Increased Mortality of Patients With Diabetes Reporting Severe Hypoglycemia

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OBJECTIVE—Hypoglycemia is a cause of significant morbidity among patients with diabetes and may be associated with greater risk of death. We conducted a retrospective study to determine whether patient self-report of severe hypoglycemia is associated with increased mortality.

RESEARCH DESIGN AND METHODS—Adult patients (N = 1,020) seen in a specialty diabetes clinic between August 2005 and July 2006 were questioned about frequency of hypoglycemia during a preencounter interview; 7 were lost to follow-up and excluded from analysis. Mild hypoglycemia was defined as symptoms managed without assistance, and severe hypoglycemia was defined as symptoms requiring external assistance. Mortality data, demographics, clinical characteristics, and Charlson comorbidity index (CCI) were obtained from the electronic medical record after 5 years. Patients were stratified by self-report of hypoglycemia at baseline, demographics were compared using the two-sample t test, and risk of death was expressed as odds ratio (95% CI). Associations were controlled for age, sex, diabetes type and duration, CCI, HbA_{1c}, and report of severe hypoglycemia.

RESULTS—In total, 1,013 patients with type 1 (21.3%) and type 2 (78.7%) diabetes were questioned about hypoglycemia. Among these, 625 (61.7%) reported any hypoglycemia, and 76 (7.5%) reported severe hypoglycemia. After 5 years, patients who reported severe hypoglycemia had 3.4-fold higher mortality (95% CI 1.5–7.4; P = 0.005) compared with those who reported mild/no hypoglycemia.

CONCLUSIONS—Self-report of severe hypoglycemia is associated with 3.4-fold increased risk of death. Patient-reported outcomes, including patient-reported hypoglycemia, may therefore augment risk stratification and disease management of patients with diabetes.

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Diabetes is the seventh leading cause of death in the U.S., affecting 11.3% of the adult population and accounting for $174 billion in direct and indirect costs per year (1). Significant strides have been made in the diagnosis and management of diabetes, yet despite early evidence suggesting that glycemic control may lower micro- and macrovascular event risk (2–5), large randomized controlled trials have failed to demonstrate clear reduction in mortality with intensification of treatment (6–8). Moreover, hypoglycemia has come to the forefront as a barrier to attaining glycemic control, causing significant morbidity among patients with diabetes (9,10).

Recent post hoc analyses of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) (11) and Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation (ADVANCE) (12) trials examining the outcomes of intensive glycemic control find an alarming association between hypoglycemia and mortality. Although neither ACCORD nor ADVANCE found evidence that any deaths were caused directly by hypoglycemia, patients who experienced severe hypoglycemia did have significantly higher rates of death (11,12) as well as micro-, macro-, and nonvascular complications (12). The cause of increased fatal and nonfatal adverse events among patients with severe hypoglycemia is uncertain, though some have proposed that hypoglycemia may be a surrogate measure of overall morbidity and disease burden (12).

The major diabetes clinical trials and the American Diabetes Association have traditionally defined severe hypoglycemia as an acute episode meeting two criteria: *1*) blood glucose level <3.9 mmol/L (70 mg/dL) or presence of typical signs and symptoms of hypoglycemia without an alternative cause that resolved with administration of glucose, and *2*) need for external assistance, whether medical or nonmedical (11–13). The ACCORD study did assess patient self-report of hypoglycemia but did not classify patient-reported symptoms as events unless also confirmed by laboratory testing (11).

Patient-reported outcomes (PROs) are readily available, less expensive and invasive to collect, and can be obtained by non–health care professionals in a variety of formats and settings. In contrast, clinical outcomes require direct contact between the patient and a health care provider and diagnostic testing, both of which increase cost of care, health system use, and opportunities for adverse events. PROs have been used extensively in cancer treatment research for >20 years (14), with significant benefit to clinical decision making (15). We propose that similar benefits may be gleaned from the use of PROs in diabetes management, specifically focusing on the relationship between patient-reported hypoglycemia and mortality.

RESEARCH DESIGN AND METHODS

—Adult (aged ≥18 years) patients with established diabetes (N = 1,020) seen by a health professional in a specialty diabetes clinic during a 12-month period (August 2005 through July 2006) had provided written informed consent for their demographics, clinical data, and contact information to be used for subsequent research. Patients who had no

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contact with our institution after the initial visit ($n = 7$) were excluded from analysis. This study was approved by the Mayo Clinic Institutional Review Board.

Measures

Prior to the index clinical encounter, each patient was questioned about the frequency of hypoglycemic events during the preceding 6 months; answers were recorded in the diabetes electronic management system as previously described (16). Mild hypoglycemia was described as symptoms of dizziness, blurry vision, confusion, and/or sweating that the patient was able to terminate without assistance. Severe hypoglycemia was described as similar symptoms that required external assistance.

Participant demographics and diabetes type (autoimmune or type 1 diabetes vs. type 2 diabetes) as well as baseline duration of disease (time from first diagnosis), treatment modality, and HbA_{1c} were obtained from the electronic medical record (EMR). Administrative data and EMR were used to derive ICD-9 diagnosis codes and calculate the Charlson comorbidity index (CCI) for the 1 year before the index visit date (2004–2005) and at follow-up (2010). The CCI is an extensively studied and widely used measure that weighs comorbid conditions by the strength of their association with 1-year mortality (17,18); it has been previously validated for use in diabetes (19). Five-year mortality data were obtained from institutional EMR and registration data, as well as the Social Security Death Index (SSDI). Participants were deemed as living if they had a clinical encounter within 6 months of ascertainment date and did not have a documented death in either the EMR or the SSDI. This strategy failed to locate two patients, who had neither a social security number nor a clinical encounter, and they were called by a member of the study team to verify their status. Both were confirmed to be living.

Statistical analyses

Univariate analyses were performed to obtain descriptive statistics of individual variables. Measures of association were tested using bivariate analyses (two-sample t test for continuous variables and χ^2 test for categorical variables) while controlling for age, sex, diabetes type and duration, CCI, and hypoglycemia history. Logistic regression was used to calculate the risk of death expressed as odds ratio (OR) and 95% CI. All analyses for this study were done using SAS version 9.2 for Windows (SAS Institute Inc., Cary, NC).

RESULTS—Patient demographics from the index visit are summarized in Table 1. Patients ranged in age from 18 to 93 years (mean 60.5 ± 15.2 years) and included 216 (21.3%) patients with type 1 diabetes and 797 (78.7%) with type 2 diabetes. Approximately half (54.8%) were male. Mean HbA_{1c} was 7.2 ± 1.4%, and CCI utility index score was 1.9 ± 1.9.

Among all patients, all-cause mortality at 5 years was 13.8% (Table 1). Deceased patients were significantly more likely to have had reported severe hypoglycemic events at baseline ($P = 0.01$), yet there was no difference in baseline HbA_{1c} between patients who had died and those who remained living. Irrespective of self-reported hypoglycemia, those who had died were significantly older (68.1 ± 13.7 vs. 59.2 ± 15.0 years; $P < 0.001$) and more likely to be male (66.4 vs. 52.9%; $P = 0.003$) compared with those who were alive at 5 years. They also had longer duration of diabetes (15.6 ± 11.6 vs. 13.3 ± 11.3 years; $P = 0.025$) and higher baseline CCI (3.6 ± 3.1 vs. 1.6 ± 1.5; $P < 0.001$) than those who did not die. This is consistent with previously reported direct relationships between CCI and mortality among patients with diabetes (19,20). Nevertheless, when controlling for these factors, self-report of severe hypoglycemia remained predictive of mortality at 5 years.

Self-report of severe hypoglycemia

Severe hypoglycemic events were reported by 76 of 1,013 (7.5%) patients. Although at baseline, those who had reported severe hypoglycemia were slightly younger than those who had reported no or mild hypoglycemia (57.1 ± 15.9 vs. 60.7 ± 15.1; $P = 0.043$), there was no difference in age at time of death between these two groups (Table 2). Patients with self-reported hypoglycemia also had longer duration of diabetes ($P < 0.001$) and higher prevalence of type 1 diabetes ($P < 0.001$) compared with those who reported no/mild hypoglycemia.

Five-year mortality was significantly higher among patients who reported severe hypoglycemia than in those who reported no/mild hypoglycemia (23.7 vs. 13.0%; $P = 0.01$). Self-report of severe hypoglycemia was also associated with higher baseline HbA_{1c} (7.6 ± 1.5 vs. 7.2 ± 1.4%; $P = 0.017$). It is important that there was no difference in either baseline or 5-year CCI between the groups, suggesting that their overall health remained comparable throughout the observation period.

Overall, patient self-report of severe hypoglycemia increased the risk of death at 5 years by nearly 3.4-fold (OR 3.381 [95% CI 1.547–7.388]); this association remained significant after adjustment for likely confounders of age, sex, diabetes type and duration, HbA_{1c}, and CCI (Table 3). Self-report of mild hypoglycemia also trended toward higher mortality risk compared with no hypoglycemia (1.564 [0.986–2.481]), but this difference failed to reach statistical significance. Additional predictive variables were, as expected, age, male sex, and overall burden of disease as measured by the CCI (Table 3). It is important that diabetes type and duration, as well as higher HbA_{1c}, did not increase mortality risk.

CONCLUSIONS—Hypoglycemia is the most common significant and treatment-limiting adverse effect in patients with diabetes (9,10). Yet current guidelines and quality accountability metrics focus almost exclusively on prevention of hyperglycemia (21) and fail to take into consideration PROs. Nearly 8% of patients in our study

Table 1—*Patient demographics and 5-year mortality*

	All	Alive	Deceased	*P* value
Number of patients (%)	1,013	873 (86.2)	140 (13.8)	
Age at baseline (years), mean (SD)	60.5 (15.2)	59.2 (15.0)	68.1 (13.7)	<0.001
Men, *n* (%)	555 (54.8)	462 (52.9)	93 (66.4)	0.003
Type 1 diabetes, *n* (%)	216 (21.3)	195 (22.3)	21 (15.0)	0.049
Diabetes duration (years), mean (SD)	13.6 (11.4)	13.3 (11.3)	15.6 (11.6)	0.025
HbA_{1c} (%), mean (SD)	7.2 (1.4)	7.2 (1.3)	7.2 (1.6)	0.792
CCI, mean (SD)	1.9 (1.9)	1.6 (1.5)	3.6 (3.1)	<0.001
Hypoglycemia, *n* (%)				
None	388 (38.3)	342 (39.2)	46 (32.9)	0.153
Mild	549 (54.2)	473 (54.2)	76 (54.3)	0.982
Severe	76 (7.5)	58 (6.6)	18 (12.9)	0.010

Mortality data were obtained from the SSDI after 5 years of follow-up. *P* value compares those alive vs. deceased at time of follow-up. Unless otherwise specified, all values refer to baseline measurements.

Table 2—*Participant demographics and mortality as a function of hypoglycemia at enrollment*

	All	None/mild	Severe	*P* value
Number of participants (%)	1,013	937 (92.5)	76 (7.5)	
Mortality, *n* (%)	140 (13.8)	122 (13.0)	18 (23.7)	0.010
Men, *n* (%)	555 (54.8)	508 (54.2)	47 (61.8)	0.199
Age (years), mean (SD)				
Baseline	60.5 (15.2)	60.7 (15.1)	57.1 (15.9)	0.043
Time of death	70.7 (13.7)	71.0 (13.8)	69.1 (13.0)	0.576
Type 1 diabetes, *n* (%)	216 (21.3)	166 (17.7)	50 (65.8)	<0.001
Diabetes duration (years), mean (SD)	13.6 (11.4)	12.6 (10.7)	26.2 (12.2)	<0.001
HbA_{1c} (%), mean (SD)	7.2 (1.4)	7.2 (1.4)	7.6 (1.5)	0.017
CCI, mean (SD)				
Baseline	1.9 (1.9)	1.9 (1.9)	1.8 (1.5)	0.578
Follow-up	2.1 (1.9)	2.1 (1.9)	2.2 (1.8)	0.681
Change	0.31 (2.0)	0.31 (2.1)	0.34 (1.7)	0.928

P value compares groups reporting none/mild vs. severe hypoglycemia at baseline. Unless otherwise specified, all values refer to baseline measurements.

reported severe hypoglycemia, which is consistent with previously reported data (22,23). However, after following our patients for 5 years, we were able to demonstrate, for the first time, a significant correlation between patient self-report of severe hypoglycemia and increased mortality.

Indeed, patients who reported severe hypoglycemia had a nearly 3.4-fold higher risk of death at 5 years compared with those who reported either no or mild hypoglycemic symptoms. This is consistent with the 2.3- and 3.3-fold excess mortality rates observed among patients with clinically verified severe hypoglycemia in the standard treatment arms of ACCORD (11) and ADVANCE (12), respectively. The association between hypoglycemia and mortality has been observed in many other observational and prospective studies (24). Yet only the ACCORD study considered patient self-report of severe hypoglycemia as a potential covariate (11), and neither study counted patient-reported symptoms as true hypoglycemic events. Patient-reported severe hypoglycemia in ACCORD did in fact correlate with increased mortality risk in situations where medical assistance was required. Nonetheless, because no such correlation was observed in case subjects where only nonmedical assistance was provided, study authors concluded that patient-reported symptoms alone did not possess adequate predictive value (11).

Table 3—*Five-year mortality risk*

	OR	95% CI	*P* value
Age	1.047	1.027–1.066	<0.001
Male sex	1.716	1.135–2.596	0.011
Type 1 diabetes	0.836	0.410–1.706	0.623
Diabetes duration	1.006	0.985–1.027	0.595
HbA_{1c}	1.127	0.965–1.316	0.131
CCI	1.437	1.323–1.561	<0.001
Hypoglycemia			
Mild	1.564	0.986–2.481	0.468
Severe	3.381	1.547–7.388	0.005

OR for 5-year mortality was adjusted for age, sex, diabetes type and duration, HbA_{1c}, CCI, and hypoglycemia history. Unless otherwise specified, all measures were obtained at baseline.

However, it is important to distinguish the unique controlled environment of a clinical trial (25) from daily life. In closely monitored settings, severe hypoglycemic episodes are much more likely to be subjected to medical evaluation than in nonstudy settings. Events that were categorized as severe hypoglycemia requiring medical assistance, which did correlate with mortality in the ACCORD trial, may be more representative of real-world severe hypoglycemia than previously thought. Self-report of any severe hypoglycemia therefore may have a clinically significant effect on mortality risk, as found in our study.

There is no evidence that hypoglycemia itself was the direct cause of death in our study, ACCORD (11), or ADVANCE (12). Some have proposed that severe hypoglycemia is a surrogate measure of greater disease burden and, thus, an indirect marker of mortality risk in both ambulatory (12) and hospitalized (26) patients with diabetes. Yet our study failed to detect an association between hypoglycemia and morbidity as measured by the CCI. The latter is an extensively studied and widely validated measure of morbidity among patients with diabetes (19). Our study was limited by the use of institutional use data alone for the calculation of CCI scores, but because our institution is one of only two regional health systems providing care to the majority of residents in the surrounding area, we believe that this is unlikely to significantly lower calculated CCI values. Moreover, we expect this limitation to equally affect all participants in the study.

Alternative hypotheses for hypoglycemia-associated increase in mortality observed in our study and others include greater susceptibility to myocardial ischemia (27,28) and dysrhythmia (29,30), both of which may be triggered by hypoglycemia. Although no comprehensive assessment of causes of death was undertaken, on surface review, we found that the most frequent documented causes of death, including cardiovascular disease, infection, cerebrovascular disease, and end-stage renal disease, may have been exacerbated by hypoglycemia. Still, we do not have evidence suggesting that any of the deaths were directly linked to severe hypoglycemia.

We also did not detect a significant association between mortality and HbA_{1c}. It is possible that our study population was underpowered and the observation period too short to detect small differences in HbA_{1c}. Another limitation to our study is the merging of type 1 and type 2 diabetes diagnoses. Yet although patients with type 1 diabetes had a higher incidence of self-reported hypoglycemia, there was no respective difference in mortality between patients with type 1 and type 2 diabetes. Multivariate analysis also did not detect any significant association between diabetes type and mortality.

There are differences between our study results and outcomes previously reported by the large randomized controlled trials. All-cause mortality rate in our study was 13.8%, which is higher than what was observed in the comparable standard treatment arms of ACCORD (3.96%) (8) and ADVANCE (9.6%) (7). In a similar manner, the prevalence of severe hypoglycemia in our study was higher than that reported for the standard treatment arms of ACCORD (5.1%) (8) and ADVANCE (1.5%) (7). These discrepancies most likely reflect careful selection of study participants and exclusion of patients at highest risk for severe hypoglycemia. Indeed, the ACCORD trial excluded all patients with

history of severe hypoglycemia within 3 months or hypoglycemic seizure/coma within 12 months of the study; older participants were similarly excluded because of high hypoglycemia rates in the vanguard phase of the trial (31). Participants were closely monitored, received regular medical care, and had greater access to health professionals (25), all of which likely contributed to lower mortality rates than could have been otherwise expected.

Patient-reported metrics are becoming more important in chronic disease management. The 2010 Patient Protection and Affordable Care Act explicitly calls for "prioritization in the development of quality measures . . . that allow for the assessment of . . . patient experience and satisfaction" (32). Self-report of hypoglycemia is simple to measure, does not require a face-to-face clinical encounter, and is obtained without reliance on costly or invasive tests. In addition, our study suggests that it has important prognostic significance and is associated with 3.4-fold increase in 5-year mortality among ambulatory patients with diabetes. Patient report of severe hypoglycemia is therefore an important outcome to be included in chronic disease quality measures. We also encourage providers to routinely question their patients about severe hypoglycemia, educate them about hypoglycemia prevention and treatment strategies, and consider modifying treatment regimens to minimize risk of recurrent hypoglycemic events.

In conclusion, hypoglycemia is common in patients with type 1 and type 2 diabetes, increasing in prevalence with disease duration and higher HbA_{1c}. Patient-reported severe hypoglycemia is associated with 3.4-fold increase in 5-year mortality. Self-report of severe hypoglycemia is therefore an important prognostic indicator that should be included in the clinical assessment of each patient with diabetes.

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R.G.M. designed the study, analyzed data, and wrote the manuscript. H.K.V.H. and J.Y.Z. analyzed data and reviewed and edited the manuscript. N.D.S. and R.A.W. contributed to discussion and reviewed and edited the manuscript. S.A.S. designed the study, analyzed data, and reviewed and edited the manuscript. R.G.M. and S.A.S. 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.

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