from another person.

A number of limitations of this study should be acknowledged. The models involve use of risk factor information that was collected in NDR clinics prior to the occurrence of the patient's CVD complication. Participation in the NDR is not compulsory and requires patients to make at least one clinic visit; hence, our analysis will tend to have excluded some of the older and sicker patients. We also analyzed the first cardiovascular complication after 2002—not necessarily the first cardiovascular complication of a person's lifetime—though we found no significant difference between the impacts of severe hypoglycemia for the first versus secondary events.

The NDR involves tracking of patients using their personal identification number; however, there are no follow-up data for patients who emigrate or information that would allow them to be censored, though those alive and without at least one insulin prescription filled per year after 2005 are excluded, which should exclude all those who migrated. As we only have data on severe hypoglycemic events from admitted hospitalizations, we are missing a number of nonadmitted events, which is a limitation from using a large observational data set. In the U.S., only 41% of nearly 14,000 emergency room visits for such events were admitted to hospital (22). An admission to hospital for severe hypoglycemic could potentially be an indicator of behavioral factors (such as poor nutrition) or health status, and thus their health outcomes may be worse than other patients with nonhospitalized hypoglycemic events. The equations also do not include any measure of socioeconomic status such as household income, which is a good predictor of mortality risk (23). Finally, since mortality may be influenced by behavioral, health care system, and genetic factors that are not captured in our models, these results may not be directly generalizable to other populations without suitable calibration of the absolute risk.

This study could not account for hypoglycemia-associated mechanisms such as release of glucagon and catecholamines (epinephrine), enhanced platelet aggregation, cardiac autonomic neuropathy, or QTc interval changes, which lead to life-threatening cardiac arrhythmias that could explain the increased risk of mortality after a major CVD event in type 1 diabetic patients with histories of severe hypoglycemia (21).

In summary, we have estimated equations for predicting mortality after a major CVD event in type 1 diabetic patients. The equations are based on age, sex, and commonly collected clinical information and thereby provide further stratification of a patient's prognosis after the occurrences of a life-threatening CVD event. This study highlights the prognostic importance of prior history of severe hypoglycemia on survival after a CVD event. More studies are required to determine whether prior severe hypoglycemia is itself a risk factor for mortality after a CVD event or a marker for another factor, such as cardiac autonomic neuropathy, which may be associated with elevated mortality (24–26).

Funding. The Swedish Association of Local Authorities and Regions funds the NDR. The study was supported in part by a National Health and Medical Research Council (NHMRC) Project Grant (1028335), and T.W.C.L. was partially funded from an NHMRC Capacity Building grant (571372).

Duality of Interest. No potential conflicts of interest relevant to this article were reported.

Author Contributions. T.W.C.L. wrote the manuscript and researched data. D.P. researched data and reviewed and edited the manuscript. A.J.P., W.H.H., A.-M.S., B.E., and P.M.C. contributed to discussion and reviewed and edited the manuscript. T.W.C.L. and D.P. are the guarantors of this work and, as such, had full access to all the data in the study and take responsibility for the integrity of the data and the accuracy of the data analysis.

References

1. Low blood sugar: definitions and symptoms [article online], 2013. Available from http://jdrf.org/life-with-t1d/type-1-diabetes-information/control-and-management/low-blood-sugar/. Accessed 22 October 2013
2. Frier BM. The incidence and impact of hypoglycemia in type 1 and type 2 diabetes. International Diabetes Monitor 2009;21:210
3. Gerstein HC, Miller ME, Byington RP, et al.; Action to Control Cardiovascular Risk in Diabetes Study Group. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008;358:2545–2559
4. Bonds DE, Miller ME, Bergenstal RM, et al. The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study. BMJ 2010;340:b4909
5. Zoungas S, Patel A, Chalmers J, et al.; ADVANCE Collaborative Group. Severe hypoglycemia and risks of vascular events and death. N Engl J Med 2010;363:1410–1418
6. Desouza CV, Bolli GB, Fonseca V. Hypoglycemia, diabetes, and cardiovascular events. Diabetes Care 2010;33:1389–1394
7. Gudbjörnsdottir S, Cederholm J, Nilsson PM, Eliasson B; Steering Committee of the Swedish National Diabetes Register. The National Diabetes Register in Sweden: an implementation of the St. Vincent Declaration for Quality Improvement in Diabetes Care. Diabetes Care 2003;26:1270–1276
8. Ludvigsson JF, Andersson E, Ekbom A, et al. External review and validation of the Swedish national inpatient register. BMC Public Health 2011;11:450
9. Rawshani A, Landin-Olsson M, Svensson AM, et al. The incidence of diabetes among 0-34 year olds in Sweden: new data and better methods. Diabetologia 2014;57:1375–1381
10. Hoelzel W, Weykamp C, Jeppsson JO, et al.; IFCC Working Group on HbA1c Standardization. IFCC reference system for measurement of hemoglobin A1c in human blood and the national standardization schemes in the United States, Japan, and Sweden: a method-comparison study. Clin Chem 2004;50:166–174
11. Nathan DM, Cleary PA, Backlund JY, et al.; Diabetes Control and Complications Trial/Epidemiology of Diabetes Interventions and Complications (DCCT/EDIC) Study Research Group. Intensive diabetes treatment and cardiovascular disease in patients with type 1 diabetes. N Engl J Med 2005;353:2643–2653
12. Levey AS, Stevens LA, Schmid CH, et al.; CKD-EPI (Chronic Kidney Disease Epidemiology Collaboration). A new equation to estimate glomerular filtration rate. Ann Intern Med 2009;150:604–612
13. Hayes AJ, Leal J, Kelman CW, Clarke PM. Risk equations to predict life expectancy of people with type 2 diabetes mellitus following major complications: a study from Western Australia. Diabet Med 2011;28:428–435

14. Carlin JB, Galati JC, Royston P. A new framework for managing and analyzing multiply imputed data in Stata. Stata J 2008;8:49–67
15. White IR, Royston P, Wood AM. Multiple imputation using chained equations: Issues and guidance for practice. Stat Med 2011;30:377–399
16. World Health Organization. Global Health Observatory Data Repository: life expectancy: life tables Sweden [article online], 2013. Available from http://apps.who.int/gho/data/view.main.61600. Accessed 18 November 2013
17. Soedamah-Muthu SS, Fuller JH, Mulnier HE, Raleigh VS, Lawrenson RA, Colhoun HM. All-cause mortality rates in patients with type 1 diabetes mellitus compared with a non-diabetic population from the UK general practice research database, 1992-1999. Diabetologia 2006;49:660–666
18. Lung TW, Clarke PM, Hayes AJ, Stevens RJ, Farmer A. Simulating lifetime outcomes associated with complications for people with type 1 diabetes. Pharmacoeconomics 2013;31:509–518
19. Farmer AJ, Stevens R, Hirst J, et al. Optimal strategies for identifying kidney disease in diabetes: properties of screening tests, progression of renal dysfunction and impact of treatment: systematic review and modelling of progression and cost-effectiveness. Health Technol Assess 2014;18:1–128
20. Gruden G, Barutta F, Chaturvedi N, et al. Severe hypoglycemia and cardiovascular disease incidence in type 1 diabetes: the EURODIAB Prospective Complications Study. Diabetes Care 2012;35:1598–1604
21. Hanefeld M, Duetting E, Bramlage P. Cardiac implications of hypoglycaemia in patients with diabetes - a systematic review. Cardiovasc Diabetol 2013;12:135
22. Budnitz DS, Lovegrove MC, Shehab N, Richards CL. Emergency hospitalizations for adverse drug events in older Americans. N Engl J Med 2011;365:2002–2012
23. Secrest AM, Costacou T, Gutelius B, Miller RG, Songer TJ, Orchard TJ. Association of socioeconomic status with mortality in type 1 diabetes: the Pittsburgh epidemiology of diabetes complications study. Ann Epidemiol 2011;21:367–373
24. Frier BM, Schernthaner G, Heller SR. Hypoglycemia and cardiovascular risks. Diabetes Care 2011;34(Suppl. 2):S132–S137
25. Pop-Busui R. Cardiac autonomic neuropathy in diabetes: a clinical perspective. Diabetes Care 2010;33:434–441
26. Schnell O, Cappuccio F, Genovese S, Standl E, Valensi P, Ceriello A. Type 1 diabetes and cardiovascular disease. Cardiovasc Diabetol 2013;12:156