Patient Characteristics Associated With Severe Hypoglycemia in a Type 2 Diabetes Cohort in a Large, Integrated Health Care System From 2006 to 2015

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OBJECTIVE

To identify severe hypoglycemia events, defined as emergency department visits or hospitalizations for hypoglycemia, in patients with type 2 diabetes receiving care in a large health system and to identify patient characteristics associated with severe hypoglycemia events.

RESEARCH DESIGN AND METHODS

This was a retrospective cohort study from January 2006 to December 2015 using the electronic medical record in the Cleveland Clinic Health System (CCHS). Participants included 50,439 patients with type 2 diabetes receiving care in the CCHS. Number of severe hypoglycemia events and associated patient characteristics were identified.

RESULTS

The incidence proportion of severe hypoglycemia increased from 0.12% in 2006 to 0.31% in 2015 (P = 0.01). Compared with patients who did not experience severe hypoglycemia, those with severe hypoglycemia had similar median glycosylated hemoglobin (HbA_{1c}) levels. More patients with severe hypoglycemia versus those without had a prior diagnosis of nonsevere hypoglycemia (9% vs. 2%, $P < 0.001$). Logistic regression confirmed an increased odds for severe hypoglycemia with insulin, sulfonylureas, increased number of diabetes medications, history of nonsevere hypoglycemia (odds ratio [OR] 3.01, $P < 0.001$), HbA_{1c} <6% (42 mmol/mol) (OR 1.95, $P < 0.001$), black race, and increased Charlson comorbidity index. Lower odds of severe hypoglycemia were noted with higher BMI and use of metformin, dipeptidyl peptidase 4 inhibitors, and glucagon-like peptide 1 agonists.

CONCLUSIONS

In this retrospective study of patients with type 2 diabetes with severe hypoglycemia, patient characteristics were identified. Patients with severe hypoglycemia had previous nonsevere hypoglycemia diagnoses more frequently than those without. Identifying patients at high risk at the point of care can allow for change in modifiable risk factors and prevention of severe hypoglycemia events.

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While optimal diabetes control can help prevent diabetes complications (1–7), hypoglycemia remains a significant risk of diabetes treatment and has been associated with mortality (8–10), and iatrogenic hypoglycemia related to diabetes treatment can limit ability to achieve glycemic control (11,12). Additional notable risks include decreased rating of health-related quality of life (13) and decreased work productivity (14) as well as accidents resulting in hospital visits (15). While documented or probable symptomatic hypoglycemia or asymptomatic hypoglycemia (16) may occur more commonly than severe hypoglycemia, the occurrence of severe hypoglycemia remains an important problem. Severe hypoglycemia is defined by the American Diabetes Association as "severe cognitive impairment requiring external assistance for recovery (17)." A recent reported estimate of severe hypoglycemia in a population of insured patients leading to an emergency department (ED) visit or hospitalization is 1.4–1.6 events per 100 person-years (18), with risk factors for severe hypoglycemia identified as older age, cardiovascular disease, congestive heart failure, chronic kidney disease, depression, higher glycosylated hemoglobin (HbA_{1c}), and use of insulin or insulin secretagogues or β-blockers (18). Socioeconomic factors can also increase risk for hypoglycemia, with more frequent admissions for hypoglycemia reported in low- versus high-income populations (19). We sought to identify all severe hypoglycemia events, defined for this study as ED visits or hospitalizations for hypoglycemia, in patients with type 2 diabetes receiving care in the Cleveland Clinic Health System (CCHS) from 2006 to 2015 to identify patient characteristics associated with severe hypoglycemia events. We focused our study on patients with type 2 diabetes, as we sought to assess in this work, in addition to patient characteristics, whether specific medications used to treat type 2 diabetes were clearly associated with severe hypoglycemia in a large health system in order to inform future preventive efforts.

RESEARCH DESIGN AND METHODS

We conducted a retrospective cohort study using the enterprise-wide electronic medical record (EMR) in the CCHS. Our study sample was a cohort with type 2 diabetes, established using data from 2005 to 2015 in the CCHS that was created using a modified version of the Kho algorithm (20,21).

Identification of Type 2 Diabetes and Study Cohort

The type 2 diabetes study cohort was created based upon ICD-9/-10 codes (250X, E11X). The algorithm was used to calculate the earliest date when a patient record contained any of the following combinations: *1*) type 2 diabetes code and type 2 diabetes medication, *2*) type 2 diabetes code and abnormal glucose, *3*) type 2 diabetes code recorded twice and outpatient insulin, *4*) type 2 diabetes medication and abnormal glucose, *5*) insulin preceded by type 2 diabetes medication. Combinations preceded by a type 1 diabetes code (ICD-9 or ICD-10) were discarded. Codes for ketoacidosis were classified as type 1 diabetes codes and also discarded. The earliest date that any of the five conditions above were met was documented as the date in which the patient met the criteria for type 2 diabetes. To be included each year in the 10-year cohort for this study from January 2006 to December 2015, a patient must have had an outpatient visit in a primary care (internal medicine [IM] or family medicine [FM]) department or in the endocrinology department at least once every 2 years. Patients with a history of gastric bypass were excluded from the study population, given the possibility that hypoglycemia may occur at different rates or be treated differently in this population.

Identification of Severe Hypoglycemia

Severe hypoglycemia events were identified based upon previous definitions (22,23). We identified ED visits and hospitalizations for hypoglycemia in the EMR using the following ICD-9 codes present in the encounter: 251.0 (hypoglycemic coma), 251.1 (other specified hypoglycemia), and 251.2 (hypoglycemia, unspecified). Additionally, the following ICD-10 codes were used: E08.641, E11.641, E11.649, E13.64, E13.641, E13.649, E16.0, E16.1, E15, and E16.2. During the course of the study, we verified with review of a subset of charts that our reported events captured these severe hypoglycemia events as intended.

Identification of Diabetes Medications

We identified a diabetes medication class as active if it was on the outpatient medication list in the EMR. Medication classes include the following: metformin, sulfonylurea, meglitinide, insulin (basal or bolus), glucagon-like peptide 1 (GLP-1) agonist, dipeptidyl peptidase 4 (DPP-4) inhibitor, α-glucosidase inhibitor (AGI), sodium–glucose cotransporter 2 (SGLT2) inhibitor, and thiazolidinedione (TZD).

Patient Characteristics

We identified the following patient demographic characteristics: age, sex, race, and income, defined as the 2011–2015 five-year estimates of median household income at the block group level obtained from the American Community Survey conducted by the U.S. Census Bureau (24). Clinical characteristics included BMI, HbA_{1c} within the last 12 months, number of diabetes medications, and Charlson comorbidity score (25,26). We also captured a previous history of nonsevere hypoglycemia diagnoses, defined as ICD codes in an EMR encounter that were not related to an ED visit or hospitalization and occurred prior to the severe hypoglycemia event for the group that experienced an event and prior to the last IM, FM, or endocrinology appointment for those who did not have a severe hypoglycemia event.

The presence of patient comorbidities was captured using the following diagnoses and associated ICD-9/-10 codes: dementia, cognitive impairment, cardiovascular disease, congestive heart failure, chronic kidney disease, depression, other psychiatric diagnoses, and alcohol or substance abuse (Supplementary Table 1). These comorbidities were chosen based upon previous literature associating risk of severe hypoglycemia with comorbid conditions.

Statistical Analysis

We identified the incidence proportion of severe hypoglycemia events in each year between 2006 and 2015 and reported these as counts and percentages. The denominator for the yearly proportions was the total number of patients with type 2 diabetes in the CCHS in each year who had either a primary care or endocrinology visit within 2 years. Specifically, the number of patients at risk was captured if the patient was present in the cohort between 1 January and 31 December for each year and the patient had an appointment with primary care or endocrinology in the time frame of 1 January from the year before through 31 December of the year reported. This was done to ensure

that the denominator captured in this calculation included active patients in our health system. In reporting the yearly event numbers, we reported the numbers of events that represented the first severe hypoglycemia event in the data set for a patient, the second event, or events in addition to the second event. As our study is an open cohort, we calculated the proportions of severe hypoglycemia per year based on the denominator of patients with type 2 diabetes each year and did not use censoring to calculate the yearly incidence proportions. However, we also calculated and reported the number of patients who were present in the denominator from the year prior.

Patient characteristics were compared at the last primary care or endocrinology outpatient visit between patients who experienced a hypoglycemia event and those who did not. In the group of patients with a hypoglycemia event, the last visit captured was the last outpatient visit before the event, and for those without an event, the last recorded outpatient visit was used. Variables are reported as median with interquartile ranges (IQRs) for continuous variables or numbers and percentages for categorical variables. We reported medians with IQR because our continuous variables were not normally distributed. The Mann-Whitney *U* test was used for continuous variables and χ^2 test was used for categorical variables with a significance level of 0.05. To adjust for the multiple comparisons, we used Bonferroni testing for variable significance. To further characterize the association of very low HbA_{1c} (<6% [42 mmol/mol]) with severe hypoglycemia events, we compared frequency of HbA_{1c} <6% (42 mmol/mol) in the groups with and without severe hypoglycemia.

In addition, to increase understanding for planning future interventions to prevent hypoglycemia, for those patients with a severe hypoglycemia event, patient characteristics were reported at the time of the first severe hypoglycemia event and compared with those at the time of the last recorded primary care or endocrinology outpatient visit, with the thought that an intervention could be implemented at the time of the outpatient assessment.

A multivariable logistic regression analysis was performed to control for potential confounding variables. All variables from the univariate analyses were included in the regression analysis with the following exceptions: *1*) medication combination variables, which are reported in the univariate analyses for clinical relevance, were not included in the regression, as these variables would cause confounding if included as separate variables; *2*) HbA_{1c} <6% (42 mmol/mol) was included in the regression instead of HbA_{1c} as a continuous variable, as only the former was significant in the univariate analysis and it may also be of significant clinical interest for hypoglycemia prevention efforts; and *3*) for number of diabetes medications, we chose only the continuous variable in the regression, as both the categorization (one, two, and three or more medications) and continuous variables were significant in the univariate analysis and use of both variables would cause confounding. To handle missing variables, for the BMI and HbA_{1c} variables we carried over the values from earlier records (if they existed). Otherwise, multiple imputation by chained equations was used. The model was constructed using patient characteristics, medication regimen, and comorbidity variables known at the time of the severe hypoglycemia event for those experiencing an event and at the last IM, FM, or endocrinology visit for those not experiencing an event. Statistical analyses were performed using the R statistical software, version 3.4.0 (https://cran.r-project.org/). This protocol was approved by the institutional review board at Cleveland Clinic.

RESULTS

Baseline characteristics of the 50,439 patients in the study cohort at time of entry with diabetes diagnosis are shown in Table 1. The highest percentage of patients who were taking a diabetes medication were taking metformin alone. The median age of the cohort was 61.0 years, and 51.7% were male. The majority of patients were Caucasian (74.1%), and 16.8% were black. The median HbA_{1c} was 6.9% (52 mmol/mol) and median BMI was 32.4 kg/m^2. A significant proportion of patients had a documented history of cardiovascular disease (32.9%), depression (14.8%), or other psychiatric diagnoses (21.8%). The study cohort had a mean follow-up time in the data set of 3.6 years (median 2.8 years [IQR 1.4, 5.3] [minimum 0 years and maximum 10 years]).

The incidence proportions of severe hypoglycemia requiring an ED visit or hospitalization increased from 0.12% (8 events/6,491 patients with type 2 diabetes) in 2006 to 0.31% (101 events/33,114 patients with type 2 diabetes) in 2015 (P = 0.01) (Table 2). A greater proportion of severe hypoglycemia episodes were hospitalizations compared with ED visits alone within each calendar year (63% in 2006 and 88% in 2015). The number of ED sites represented increased from 4 in 2006 to 14 in 2015, while the number of hospital sites represented increased from 10 to 14 in the same time period. Most of the severe hypoglycemia events were the first such event for patients in the data set, although recurrent events were frequent.

The univariate analyses of characteristics of patients with a severe hypoglycemia event compared with those without a severe hypoglycemia event captured at the last primary care or endocrinology visit are reported by hypoglycemia group in Supplementary Table 2 and by variable group in Supplementary Table 3. Compared with patients who did not experience a severe hypoglycemia episode, those with severe hypoglycemia included a greater proportion of patients who were older (71.9 vs. 64.1 years, $P < 0.001$) and had a lower BMI (29.2 vs. 31.7 kg/m^2, $P < 0.001$), but median HbA_{1c} was similar (6.8% [51 mmol/mol] vs. 6.7% [50 mmol/mol], P = 0.925). A significantly higher proportion of patients treated with insulin alone, a sulfonylurea alone, insulin with a sulfonylurea in addition to another diabetes medication, or a sulfonylurea with another diabetes medication (other than insulin) had severe hypoglycemia. A greater percentage of patients treated with three or more diabetes medications in any class had severe hypoglycemia (26.5% vs. 18.5%, $P < 0.001$). A significant proportion of black patients experienced severe hypoglycemia compared with the prevalence of black race at baseline—32.2% of patients with severe hypoglycemia were black vs. 60.4% Caucasian ($P < 0.001$)—and those with severe hypoglycemia had a lower median income ($48,000 vs. $54,000, $P < 0.001$). There was a significantly greater prevalence of comorbidities in patients with severe hypoglycemia, including dementia, cognitive impairment, cardiovascular disease, congestive heart failure, and chronic kidney disease, and a higher Charlson comorbidity score (4 vs. 2,

Table 1—Baseline characteristics of study cohort

Variable	Number missing	All patients = 50,439
Diabetes medication		
No medication		10,357 (20.5)
AGI		30 (0.1)
DPP-4 inhibitor alone		564 (1.1)
GLP-1 agonist alone		163 (0.3)
Metformin alone		18,694 (37.1)
Meglitinide alone		35 (0.1)
TZD alone		915 (1.8)
Insulin alone		2,201 (4.4)
Insulin + other diabetes medication		2,030 (4.0)
Insulin + sulfonylureas + other diabetes medication		1,869 (3.7)
No insulin and no sulfonylureas + 2 or more diabetes medications		3,077 (6.1)
SGLT2 inhibitor alone		22 (0)
Sulfonylureas alone		2,991 (5.9)
Sulfonylureas + other diabetes medication		7,491 (14.9)
Number of diabetes medications		
0		10,357 (20.5)
1–2		34,291 (68)
≥3		5,791 (11.5)
Age at entering cohort (years)		61.0 (51.9, 69.9)
Race	1,222 (2.4)	
Caucasian		37,386 (74.1)
Black		8,439 (16.8)
Asian/Pacific Islander		753 (1.5)
Other		2,639 (5.2)
Sex	1 (0)	
Female		24,344 (48.3)
Male		26,094 (51.7)
Income (in thousands)	5,906 (12)	54.2 (39.4, 73.0)
BMI, kg/m^2	12,687 (25)	32.4 (28.3, 37.8)
HbA_{1c}, % [mmol/mol]	20,104 (40)	6.9 (6.5, 8) [52 (48, 64)]
Dementia		627 (1.2)
Cognitive impairment		810 (1.6)
Cardiovascular disease		16,605 (32.9)
Congestive heart failure		2,984 (5.9)
Chronic kidney disease		2,577 (5.1)
Depression		7,464 (14.8)
Other psychiatric diagnoses		10,984 (21.8)
Alcohol or substance abuse		4,604 (9.1)
Charlson comorbidity index		1 (1, 2)
History of hypoglycemia		412 (0.8)

Data are *n* (%) or median (IQR).

$P < 0.001$). There was a similar prevalence of depression, other psychiatric diagnoses, and alcohol or substance abuse in those with and those without severe hypoglycemia. Nine percent of patients who experienced severe hypoglycemia had a documented previous history of nonsevere hypoglycemia in the EMR prior to the severe hypoglycemia episode compared with 2.2% documented in patients who did not experience severe hypoglycemia prior to their last IM, FM, or endocrinology visit in the data set ($P < 0.001$).

In the subset of patients with severe hypoglycemia (N = 366), 16.1% (N = 59) had HbA_{1c} <6% (42 mmol/mol), while in patients without severe hypoglycemia (N = 50,073), only 12.0% (N = 5,990) had HbA_{1c} <6% (42 mmol/mol) (P for difference = 0.01).

The multivariable logistic regression analysis based upon variables obtained at the last IM, FM, or endocrinology visit for patients without hypoglycemia and at the time of the severe hypoglycemia event for those with severe hypoglycemia is shown in Table 3. This confirms an increased odds for severe hypoglycemia event with the use of insulin (odds ratio [OR] 2.77, $P < 0.001$), with the use of sulfonylureas (OR 2.49, $P < 0.001$), with an increased number of diabetes medications (OR 1.56, $P < 0.001$), with history of nonsevere hypoglycemia (OR 3.01, $P < 0.001$), and with HbA_{1c} <6% (42 mmol/mol) (OR 1.95, $P < 0.001$), black race (OR 2.55, $P < 0.001$), cardiovascular disease (OR 1.68, P 0.001), congestive heart failure (OR 1.33, P 0.04), and increased Charlson comorbidity index (OR 1.15, $P < 0.001$). Other comorbidities including dementia, cognitive impairment, chronic kidney disease, depression, other psychiatric diagnoses, and alcohol/substance abuse were not significantly associated with severe hypoglycemia in this model. Lower odds of severe hypoglycemia were noted with higher BMI and use of metformin, DPP-4 inhibitors, or GLP-1 agonists. The model was adjusted for age, sex, and median income.

Characteristics of patients captured at their last primary care or endocrinology outpatient visit compared with the time of the severe hypoglycemia event are shown in Table 4. The visits reported represent visits with 41 unique endocrinology providers and 208 unique IM or FM providers. The time elapsed between the last primary care or endocrinology visit and the severe hypoglycemia event was a mean of 3.3 and median of 1.5 months (IQR 0.5, 3.5). A significantly greater proportion of patients were taking insulin, either alone or with other diabetes medications, were taking three or more diabetes medications in any class, had a diagnosis of cardiovascular disease, had a trend toward diagnoses of chronic kidney disease, and had a higher Charlson comorbidity score at the time of the severe hypoglycemia event as compared with their last outpatient IM, FM, or endocrinology visit. There was no significant difference between HbA_{1c} values at the last visit and at the time of the severe hypoglycemia episode (median HbA_{1c} 6.8% [51 mmol/mol] vs. 6.7% [50 mmol/mol], P = 0.41).

CONCLUSIONS

In this retrospective study of patients with type 2 diabetes in a large health system, we found that the incidence proportion of severe hypoglycemia defined as an

Table 2—Annual incidence proportion of severe hypoglycemia events in a type 2 diabetes prevalence cohort from 2006 to 2015

	Year									
	2006	2007	2008	2009	2010	2011	2012	2013	2014	2015
Emergency sites	4	4	4	5	6	12	13	13	14	14
Hospitalization sites	10	10	10	11	11	13	13	13	14	14
Patients at risk	6,491	9,331	11,314	12,562	15,150	17,888	20,726	24,419	27,796	33,114
Patients at risk from previous year		5,608	7,991	8,797	11,236	13,549	16,052	18,771	21,839	24,758
SH	8 (0.12)	7 (0.07)	7 (0.06)	34 (0.27)	42 (0. 28)	45 (0.25)	72 (0.35)	79 (0.32)	92 (0.33)	101 (0.31)
1st SH in data set	8	7	5	26	28	31	56	58	68	81
2nd SH in data set			2	8	14	14	11	15	18	16
>2 SHs in data set							5	6	6	4
SH ED visits	3 (38)	2 (29)	2 (29)	4 (12)	3 (7)	4 (9)	7 (10)	5 (6)	4 (4)	12 (12)
SH hospitalizations	5 (63)	5 (71)	5 (71)	30 (88)	39 (93)	41 (91)	65 (90)	74 (94)	88 (96)	89 (88)

Data are *n* or *n* (%). SH, severe hypoglycemia event.

ED visit or hospitalization significantly increased over 10 years from 2006 to 2015 from 0.12% to 0.31%, with most events resulting in hospitalization. The median HbA_{1c} was <7% (53 mmol/mol) in the cohort and was not significantly different in those who developed severe hypoglycemia and those who did not. Our regression model demonstrated an increased odds for severe hypoglycemia with a history of nonsevere hypoglycemia, HbA_{1c} <6% (42 mmol/mol), black race, and increased comorbidities, as well as with the use of insulin, sulfonylureas, and increased number of diabetes medications.

Table 3—Regression model of severe hypoglycemia events to identify important patient characteristics associated with severe hypoglycemia

Variables	OR (95% CI)	*P*
Intercept	0.001 (0, 0.004)	<0.001
Insulin	2.773 (1.975, 3.892)	<0.001
Sulfonylureas	2.487 (1.919, 3.223)	<0.001
AGI	2.049 (0.699, 6.009)	0.19
DPP-4 inhibitor	0.514 (0.354, 0.744)	0.001
GLP-1 agonist	0.225 (0.081, 0.623)	0.004
Metformin	0.431 (0.321, 0.578)	<0.001
Meglitinide	1.181 (0.492, 2.833)	0.71
SGLT2 inhibitor	0.001 (0, 1.8e+14)	0.71
TZD	0.725 (0.433, 1.215)	0.22
Number of diabetes medications	1.558 (1.357, 1.789)	<0.001
History of nonsevere hypoglycemia diagnosis	3.01 (2.087, 4.343)	<0.001
Age	1.009 (0.998, 1.02)	0.10
BMI	0.962 (0.945, 0.98)	<0.001
HbA_{1c} <6% (42 mmol/mol)	1.952 (1.436, 2.652)	<0.001
Median income	1.002 (0.997, 1.006)	0.41
Male sex	0.672 (0.532, 0.849)	0.001
Race		
Caucasian	Reference	
Black	2.553 (1.962, 3.322)	<0.001
Asian/Pacific Islander	1.221 (0.38, 3.928)	0.73
Other	0.798 (0.389, 1.638)	0.54
Dementia	0.773 (0.487, 1.226)	0.27
Cognitive impairment	1.398 (0.949, 2.057)	0.09
Cardiovascular disease	1.684 (1.242, 2.283)	0.001
Congestive heart failure	1.331 (1.013, 1.75)	0.04
Chronic kidney disease	1.266 (0.949, 1.688)	0.11
Depression	1.081 (0.815, 1.434)	0.59
Other psychiatric diagnoses	0.924 (0.712, 1.199)	0.55
Alcohol or substance abuse	1.045 (0.765, 1.428)	0.78
Charlson comorbidity index	1.153 (1.096, 1.212)	<0.001

Previous work has identified black race, recent hospital discharge, and use of medication from five or more therapeutic classes (27), as well as dementia and cognitive impairment (28), as risk factors for severe hypoglycemia in older adults, and cardiovascular disease, congestive heart failure, chronic kidney disease, and depression have been associated with severe hypoglycemia (18). Intensive treatment of diabetes in clinically complex patients has also been associated with increased risk of severe hypoglycemia (29). However, hospitalizations for severe hypoglycemia have been shown to remain high in adults over age 75 years and in black patients covered by Medicare fee-for-service insurance (30). Our study supports these previous findings of increased proportions of patients with severe hypoglycemia in the groups on multiple antidiabetes drugs, those with multiple comorbidities, and those of black race.

In our study, the median HbA_{1c} was <7% (53 mmol/mol) both in patients with and in patients without severe hypoglycemia but with a greater proportion of those with HbA_{1c} <6% (42 mmol/mol) in the group with severe hypoglycemia. The increased odds of severe hypoglycemia with a very low HbA_{1c} was also demonstrated in our regression model. This is different from a previous report that found higher HbA_{1c} to be associated with severe hypoglycemia (18). However, consideration of deintensification of diabetes treatment in patients at risk for hypoglycemia has previously been advocated (31) and may be beneficial in a population similar to our study cohort with multiple comorbidities. The possibility of glycemic overtreatment

Table 4—Patients with severe hypoglycemia: characteristics at last IM, FM, or endocrinology visit compared with those at the hypoglycemia event

Variable	Characteristic at last visit (*N* = 366)	Characteristic at severe hypoglycemia event (*N* = 366)	*P*
Diabetes medication*			<0.001
No medication	20 (5.5)	15 (4.1)	
AGI alone	2 (0.5)	1 (0.3)	
DPP-4 inhibitor alone	3 (0.8)	4 (1.1)	
GLP-1 agonist alone	0 (0)	0 (0)	
Metformin alone	24 (6.6)	14 (3.8)	
Meglitinide alone	0 (0)	0 (0)	
TZD alone	3 (0.8)	0 (0)	
Insulin alone	88 (24)	107 (29.2)	
Insulin + other diabetes medication	23 (6.3)	36 (9.8)	
Insulin + sulfonylureas + other diabetes medication	41 (11.2)	87 (23.8)	
No insulin and no sulfonylureas + 2 or more diabetes medications	4 (1.1)	0 (0)	
SGLT2 inhibitor alone	0 (0)	0 (0)	
Sulfonylureas alone	59 (16.1)	45 (12.3)	
Sulfonylureas + other diabetes medication	99 (27)	57 (15.6)	
Number of diabetes medications†			0.002
0	20 (5.4)	15 (4.1)	
1–2	249 (68)	210 (57.4)	
≥3	97 (26.5)	141 (38.5)	
History of nonsevere hypoglycemia diagnosis	33 (9)	42 (11.5)	0.27
Age at visit, years	71.85 (61.35, 80.54)	72.04 (61.48, 80.75)	0.74
BMI, kg/m^2	29.2 (25.0, 34.1)	29.22 (24.68, 34.38)	0.77
HbA$_{1c}$, % [mmol/mol]	6.8 (6.1, 8) [51 (43, 64)]	6.7 (6, 7.8) [50 (42, 62)]	0.41
Dementia	25 (6.8)	33 (9)	0.27
Cognitive impairment	36 (9.8)	47 (12.8)	0.20
Cardiovascular disease	260 (71)	284 (77.6)	0.04
Congestive heart failure	121 (33.1)	144 (39.3)	0.08
Chronic kidney disease	134 (36.6)	160 (43.7)	0.05
Depression	96 (26.2)	104 (28.4)	0.51
Other psychiatric diagnoses	131 (35.8)	153 (41.8)	0.10
Alcohol or substance abuse	61 (16.7)	71 (19.4)	0.34
Charlson comorbidity index	4 (3, 7)	5.5 (3, 7)	<0.001

Data are *n* (%) or median (IQR). *Bonferroni-adjusted pairwise χ^2 test for insulin + sulfonylureas + other diabetes medication versus sulfonylureas alone, as well as for insulin + sulfonylureas + other diabetes medication versus sulfonylureas + other diabetes medication, is significant. †Bonferroni-adjusted pairwise χ^2 test for one to two medications versus three or more medications is significant.

in patients at high risk for severe hypoglycemia has also been a target for awareness in the Veterans Health Administration as part of the Choosing Wisely initiative (32,33). Tseng et al. (34) demonstrated that a significant proportion of patients with risk factors for severe hypoglycemia cared for in the Veterans Health Administration were receiving treatment with insulin and or sulfonylureas and had evidence of intensive treatment, suggesting possible overtreatment in these high-risk groups.

In our study of real-world practice EMR data, the fact that 9% of patients experiencing severe hypoglycemia had a previous history of documented nonsevere hypoglycemia is a significant observation, and our regression model also shows a significantly higher odds (3.01) of severe hypoglycemia in patients with this history. The ability to capture documented nonsevere hypoglycemia in the EMR presents an additional opportunity to use our EMR systems to identify patients who may be at increased risk for severe hypoglycemia based upon this history in addition to demographic characteristics and comorbidities previously identified as associated with severe hypoglycemia. Identifying patients at risk for severe hypoglycemia using data readily available in the EMR can promote appropriate strategies for either deintensification of diabetes treatment or a change in treatment choices at the point of care for prevention of severe hypoglycemia events. Our finding that a greater proportion of patients were taking insulin or were taking three or more diabetes medications and had more comorbidities at the time of the severe hypoglycemia event as compared with their last outpatient primary care or endocrinology visit leads us to question whether treatment may have actually been inappropriately intensified at that last visit, especially in patients at risk for comorbidities. The EMR may be used to reduce missed opportunities at the time of the outpatient visit to identify at-risk patients and to make changes in modifiable risk factors, such as switching to medications that may have lower risk of hypoglycemia, to prevent a severe hypoglycemia event.

While hypoglycemia can limit the ability for patients with type 2 diabetes to reach a target treatment goal and is associated with additional risks that can affect quality of life, the health care costs of hypoglycemia in type 2 diabetes can also be significant, with a mean cost previously estimated at $17,564 for a hospital admission and $1,387 for an ED visit (35). Thus, identifying patients who may be at risk for severe hypoglycemia and implementing prevention strategies is of utmost importance to both improve health outcomes of patients with type 2 diabetes and reduce costs.

Our study is strengthened by our use of a shared EMR across our entire health system, but a limitation is the documentation of hypoglycemia as well as comorbidities using ICD codes, which relies on provider coding practices. It may be that improved coding for hypoglycemia as a diagnosis in an ED or hospital encounter could have explained some of the increase in rate of severe hypoglycemia events captured in the time frame of our study, specifically, between 2008 and 2009. However, the number of patients with type 2 diabetes in our data set also steadily increased during the time period of our study, as did the number of sites in our health system. Our model did not adjust for clustering of severe hypoglycemia by site or for recurrent events, given the low number of events per site, but this will be

explored in future work as we improve our ability to capture severe hypoglycemia in the EMR through more accurate coding practices. In addition, the mean follow-up time in our cohort was 3.6 years. This may have limited our ability to model factors associated with severe hypoglycemia because of survivorship bias. However, as we took care to limit our population to patients who had evidence of obtaining regular care in our health system, our findings reflect real-world health system data and thus have implications for preventive efforts using our current EMR systems.

It is also likely that we have underestimated the occurrence of nonsevere hypoglycemia by solely using ICD codes to identify the events. Adding the use of natural language processing of "free-text" progress notes may allow for better capture of documented hypoglycemia (both severe and nonsevere episodes) (36) in future work. In addition, while our focus in this work was on severe hypoglycemia episodes, which are more likely to be documented than less severe hypoglycemia, we have not captured episodes of severe hypoglycemia that may have been treated outside our health system. For example, patients may have been assessed and treated for severe hypoglycemia by calling an emergency medical service to their home and subsequently not transferred to an ED if symptoms had resolved. Finally, our record of medication use was based upon EMR documentation and not on pharmacy data documenting that the medication prescription was indeed filled. However, even with pharmacy data, it may not be possible to ascertain compliance with a medication regimen in a retrospective study.

In this retrospective study of patients with type 2 diabetes in a large, integrated health system, we identified characteristics of patients experiencing severe hypoglycemia. Importantly, many patients with severe hypoglycemia had previously documented nonsevere hypoglycemia. Future work should focus on identification of patients at high risk at the point of care to allow for change in modifiable risk factors and prevention of severe hypoglycemia events.

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