Severe Hypoglycemia Identifies Vulnerable Patients With Type 2 Diabetes at Risk for Premature Death and All-Site Cancer: The Hong Kong Diabetes Registry

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EPIDEMIOLOGY/HEALTH SERVICES RESEARCH

OBJECTIVE

We examined the associations of clinical profiles in type 2 diabetic patients who developed severe hypoglycemia and their clinical outcomes, including death and all-site cancer.

RESEARCH DESIGN AND METHODS

A consecutive cohort of 8,767 type 2 diabetic patients with and without severe hypoglycemia in the 12 months before enrollment were recruited between 1995 and 2007, with follow-up until 2009. Severe hypoglycemia was defined by ICD-9 codes as hospitalizations resulting from hypoglycemia. Cox proportional hazards regression was used to calculate the hazard ratio (HR) and 95% CIs of clinical factors collected at enrollment for severe hypoglycemia.

RESULTS

In this cohort, mean age was 57.4 (SD 13.2) years and median disease duration of diabetes was 5 (interquartile range [IQR] 1–11) years. During a median follow-up of 6.71 (IQR 3.47–10.38) years, 235 patients had severe hypoglycemia (incidence 3.96 [95% CI 3.45–4.46] per 1,000 patient-years). At enrollment, patients with and without severe hypoglycemia had similar cancer rates. During follow-up, patients with severe hypoglycemia had a higher incidence of all-site cancer (13.4 vs. 6.4%, $P < 0.0001$) and mortality (32.8 vs. 11.2%, $P < 0.0001$) than those without severe hypoglycemia. After adjusting for confounders, old age, low BMI, high glycated hemoglobin, low triglyceride (TG), low LDL cholesterol (LDL-C), albuminuria, and chronic kidney disease were independent predictors for severe hypoglycemia.

CONCLUSIONS

In type 2 diabetes, severe hypoglycemia is associated with advanced age, renal dysfunction, poor glycemic control, and cancer subphenotypes (low BMI, low LDL-C, and low TG).

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Hypoglycemia is an important but often neglected aspect in diabetes management. The increased risk of hypoglycemia during intensive blood glucose lowering in the ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation) (1,2) and ACCORD (Action to Control Cardiovascular Risk in Diabetes) (3) studies have rekindled the subject of a risk–benefit ratio of intensive glycemic control in type 2 diabetes. In both the ADVANCE (2) and the ACCORD (4) studies, intensive blood glucose lowering was associated with an increased risk of severe hypoglycemia. Although in both studies researchers reported high rates of multiple adverse events, including hospitalizations and all-cause death in the 12 months after the incident event of hypoglycemia, detailed analysis did not reveal increased risk of cardiovascular disease (CVD) (2). Furthermore, although intensive treatment was associated with an increased risk of hypoglycemia, in both ACCORD (4) and ADVANCE (2), patients treated intensively tended to have a lower risk of death than those treated conventionally (4). These findings suggest that intensive monitoring in the former group might have prompted corrective actions to reduce adverse clinical outcomes.

On the other hand, hypoglycemia is known to increase the risk of CVD and mortality in diabetic patients (5) due to arrhythmia (5), abnormal hemostasis, and neurohormonal dysregulation, among other conditions. Other host factors such as age, comorbidities, and, notably, chronic kidney disease (CKD) might also influence clinical outcomes (6). In a hospital-based survey, age, CKD, presence of other complications, and institutionalizations were independent predictors for hospitalizations caused by hypoglycemia (7). Against this background, professional bodies and experts have recommended comprehensive assessments and individualizing treatment goals based on patient risk profiles, comorbidities, coping skills, cognitive states, and social support to maximize benefits and minimize harm (8,9).

Although the nature of the association between hypoglycemia and increased risk of death remain elusive, the 1.3- to 2.3-fold increased risk of all-site cancer and related death in type 2 diabetes has gained increasing attention (10). Our group first reported the linear association of glycated hemoglobin (HbA_{1c}) and nonlinear risk associations of lipids and BMI with all-site cancer in type 2 diabetes (11). Through the Hong Kong Diabetes Registry, a prospective cohort with detailed documentation of risk factors and clinical outcomes, we asked the question of whether type 2 diabetic patients with severe hypoglycemia exhibited particular phenotypes that might predict future events, including premature death and all-site cancer.

RESEARCH DESIGN AND METHODS

Subjects

The methodology of the Hong Kong Diabetes Registry, established as a quality improvement program, has been previously described (11,12). Briefly, the registry was established in 1995 at the Prince of Wales Hospital, which serves a population of >1.2 million. Patients with diabetes attending medical clinics at the Prince of Wales Hospital can be referred to the Diabetes Mellitus and Endocrine Centre for comprehensive assessment based on the European DIABCARE protocol (13). Hong Kong has a heavily subsidized health-care system. The majority of patients with diabetes and chronic illnesses are managed in public hospitals governed by the Hospital Authority, which provides 95% of the total hospital bed-days in Hong Kong (14). After participants are enrolled in the registry, their outcomes, including hospital admissions, are monitored until their time of death (11,14). Up to 31 December 2007, 10,129 patients were enrolled in the cohort. After excluding 417 patients with type 1 diabetes (including missing data on classification of diabetes type) and 945 with missing variables used in the analysis, 8,767 patients were included in the present study.

At enrollment and regularly thereafter, type 2 diabetic patients underwent a comprehensive 4-h assessment for diabetes-related complications and risk factors (13). The assessment included an interview by diabetes nurses, anthropometric measurements, biochemical evaluations, fundus examination, and podiatry assessment. After fasting for 8 h overnight, blood was sampled for assays of fasting lipids, glucose, HbA_{1c}, and renal and liver function tests. Treatment goals were defined as HbA_{1c} <7%, blood pressure (BP) <130/80 mmHg, and LDL cholesterol (LDL-C) <2.6 mmol/L (12). We used spot urinary albumin-to-creatinine ratio (ACR) to define albuminuria (ACR ≥2.5 mg/mmol in men and ≥3.5 mg/mmol in women). The abbreviated Modification of Diet in Renal Disease equation recalibrated for Chinese (15) was used to define CKD as an estimated glomerular filtration rate (eGFR) <60 mL/min/1.73 m^2. All laboratory analyses were performed with standard methods in the Department of Chemical Pathology of the Prince of Wales Hospital. The laboratory is accredited by the Australian National Association of Testing Authorities. Informed written consent was obtained from all participants, and the study was approved by The Chinese University of Hong Kong Clinical Research Ethics Committee.

Severe hypoglycemia was defined as one or more hospitalizations for hypoglycemia in the 12 months before enrollment (at enrollment) or during the follow-up period from enrollment to death or 31 January 2009 to ensure that the last enrolled patient in 2007 had at least 2 years of observation. We ascertained all clinical outcomes through the Hospital Authority Central Computer Management System, which records diagnoses of all hospital discharges, including mortality, based on ICD-9 codes. The mortality data were cross-checked with the Hong Kong Death Registry, and the cause of death was defined by the principal discharge diagnosis.

Statistical Analysis

The statistical analysis was performed with SAS release 9.30 software (SAS Institute Inc., Cary, NC), unless otherwise specified. Cox proportional hazards analysis was used to obtain hazard ratios (HRs) and 95% CIs. Data analysis was divided into two parts: *1*) identification of risk factors for severe hypoglycemia and *2*) identification of

cancer-associated subphenotypes for severe hypoglycemia.

Follow-up time was calculated as the period from enrollment to the date of the first admission for severe hypoglycemia, death, or 31 January 2009, whichever came first. We also ascertained the temporal relationship among severe hypoglycemia, all-site cancer, and death. A two-step scheme was used to identify risk factors for severe hypoglycemia. First, we examined the demographic, lifestyle, and clinically relevant factors measured at enrollment, including age, sex, BMI, high BP (systolic BP ≥130 mmHg or diastolic BP ≥80 mmHg), suboptimal glycemic control (HbA_{1c} ≥7.0%), high LDL-C (≥2.60 mmol/L), low HDL cholesterol (HDL-C) (<1.03 mmol/L in men and <1.29 mmol/L in women), high triglyceride (TG) (≥1.70 mmol/L), albuminuria, and CKD. Second, we further adjusted for drug use at enrollment, including insulin, oral glucose-lowering drugs, lipid-lowering drugs, and renin-angiotensin system (RAS) inhibitors.

Because we detected an increased occurrence of all-site cancer in patients who developed severe hypoglycemia in the first stage of analysis, we further examined risk associations between severe hypoglycemia and cancer phenotypes previously reported by our group. In brief, we identified five phenotypes in the Hong Kong Diabetes Registry predictive of incident cancers in type 2 diabetes in addition to the linear association between HbA_{1c} and cancer (16). These cancer phenotypes included *1*) high LDL-C (≥3.80 mmol/L) (11), *2*) copresence of low LDL-C (<2.60 mmol/L) and albuminuria (17), *3*) copresence of low LDL-C (<2.60 mmol/L) and low TG (<1.70 mmol/L) (18), *4*) low HDL-C (<1.0 mmol/L) (19), and *5*) high and low BMI (≥27.6 and <24.0 kg/m^2) (20). By examining their associations with severe hypoglycemia, we aimed to ascertain whether the high incidences of cancer in patients who developed severe hypoglycemia could be predicted by these lipid phenotypes.

To assess whether the type of oral antidiabetic agents used in this study population, specifically sulfonylureas, compared with other agents with less risk of hypoglycemia, such as metformin, would have an impact on the analyses, we performed a sensitivity analysis among patients enrolled between December 1996 and January 2005, and followed up to July 2005 (because we censored data related to drug use during this period). We used this analysis to check whether the results were valid after further adjustment for drug use, similar to what we did and reported previously (19).

The plots of LOG [−LOG (survival function)] versus LOG (follow-up time in years) were used to check the proportional hazards assumption for categorical variables, whereas the Supremum test was used to check the assumption for continuous variables (21). $P < 0.05$ was considered statistically significant.

RESULTS

Characteristics of the Study Cohort

The mean age of the cohort was 57.4 (SD 13.2) years, with a median duration of diabetes of 5 (interquartile range 1–11) years. During a total of 59,375 years (median 6.71 [interquartile range 3.47–10.38] years) of follow-up, 235 patients were hospitalized for hypoglycemia, with an incidence of 3.96 (95% CI 3.45–4.46) per 1,000 patient-years. Compared with patients without severe hypoglycemia, patients with severe hypoglycemia were older, were more likely to be ex-smokers and ex-drinkers, had longer disease duration, and had lower BMI. They also had higher HbA_{1c} and BP but lower TG and LDL-C and worse renal function and were more likely to have a history of CVD and insulin treatment at enrollment (Table1).

Risk Factors for Severe Hypoglycemia

After adjustment for confounders, old age, low BMI, high HbA_{1c}, high BP, low LDL-C, low TG, albuminuria, and CKD were independent risk factors for severe hypoglycemia. After further adjustment for drug use at enrollment, a 10-year increase in age was associated with an 86% increased risk, whereas 1 kg/m^2 BMI increase was associated with 5% reduced risk of severe hypoglycemia. Patients with suboptimal glycemic control (HbA_{1c} ≥7%) were at a 1.78-fold risk of experiencing severe hypoglycemia compared with those with HbA_{1c} <7%. Nonattainment of LDL-C (≥2.60 mmol/L) and TG (≥1.7 mmol/L) targets was associated with reduced risks of severe hypoglycemia (HR 0.71 [95% CI 0.53–0.96] and 0.70 [0.51–0.95], respectively). Apart from age, low BMI, high HbA_{1c}, albuminuria, and CKD, low TG and low LDL-C remained highly predictive of severe hypoglycemia after adjustment for drug use (Table 2).

Associations Between Cancer Phenotypes and Severe Hypoglycemia

The consistent associations of low HDL-C (<1.0 mmol/L), low TG (<1.7 mmol/L), and low LDL-C (<2.6 mmol/L) with severe hypoglycemia in the two multivariable analyses prompted us to investigate whether these lipid phenotypes, reported to be associated with all-site cancer by our group (11,19,22,23), might also be associated with hypoglycemia. These relationships were nonlinear, with both high and low TG, HDL-C, and LDL-C values being associated with cancer risk, even in patients not using lipid-regulating drugs (11,19,22,23). After adjusting for all covariables, the HR of HDL-C <1.0 mmol/L versus HDL-C of 1.10–1.29 mmol/L (reference) was 1.88 (1.37–2.58) and that of low LDL-C plus low TG was 1.69 (1.15–2.47) (Table 3). Other cancer phenotypes were not found to be predictive of severe hypoglycemia.

Sensitivity Analysis

The significant results in multivariable analysis remained statistically significant, except for albuminuria, which became insignificant ($P = 0.1025$) after adjustment for drug use in the 2.5 years before enrollment and during follow-up (Table 4).

CONCLUSIONS

In this large prospective cohort of type 2 diabetes, the rate of severe hypoglycemia requiring hospitalization was 3 per 1,000 patient-years. Similar to the ACCORD and ADVANCE studies, this cohort had high rates of death, including all-site cancer. After adjusting for confounders, apart from old age, high HbA_{1c}, and CKD, previously reported cancer-associated phenotypes, including low BMI, low HDL-C, low LDL-C, and low TG, were also predictors of severe hypoglycemia. These results concurred with those reported in the ADVANCE

Table 1—Clinical and biochemical characteristics of the study cohort stratified by with and without severe hypoglycemia

	Patients with type 2 diabetes		
	Without severe hypoglycemia* (*n* = 8,323)	With severe hypoglycemia* (*n* = 235)	*P* value†
Age (years)	58 (48–67)	69 (61–74)	<0.0001
Male sex	3,933 (47.3)	100 (42.6)	0.1545
Smoking status			0.0379
Ex-smoker	1,261 (15.2)	48 (20.4)	
Current smoker	1,451 (17.4)	31 (13.2)	
Alcohol intake			0.0108
Ex-drinker	976 (11.7)	37 (15.7)	
Current drinker	755 (9.1)	10 (4.3)	
BMI (kg/m^2)	24.8 (22.5–27.5)	24.3 (21.1–27.3)	0.0021
Duration of diabetes (years)	5 (1–10)	10 (5–15)	<0.0001
Systolic BP (mmHg)	133 (120–147)	142 (128–157)	<0.0001
Diastolic BP (mmHg)	75 (68–82)	74 (67–82)	0.1250
Systolic BP ≥135 mmHg or diastolic BP ≥85 mmHg	5,153 (61.9)	175 (74.5)	<0.0001
HbA_{1c} (%)	7.2 (6.3–8.4)	7.9 (7.0–9.5)	<0.0001
HbA_{1c} ≥7.0%	4,747 (57.0)	177 (75.3)	<0.0001
LDL-C (mmol/L)	3.0 (2.4–3.68)	2.91 (2.40–3.80)	0.7227
LDL-C ≥2.60 mmol/L	5,698 (68.5)	164 (69.8)	0.6660
HDL-C (mmol/L)	1.27 (1.08–1.51)	1.35 (1.08–1.63)	0.0298
HDL-C <1.03 mmol/L in men or <1.29 mmol/L in women	2,878 (34.6)	74 (31.5)	0.3258
TG (mmol/L)	1.38 (0.97–2.00)	1.18 (0.88–1.76)	0.0028
TG ≥1.70 mmol/L	2,894 (34.8)	64 (27.2)	0.0166
Spot urinary ACR (mg/mmol)	1.88 (0.76–9.44)	8.78 (1.78–58.83)	<0.0001
Albuminuria‡	3,426 (41.2)	154 (65.5)	<0.0001
eGFR (mL/min/1.73 m^2)	104.0 (84.0–125.0)	83.1 (61.0–104.7)	<0.0001
CKD‡	766 (9.2)	58 (24.7)	<0.0001
Prior coronary heart disease	643 (7.73)	27 (11.49)	0.0342
Prior stroke	198 (2.38)	9 (3.83)	0.1534
Prior peripheral artery disease	451 (5.42)	20 (8.51)	0.0404
Prior cancer	230 (2.76)	3 (1.28)	0.1672
Use of medications at baseline			
RAS inhibitors	1,845 (22.2)	84 (35.7)	<0.0001
Lipid-lowering drugs	1,595 (19.2)	41 (17.5)	0.5092
Oral antidiabetes drugs	5,688 (68.3)	143 (60.9)	0.0151
Insulin	1,340 (16.1)	88 (37.5)	<0.0001
Incident events during follow-up‡‡			
CVD	1,206 (14.5)	84 (35.7)	<0.0001
CKD	1,366 (16.4)	1,419 (60)	<0.0001
All-site cancer	533 (6.4)	32 (13.4)	<0.0001
Before hypoglycemia event	533 (6.4)	17 (7.23)	
After hypoglycemia event	0 (0)	15 (6.38)	
Death	930 (11.2)	77 (32.8)	<0.0001
Due to circulatory disease	222 (2.7)	13 (5.5)	0.0080
Due to respiratory disease	146 (1.8)	9 (3.8)	0.0186
Due to renal disease	118 (1.4)	17 (7.2)	<0.0001
Due to cancer	223 (2.7)	16 (6.8)	0.0002

Data are median (interquartile range) or *n* (%). *Severe hypoglycemia was defined as having hypoglycemia events during follow-up that required hospital admissions. †Derived from Wilcoxon two-sample test or χ^2 test where appropriate. ‡Albuminuria was defined as ACR ≥2.5 mg/mmol in men and ≥3.5 mg/mmol in women; CKD was defined as eGFR <60 mL/min/1.73 m^2. ‡‡Incident events from enrollment to death or the censoring date.

study (2), where old age, long disease duration, high serum creatinine levels, low BMI, low cognitive function, use of two or more oral blood glucose–lowering drugs, history of smoking or microvascular disease, and assignment to intensive glucose control were all independent risk factors for severe hypoglycemia.

The nonlinear relationship between BMI and premature mortality, including cancer deaths, has been widely reported (24). The associations between cancer

Table 2—Risk factors for severe hypoglycemia in patients with type 2 diabetes

Exposures	HR (95% CI)	*P* value
Model 1		
Age (per 10 years)	1.92 (1.68–2.18)	<0.0001
BMI (per kg/m^2)	0.97 (0.93–1.00)	0.0754
HbA_{1c} (per 1%)	1.24 (1.16–1.32)	<0.0001
Systolic BP (per 10 mmHg)	1.01 (0.95–1.08)	0.7227
LDL-C (per mmol/L)	0.82 (0.72–0.94)	0.0055
HDL-C (per mmol/L)	1.22 (0.99–1.49)	0.0619
TG (per mmol/L)	0.76 (0.63–0.91)	0.0028
Albuminuria‡	1.79 (1.27–2.29)	0.0004
CKD‡	2.30 (1.60–3.20)	<0.0001
Model 2		
Age (per 10 years)	1.92 (1.68–2.20)	<0.0001
BMI (per kg/m^2)	0.96 (0.93–0.99)	0.0210
HbA_{1c} (per 1%)	1.21 (1.33–1.29)	<0.0001
Systolic BP (per 10 mmHg)	1.01 (0.95–1.08)	0.7470
LDL-C (per mmol/L)	0.86 (0.74–0.99)	0.0328
HDL-C (per mmol/L)	1.25 (0.99–1.57)	0.0592
TG (per mmol/L)	0.80 (0.66–0.96)	0.0155
Albuminuria‡	1.47 (1.09–1.99)	0.0125
CKD‡	1.91 (1.36–2.69)	0.0002

Model 1: adjusted for sex, smoking habit, drinking habit, and duration of disease. Model 2: further adjusted for prior coronary heart disease, prior stroke, prior cancer, peripheral artery disease, and use of drugs at enrollment, including insulin, oral antidiabetes drugs, lipid-lowering drugs, and RAS inhibitors. ‡Albuminuria was defined as ACR ≥2.5 mg/mmol in men and ≥3.5 mg/mmol in women. CKD was defined as eGFR <60 mL/min/1.73 m^2.

and CKD is now emerging, which may be due to sharing of common risk factors and improved survival from CVD (25). Low BMI may denote a state of catabolism and malnutrition, which are often found in patients with occult malignancy and renal impairment. Besides, CKD can be both a cause and a consequence of hypoglycemia. Aside from reduced glucose production (about one-fifth of the plasma glucose originated from renal gluconeogenesis), diabetic patients with CKD often have altered drug metabolism, autonomic neuropathy, and hypoglycemic unawareness, which culminate and place them at high risk of hypoglycemia (6).

Based on 24-h monitoring of blood glucose and electrocardiogram, silent hypoglycemia and cardiac ischemia were not uncommon in type 2 diabetic patients who had long disease duration, prior CVD, and insulin treatment (26). Thus, when the ACCORD study was stopped prematurely because of an increased death rate in the intensively treated group, hypoglycemia-associated cardiovascular death was considered a possible culprit (27). Indeed, there were many plausible mechanisms for hypoglycemia to increase the risk of CVD, including sympathetic activation, prolongation of QT interval, increased thrombogenesis, inflammation, and vasoconstriction (28). However, subsequent analysis of ACCORD (4) failed to confirm increased CVD-related death in patients treated intensively. Indeed, in patients without prior CVD and HbA_{1c} <8%, intensive treatment was associated with a trend of reduced CVD (4). Further analysis of the ADVANCE databases revealed that diabetic patients with severe hypoglycemia were more likely to die of non-CVD causes, including cancer, compared with those without severe hypoglycemia (2). In support of these findings, patients with severe hypoglycemia in the present observational cohort had a higher mortality rate mainly attributable to cancer, with rates of CVD similar to patients without hypoglycemia.

The present findings and those of others (2) thus raise the possibility that severe hypoglycemia might actually reflect the consequences of coexisting conditions and denote a subgroup of diabetic patients who are particularly fragile and deserve more clinical attention. A novel observation from this study is that cancers occurred more frequently among diabetic patients who had developed severe hypoglycemia during the follow-up period. This adverse event could be predicted by our previously reported cancer subphenotypes, notably low BMI, low TG, and low LDL-C. Large-scale randomized studies have reported an annual cancer rate of 1% in type 2 diabetes (ORIGIN [Outcome Reduction With Initial Glargine Intervention]), although few studies have reported an association between hypoglycemia and cancer except as a terminal event in patients with metastatic disease (29).

Our group was the first to report the high rates of cancer in type 2 diabetic patients, which accounted for 20% of all-cause death (30). Using the same registry, apart from the linear association of cancer with HbA_{1c} levels (16), we also reported nonlinear associations between cancer and lipid subphenotypes (11). From Hong Kong Diabetes Registry data, we reported an association between low TG level (<1.7 mmol/L) and increased cancer risk that was attenuated by statin use (23), implicating that the activation of the hydroxymethylglutaryl-CoA reductase with increased production of Ras signals, which are known to be oncogenes, may be involved (23). In this connection, sterol regulatory element-binding proteins (SREBPs), regulated by both insulin and insulin-like growth factor 1 (IGF1), are involved in lipid synthesis and may play a plausible biological link for cancer development in type 2 diabetic patients (23). Based on these observations and experimental studies by others, we argued that dysregulation of lipid and glucose metabolism with activation of the SREBP-IGF1-hydroxymethylglutaryl-CoA reductase pathway might be a possible mechanism (23,31,32).

Apart from highlighting the high-risk nature of type 2 diabetic patients with severe hypoglycemia, the present findings might have implications for clinical management. In this analysis, patients with severe hypoglycemia were less likely to be at HbA_{1c} or BP goals and had renal dysfunction despite being more likely to be taking insulin and RAS inhibitors. These difficult-to-treat

Table 3—Previously reported cancer phenotypes for severe hypoglycemia in patients with type 2 diabetes without cancer at baseline

Exposure	Patients with severe hypoglycemia (%)	HR (95% CI)	*P* value
Model 1			
Age (per 10 years)		1.91 (1.68–2.18)	<0.0001
BMI			
≥27.6 kg/m^2	52 (2.58)	1.19 (0.85–1.67)	0.3188
24–27.5 kg/m^2	103 (3.11)	Reference	
<24 kg/m^2	75 (2.52)	0.85 (0.63–1.15)	0.2919
HbA_{1c} (per 1%)		1.23 (1.16–1.31)	<0.0001
Systolic BP (per 10 mmHg)		1.01 (0.95–1.07)	0.8303
LDL-C <2.8 mmol/L and TG <1.7 mmol/L* (yes vs. no)	53 (3.05) vs. 179 (2.72)	1.78 (1.22–2.59)	0.0026
LDL-C <2.6 mmol/L and albuminuria (yes vs. no)	44 (4.21) vs. 188 (2.58)	0.99 (0.64–1.54)	0.9690
LDL-C ≥3.8 vs. <3.8 mmol/L	58 (3.16) vs. 174 (2.68)	0.93 (0.67–1.31)	0.6910
HDL-C			
<1.0 mmol/L	134 (3.36)	1.92 (1.40–2.64)	<0.0001
1.0–1.29 mmol/L	57 (1.86)	Reference	
≥1.30 mmol/L	41 (3.23)	1.34 (0.89–2.01)	0.1602
Albuminuria	153 (4.38) vs. 79 (1.63)	1.68 (1.19–2.38)	0.0033
CKD	58 (7.25) vs. 174 (2.31)	2.25 (1.62–3.12)	<0.0001
Model 2			
Age (per 10 years)		1.92 (1.68–2.19)	<0.0001
BMI*			
≥27.6 kg/m^2	52 (2.58)	1.11 (0.79–1.56)	0.5508
24–27.5 kg/m^2	103 (3.11)	Reference	
<24 kg/m^2	75 (2.52)	0.80 (0.60–1.09)	0.1550
HbA_{1c} (%)		1.21 (1.13–1.29)	<0.0001
Systolic BP (per 10 mmHg)		1.01 (0.95–1.08)	0.7897
LDL-C <2.8 mmol/L and TG <1.7 mmol/L* (yes vs. no)	76 (3.25) vs. 15 (2.56)	1.69 (1.15–2.47)	0.0065
LDL-C <2.8 mmol/L and albuminuria* (yes vs. no)	63 (4.53) vs. 172 (2.40)	1.02 (0.66–1.59)	0.9203
LDL-C ≥3.8 vs. <3.8 mmol/L	58 (3.16) vs. 174 (2.68)	1.00 (0.72–1.40)	0.9917
HDL-C			
<1.0 mmol/L	134 (3.36)	1.88 (1.37–2.58)	0.0001
1.0–1.29 mmol/L	57 (1.86)	Reference	
≥1.30 mmol/L	41 (3.23)	1.34 (0.89–2.01)	0.1779
Albuminuria	153 (4.38) vs. 79 (1.63)	1.45 (1.02–2.06)	0.0386
CKD	58 (7.25) vs. 174 (2.31)	1.87 (1.33–2.62)	0.0003

Data are *n* (%) unless otherwise indicated. *The previously defined cancer phenotypes of BMI (37), LDL-C (11,17, 37), and HDL-C (19) in this cohort were used in the analysis of their associations with hypoglycemia. Model 1: adjusted for sex, use of tobacco and alcohol, and duration of disease. Model 2: further adjusted for prior coronary heart disease, prior stroke, peripheral artery disease, and use of drugs at enrollment, including insulin, oral antidiabetes drugs, lipid-lowering drugs, and RAS inhibitors.

patients might have other unmet needs, such as treatment noncompliance and psychological distress. Of note, several studies have now reported high rates of depression associated with hypoglycemia in type 2 diabetes (33). These epidemiological data once again highlight the complex and high-risk nature of type 2 diabetic patients with hypoglycemia who would require comprehensive assessment for individualized care.

On the other hand, patients with hypoglycemia were more likely not to reach LDL-C and TG treatment goals despite having similar usage rates of lipid-lowering drugs as those without hypoglycemia. Given the predictive values of low TG and low LDL-C levels on severe hypoglycemia, physicians might need to be more cautious when interpreting these treatment goals, especially in patients with long disease duration, low BMI, and CKD. The nature of the association between low HDL-C level and hypoglycemia was not clear, although we have reported that reduced renal function might predict low HDL-C (23). Taken together, understanding these complex interrelationships among renal impairment, dyslipidemia (low HDL-C, low LDL-C, low TG), severe hypoglycemia, and cancer may shed light on the nature of comorbidities in type 2 diabetes (10).

The strengths of this study are its large sample size, long follow-up duration, and detailed documentation of risk factors, complications, drug use, and outcome within a heavily subsidized health-care system with a high retention rate. These real-world data confirm findings collected in clinical trial settings and provide alternative perspectives regarding the clinical significance of severe hypoglycemia with possible therapeutic implications. On the other hand, we acknowledge the retrospective and hypothesis-generating nature of epidemiological analysis and its inherent limitations. The ascertainment of hypoglycemia through ICD-9 codes might contain errors due to misclassification and/or undercoding. However, there is a general consensus that administrative data for clinical outcomes are generally satisfactory, with an accuracy rate as high as 95% for acute myocardial infarction and stroke

Table 4—Sensitivity analysis of multivariable HRs of previously reported cancer phenotypes for severe hypoglycemia in patients with type 2 diabetes without cancer at baseline enrolled between 1996 and 2005 with follow-up to 2005 (19)

Exposure	Patients with severe hypoglycemia (%, *n* = 5,989)	HR (95% CI)	*P* value
Age (per 10 years)		1.50 (1.24–1.81)	<0.0001
HbA_{1c} (per 1%)		1.13 (1.02–1.26)	0.0250
LDL-C <2.8 mmol/L + TG <1.7 mmol/L	23 (2.08) vs. 88 (1.80)	1.19 (0.61–2.29)	0.6109
HDL-C			
<1.0 mmol/L	65 (2.36)	2.03 (1.27–3.23)	0.0030
1.0–1.29 mmol/L	27 (1.22)	Reference	
≥1.30 mmol/L	19 (1.88)	1.10 (0.60–2.00)	0.7622
Albuminuria	81 (3.13) vs. 30 (0.88)	1.55 (0.92–2.64)	0.1025
CKD	39 (6.79) vs. 72 (1.33)	2.82 (1.72–4.62)	<0.0001
Use of drugs in 2.5 years before enrollment			
Acarbose	7 (1.94) vs. 104 (1.85)	0.95 (0.40–2.23)	0.8979
Sulfonylurea	68 (1.82) vs. 43 (1.91)	0.97 (0.57–1.66)	0.9186
Metformin	56 (1.65) vs. 55 (2.12)	0.78 (0.47–1.30)	0.3428
Thiazolidinedione	0 (0) vs. 111 (1.86)	—	
Insulin	57 (4.08) vs. 54 (1.18)	1.31 (0.78–2.20)	0.3011
Use of drugs during follow-up			
Acarbose	16 (2.25) vs. 95 (1.80)	1.10 (0.60–2.00)	0.7678
Sulfonylurea	69 (1.61) vs. 42 (2.47)	0.89 (0.50–1.56)	0.6830
Metformin	68 (1.52) vs. 43 (2.83)	0.89 (0.52–1.53)	0.6805
Thiazolidinedione	5 (1.27) vs. 106 (1.89)	0.69 (0.27–1.74)	0.4301
Insulin	84 (3.73) vs. 27 (0.72)	2.75 (1.56–4.86)	0.0005

Data are *n* (%) unless otherwise indicated. Adjusted for age, sex, BMI, systolic BP, use of tobacco and alcohol, duration of disease, LDL-C <2.8 mmol/L and albuminuria, LDL-C ≥3.8 vs. <3.8 mmol/L, prior coronary heart disease, prior stroke, peripheral artery disease, and use of RAS inhibitors and statins in the 2.5 years before enrollment as well as during follow-up.

(34,35). Furthermore, the impact of the use of oral antidiabetic agents on severe hypoglycemia shown in the present sensitivity analysis should be interpreted with caution because the use of observational studies to address drug effects might introduce potential bias, requiring studies designed specifically to confirm the results (36). Finally, we only included severe hypoglycemic episodes requiring hospitalizations, which were specific but not sensitive indicators of these adverse events. Because this database did not systematically capture minor hypoglycemia events not requiring admission, it is likely that we underestimated the true rates of hypoglycemia. The analysis did not confirm the risk association between severe hypoglycemia and CVD-related deaths, but we cannot exclude the possibility that repeat minor hypoglycemic episodes could have cumulative adverse effects on cardiovascular and cerebrovascular functions with direct or indirect impacts on mortality. In addition, there are different definitions of severe hypoglycemia adopted by various research groups, and the commonly used one would be a hypoglycemic event requiring assistance of another person to actively administer carbohydrates, glucagons, or other resuscitative actions. The definition we used in this study might not be useful in a comparison with other cohort data using different definitions.

In conclusion, in this real-world pragmatic study, we identified risk factors predictive of severe hypoglycemia in type 2 diabetes, including old age, low BMI, high HbA_{1c}, low TG, low LDL-C, albuminuria, and CKD. Patients with severe hypoglycemia were also more likely to die and to develop all-site cancer (2) than those without severe hypoglycemia. Given the complexity and multiple comorbidities of type 2 diabetes, experts have emphasized the importance of periodic phenotyping, individualizing treatment goals, and comanagement of specialist and primary care, especially in difficult-to-treat patients such as those with hypoglycemia, poor glycemic control, and comorbidities. To this end, the present analysis has provided additional evidence to support these expert recommendations, highlighting the vulnerability of patients with severe hypoglycemia who are at high risk for all-cause death and all-site cancer.

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References

1. Patel A, MacMahon S, Chalmers J, et al.; ADVANCE Collaborative Group. Effects of a fixed combination of perindopril and indapamide on macrovascular and microvascular outcomes in patients with type 2 diabetes mellitus (the ADVANCE trial): a randomised controlled trial. Lancet 2007;370:829–840
2. 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
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. Desouza CV, Bolli GB, Fonseca V. Hypoglycemia, diabetes, and cardiovascular events. Diabetes Care 2010;33:1389–1394
6. Moen MF, Zhan M, Hsu VD, et al. Frequency of hypoglycemia and its significance in chronic kidney disease. Clin J Am Soc Nephrol 2009;4:1121–1127
7. So WY, Chan JC, Yeung VT, et al. Sulphonylurea-induced hypoglycaemia in institutionalized elderly in Hong Kong. Diabet Med 2002;19:966–968
8. Pozzilli P, Leslie RD, Chan J, et al. The A1C and ABCD of glycaemia management in type 2 diabetes: a physician's personalized approach. Diabetes Metab Res Rev 2010; 26:239–244
9. Inzucchi SE, Bergenstal RM, Buse JB, et al.; American Diabetes Association (ADA); European Association for the Study of Diabetes (EASD). Management of hyperglycemia in type 2 diabetes: a patient-centered approach: position statement of the American Diabetes Association (ADA) and the European Association for the Study of Diabetes (EASD). Diabetes Care 2012;35:1364–1379
10. Seshasai SR, Kaptoge S, Thompson A, et al.; Emerging Risk Factors Collaboration. Diabetes mellitus, fasting glucose, and risk of cause-specific death. N Engl J Med 2011; 364:829–841
11. Yang X, So W, Ko GT, et al. Independent associations between low-density lipoprotein cholesterol and cancer among patients with type 2 diabetes mellitus. CMAJ 2008;179:427–437
12. Kong AP, Yang X, Ko GT, et al. Effects of treatment targets on subsequent cardiovascular events in Chinese patients with type 2 diabetes. Diabetes Care 2007; 30:953–959
13. Piwernetz K, Home PD, Snorgaard O, Antsiferov M, Staehr-Johansen K, Krans M; The DIABCARE Monitoring Group of the St. Vincent Declaration Steering Committee. Monitoring the targets of the St. Vincent Declaration and the implementation of quality management in diabetes care: the DIABCARE initiative. Diabet Med 1993;10:371–377
14. Yang X, So WY, Tong PC, et al. Development and validation of an all-cause mortality risk score in type 2 diabetes: The Hong Kong Diabetes Registry. Arch Intern Med 2008; 168:451–457
15. Ma YC, Zuo L, Chen JH, et al. Modified glomerular filtration rate estimating equation for Chinese patients with chronic kidney disease. J Am Soc Nephrol 2006;17:2937–2944
16. Yang X, Ko GT, So WY, et al. Associations of hyperglycemia and insulin usage with the risk of cancer in type 2 diabetes: the Hong Kong diabetes registry. Diabetes 2010;59: 1254–1260
17. Yang X, So WY, Ma RC, et al. Low LDL cholesterol, albuminuria, and statins for the risk of cancer in type 2 diabetes: the Hong Kong diabetes registry. Diabetes Care 2009; 32:1826–1832
18. Yang X, So WY, Ma RC, et al. Synergistic effects of low LDL cholesterol with other factors for the risk of cancer in type 2 diabetes: the Hong Kong Diabetes Registry. Acta Diabetol 2012;49(Suppl. 1):S185–S193
19. Yang X, So WY, Ma RC, et al. Low HDL cholesterol, metformin use, and cancer risk in type 2 diabetes: the Hong Kong Diabetes Registry. Diabetes Care 2011;34:375–380
20. Yang X, So WY, Ma RC, et al. Predicting values of lipids and white blood cell count for all-site cancer in type 2 diabetes. Endocr Relat Cancer 2008;15:597–607
21. Lin DY, Wei LJ, Ying Z. Checking the Cox model with cumulative sums of martingale-based residuals. Biometrika 1993;80:557–572
22. Yang X, So WY, Ma RC, Kong AP, Xu G, Chan JC. Diabetes and cancer: the mechanistic implications of epidemiological analyses from the Hong Kong Diabetes Registry. Diabetes Metab Res Rev 2012;28:379–387
23. Yang X, Ma RC, So WY, et al. Low triglyceride and nonuse of statins is associated with cancer in type 2 diabetes mellitus: the Hong Kong Diabetes Registry. Cancer 2011;117: 862–871
24. Pischon T, Boeing H, Hoffmann K, et al. General and abdominal adiposity and risk of death in Europe. N Engl J Med 2008;359: 2105–2120
25. Stengel B. Chronic kidney disease and cancer: a troubling connection. J Nephrol 2010;23:253–262
26. Desouza C, Salazar H, Cheong B, Murgo J, Fonseca V. Association of hypoglycemia and cardiac ischemia: a study based on continuous monitoring. Diabetes Care 2003;26:1485–1489
27. Goto A, Arah OA, Goto M, Terauchi Y, Noda M. Severe hypoglycaemia and cardiovascular disease: systematic review and meta-analysis with bias analysis. BMJ 2013;347:f4533
28. Wright RJ, Frier BM. Vascular disease and diabetes: is hypoglycaemia an aggravating factor? Diabetes Metab Res Rev 2008;24: 353–363
29. Gerstein HC, Bosch J, Dagenais GR, et al.; ORIGIN Trial Investigators. Basal insulin and cardiovascular and other outcomes in dysglycemia. N Engl J Med 2012;367:319–328
30. So WY, Yang X, Ma RC, et al. Risk factors in V-shaped risk associations with all-cause mortality in type 2 diabetes—The Hong Kong Diabetes Registry. Diabetes Metab Res Rev 2008;24:238–246
31. Kong AP, Chan JC. Cancer risk in type 2 diabetes. Curr Diab Rep 2012;12:325–328
32. Yang X, So WY, Ma RC, Kong AP, Xu G, Chan JC. Diabetes and cancer: the mechanistic implications of epidemiological analyses from the Hong Kong Diabetes Registry. Diabetes Metab Res Rev 2012;28:379–387
33. Katon WJ, Young BA, Russo J, et al. Association of depression with increased risk of severe hypoglycemic episodes in patients with diabetes. Ann Fam Med 2013; 11:245–250
34. Kiyota Y, Schneeweiss S, Glynn RJ, Cannuscio CC, Avorn J, Solomon DH. Accuracy of Medicare claims-based diagnosis of acute myocardial infarction: estimating positive predictive value on the basis of review of hospital records. Am Heart J 2004;148:99–104
35. Birman-Deych E, Waterman AD, Yan Y, Nilasena DS, Radford MJ, Gage BF. Accuracy of ICD-9-CM codes for identifying cardiovascular and stroke risk factors. Med Care 2005;43:480–485
36. Yang XL, Ma RC, So WY, Kong AP, Xu G, Chan JC. Addressing different biases in analysing drug use on cancer risk in diabetes in non-clinical trial settings—what, why and how? Diabetes Obes Metab 2012;14:579–585
37. Yang X, Wang Y, Luk AO, et al. Enhancers and attenuators of risk associations of chronic hepatitis B virus infection with hepatocellular carcinoma in type 2 diabetes. Endocr Relat Cancer 2013;20:161–171