

# HbA<sub>1c</sub> and Risk of Severe Hypoglycemia in Type 2 Diabetes

## The Diabetes and Aging Study

KASIA J. LIPSKA, MD, MHS<sup>1</sup>  
E. MARGARET WARTON, MPH<sup>2</sup>  
ELBERT S. HUANG, MD, MPH<sup>3</sup>  
HOWARD H. MOFFET, MPH<sup>2</sup>

SILVIO E. INZUCCHI, MD<sup>1</sup>  
HARLAN M. KRUMHOLZ, MD, SM<sup>4,5,6</sup>  
ANDREW J. KARTER, PHD<sup>2</sup>

**OBJECTIVE**—We examined the association between HbA<sub>1c</sub> level and self-reported severe hypoglycemia in patients with type 2 diabetes.

**RESEARCH DESIGN AND METHODS**—Type 2 diabetic patients in a large, integrated healthcare system, who were 30–77 years of age and treated with glucose-lowering therapy, were asked about severe hypoglycemia requiring assistance in the year prior to the Diabetes Study of Northern California survey conducted in 2005–2006 (62% response rate). The main exposure of interest was the last HbA<sub>1c</sub> level collected in the year preceding the observation period. Poisson regression models adjusted for selected demographic and clinical variables were specified to evaluate the relative risk (RR) of severe hypoglycemia across HbA<sub>1c</sub> levels. We also tested whether the HbA<sub>1c</sub>-hypoglycemia association differed across potential effect modifiers (age, diabetes duration, and category of diabetes medication).

**RESULTS**—Among 9,094 eligible survey respondents (mean age 59.5 ± 9.8 years, mean HbA<sub>1c</sub> 7.5 ± 1.5%), 985 (10.8%) reported experiencing severe hypoglycemia. Across HbA<sub>1c</sub> levels, rates of hypoglycemia were 9.3–13.8%. Compared with those with HbA<sub>1c</sub> of 7–7.9%, the RR of hypoglycemia was 1.25 (95% CI 0.99–1.57), 1.01 (0.87–1.18), 0.99 (0.82–1.20), and 1.16 (0.97–1.38) among those with HbA<sub>1c</sub> <6, 6–6.9, 8–8.9, and ≥9%, respectively, in a fully adjusted model. Age, diabetes duration, and category of diabetes medication did not significantly modify the HbA<sub>1c</sub>-hypoglycemia relationship.

**CONCLUSIONS**—Severe hypoglycemia was common among patients with type 2 diabetes across all levels of glycemic control. Risk tended to be higher in patients with either near-normal glycemia or very poor glycemic control.

*Diabetes Care* 36:3535–3542, 2013

The goals of glucose-lowering therapy in type 2 diabetes are to reduce the risk of diabetes complications while minimizing harms associated with therapy, and thus increase both longevity and health-related quality of life. Intensive glucose-lowering strategies modestly reduce the risk of surrogates for microvascular complications, but the benefits for macrovascular outcomes are less clear (1–5). A recent position statement from

the American Diabetes Association (ADA) has called for individualized decision making in diabetes that integrates patient goals and preferences and takes into account the benefits and risks associated with therapy to set glycemic targets for care (6). The ADA and American Geriatrics Society have made similar recommendations for older patients with diabetes (7). However, data are lacking on how to individualize glycemic targets.

Several analyses of observational data have focused on determining what levels of glycemic control maximize benefits (8,9), but less is known about the risks associated with various levels of glucose control. Hypoglycemia is the most common adverse effect of diabetes therapy and is associated with unfavorable health outcomes (higher risk of dementia [10], falls [11], fall-related fractures [12], cardiovascular events [13,14], poor health-related quality of life [15,16], and increased mortality [17]). Therefore, data on the relationship between glucose control and risk of severe hypoglycemia are critical for making informed decisions about type and intensity of therapy.

Clinicians may assume that the risk of hypoglycemia is highest among patients with the lowest HbA<sub>1c</sub> levels. Compelling evidence for this comes from the Diabetes Control and Complications Trial (DCCT), which reported an inverse relationship between HbA<sub>1c</sub> levels and the occurrence of severe hypoglycemia in participants with type 1 diabetes (4). Additionally, intensive glucose control strategies implemented in randomized control trial settings in patients with both type 1 and type 2 diabetes resulted in lower HbA<sub>1c</sub> and were associated with an increased risk of hypoglycemia (1–5). However, recent post hoc analyses of the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial indicated an increased hypoglycemia risk in type 2 diabetic participants with poorer glycemic control compared with subjects with more desirable HbA<sub>1c</sub> levels, irrespective of assigned treatment group (18). In ACCORD, the intensive treatment arm and poorer achieved glycemic control in both the treatment and control arms increased hypoglycemia risk. Less is known about the relationship between glycemic control and hypoglycemia in usual care settings, where clinical decision making about treatment intensity occurs and is modified over the patient's life course. Prior observational studies have yielded conflicting results; some have indicated increased risk of hypoglycemia at lower

From the <sup>1</sup>Section of Endocrinology, Yale School of Medicine, New Haven, Connecticut; the <sup>2</sup>Division of Research, Kaiser Permanente Northern California, Oakland, California; the <sup>3</sup>Section of General Internal Medicine, University of Chicago, Chicago, Illinois; the <sup>4</sup>Section of Cardiovascular Medicine, Yale School of Medicine, New Haven, Connecticut; the <sup>5</sup>Robert Wood Johnson Clinical Scholars Program, Department of Internal Medicine, Yale School of Medicine, New Haven, Connecticut; and the <sup>6</sup>Center for Outcomes Research and Evaluation, Yale-New Haven Hospital, New Haven, Connecticut.

Corresponding author: Kasia J. Lipska, kasia.lipska@yale.edu.

Received 12 March 2013 and accepted 22 May 2013.

DOI: 10.2337/dc13-0610

© 2013 by the American Diabetes Association. Readers may use this article as long as the work is properly cited, the use is educational and not for profit, and the work is not altered. See <http://creativecommons.org/licenses/by-nc-nd/3.0/> for details.

HbA<sub>1c</sub> levels (19), whereas others have shown increased risk of hypoglycemia at higher HbA<sub>1c</sub> levels (16,17), but none of these prior analyses were specifically designed to test the association between HbA<sub>1c</sub> and hypoglycemia. Moreover, most studies were based on hypoglycemic events that came to clinical attention (as ascertained from emergency department or hospital records) and thus may miss the majority of events that are treated outside of the medical system.

To investigate the relationship between HbA<sub>1c</sub> level and hypoglycemia among patients with type 2 diabetes treated with glucose-lowering medications in a usual care setting, we analyzed data from the Diabetes Study of Northern California (DISTANCE) survey. We hypothesized that the risk of severe hypoglycemia may be higher in type 2 diabetic patients with either very low or high HbA<sub>1c</sub> levels compared with those with glycemic control similar to the standard arm in clinical trials (mean HbA<sub>1c</sub> ~7.5%). The current standards of care recommend less intensive glucose control strategies in older patients with limited life expectancy, advanced diabetes, cognitive impairment, or very poor health given the limited potential for future benefits and the need to reduce the risk of hypoglycemia in these high-risk patients (7,20). Therefore, we further hypothesized that lower HbA<sub>1c</sub> levels may be more strongly associated with hypoglycemia risk in older (vs. younger) patients with longer (vs. shorter) diabetes duration. Since hypoglycemia occurs as a result of glucose-lowering therapy and is not directly due to HbA<sub>1c</sub> level, we speculated that the relationship between HbA<sub>1c</sub> and hypoglycemia may differ by type of glucose-lowering regimen.

**RESEARCH DESIGN AND METHODS**

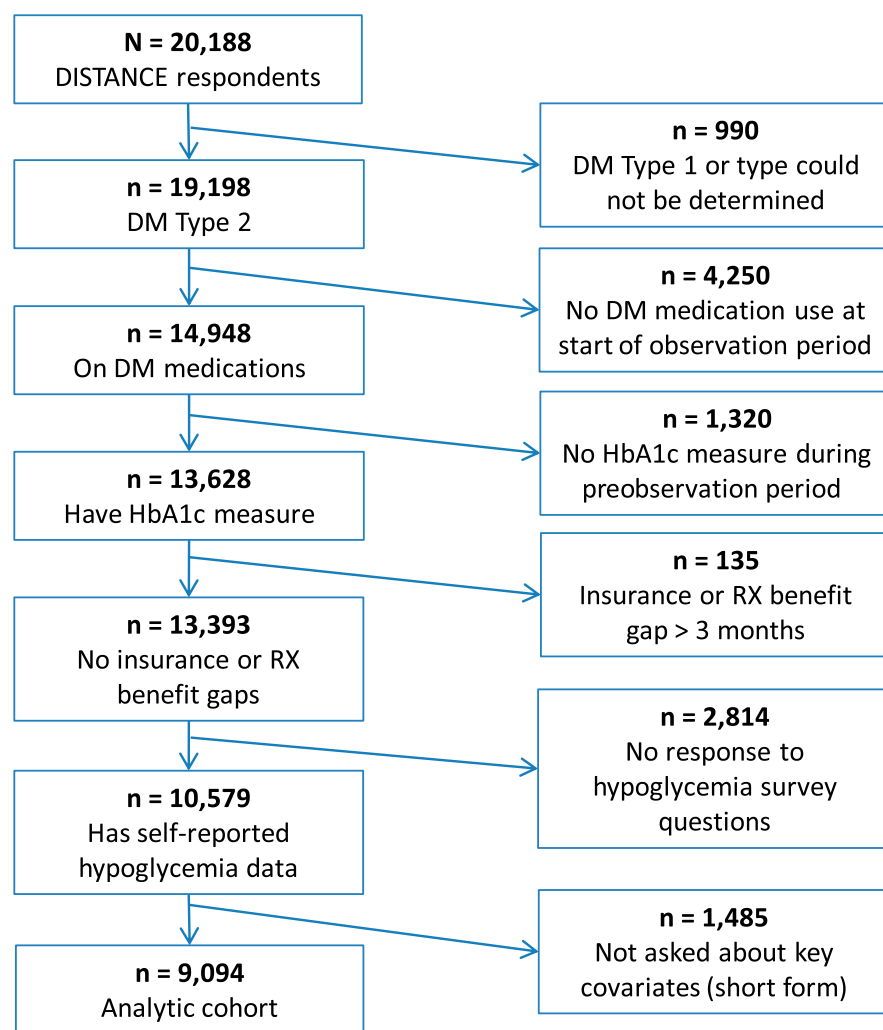
**Study population**

Kaiser Permanente Northern California (KPNC), a large, integrated healthcare delivery system, provides care for ~30% of the residents in its service area. KPNC established the KPNC Diabetes Registry in 1993. The registry now includes >230,000 adults with diabetes and is updated annually by identifying all health plan members with diabetes. Diabetes identification was based on multiple sources of data, including pharmacy utilization, laboratory results, and outpatient, emergency room, and hospitalization

diagnoses of diabetes according to a published algorithm (21). Study methods and a validation study of the KPNC Diabetes Registry (99% sensitivity for diabetes based on chart review registration) have been published previously (22). The institutional review boards of the Kaiser Foundation Research Institute, the University of Chicago, and the University of California, San Francisco approved the study.

Subjects in the study responded to a survey conducted in 2005–2006 among a race/ethnicity-stratified random sample of registry members 30–77 years of age. The overall response rate for the survey was 62% (n = 20,188). Individuals could complete the survey in written, telephone interview, or web-based formats in various languages (23). The survey was conducted to assess a wide range of factors that may explain observed variations in

the incidence of diabetes complications among patients receiving care at KPNC and includes detailed information on self-reported severe hypoglycemia and sociodemographic factors. These data were linked with clinical, pharmacy, and laboratory data from electronic medical records (EMRs). For this analysis, we included 9,094 survey responders with type 2 diabetes who had continuous KPNC membership and pharmacy benefits (no gap in membership or pharmacy benefits >3 months) in the 24 months before their survey date (which served as the baseline for each individual), were taking antihyperglycemic medications, and were not missing data on key variables (Fig. 1). We excluded individuals with type 1 diabetes or those in whom type of diabetes could not be determined (n = 990) according to a previously published algorithm (24).



**Figure 1**—DISTANCE survey respondents selected for study analysis. DM, diabetes mellitus.

### Primary outcome

The primary outcome of the study was the occurrence of severe hypoglycemia based on self-report of at least one episode in response to the following question: "In the past year, how many times have you had a severe low blood sugar reaction such as passing out or needing help to treat the reaction?" Response options for the number of hypoglycemic reactions were 0, 1–3, 4–6, 7–11, or 12 or more episodes. The 12 months preceding the date of each individual's baseline survey was termed the observation period, as this is the time period for which hypoglycemia occurrence was self-reported. The period of time 12–24 months before baseline was termed the preobservation period as variables measured during this time could conceivably contribute to hypoglycemia during the observation period (Fig. 2).

### Exposure of interest

The main exposure of interest was the last HbA<sub>1c</sub> level collected during the preobservation period. In this way, we could study the effect of HbA<sub>1c</sub> measured prior to the occurrence of the outcome on the subsequent risk of hypoglycemia occurring during the observation period. KPNC medical facilities send all their HbA<sub>1c</sub> samples to be analyzed by a single regional laboratory. This laboratory is licensed by the California Department of Health Services, inspected and accredited by the College of American Pathologists, and uses the standardization of HbA<sub>1c</sub> implemented by the National Glycohemoglobin Standardization Group.

HbA<sub>1c</sub> was categorized into five groups to facilitate detection of nonlinearity in the relationship between HbA<sub>1c</sub> and hypoglycemia. The categories convey a practical understanding of the level

of achieved diabetes control and denote near-normal glycemia (<6%) and very good (6–6.9%), good (7–7.9%), suboptimal (8–8.9%), or very poor (≥9%) glycemic control of diabetes in clinical practice.

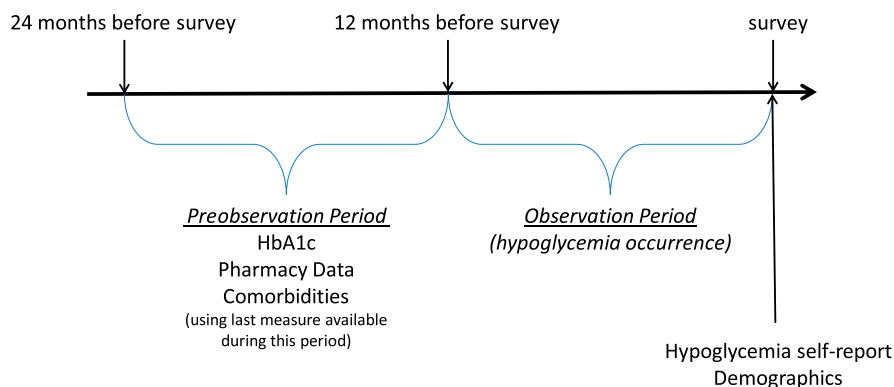
### Other covariates

Data collected on other factors that may contribute to hypoglycemia risk included age (categorized as <50, 50–59, 60–69, and 70–79 years), sex, self-reported race, and clinical factors. Duration of diabetes was based upon self-report from the survey (categorized as ≤10 or >10 years). In cases where self-report was missing from the survey, disease duration was based on first occurrence of diabetes in the medical record unless the patient joined the health plan with pre-existing diabetes, in which case it was considered missing. Polypharmacy (25,26) was ascertained by identifying subjects dispensed more than four chronically used medications during the period 12 months before the survey date. The threshold of more than four medications has been previously shown to be associated with severe hypoglycemia (27) and fall risk (26). When counting medications, we required that medications have the potential for long-term use and that they represent distinct pharmacological agents; for combination medications, we counted each distinct pharmacological agent. Renal function was ascertained using a combination of indicators. Estimated glomerular filtration rate (eGFR) was based on the last noninpatient laboratory result during the preobservation period and was calculated using the Chronic Kidney Disease Epidemiology Collaboration (CKD-EPI) formula (28). Evidence of end-stage renal disease (ESRD) or dialysis was based on ICD-9

codes and the KPNC ESRD registry. Prevalent comorbidities, including myocardial infarction, congestive heart failure, cerebrovascular disease, and chronic lung disease, were determined based on ICD-9 codes from inpatient and outpatient clinical encounters any time prior to the end of the preobservation period. Depression was based on ICD-9 codes or the use of antidepressant medications during the preobservation period. Prior history of hypoglycemia was based upon at least one emergency department or inpatient visit for hypoglycemia during the preobservation period identified using previously validated ICD-9 codes (29). Use of glucose-lowering therapies was identified from KPNC pharmacy dispensing records during the preobservation period and was divided into three mutually exclusive categories based on known effects on hypoglycemia risk: any use of insulin (with or without oral medications), use of insulin secretagogues but not insulin (with or without other oral medications), or all other oral medications for diabetes.

### Statistical analysis

The primary outcome was severe hypoglycemia, coded as a binary variable (zero vs. one or more events) based upon survey responses. We calculated the prevalence of severe hypoglycemia across HbA<sub>1c</sub> categories and further stratified by the three potential effect modifiers: age, duration of diabetes, and category of diabetes medication (insulin, insulin secretagogues, or other). Differences in categorical and continuous variables were tested with  $\chi^2$  and Student *t* tests, respectively. We specified modified Poisson regression models (30) with robust standard errors and a log-link function to estimate the relative risk (RR) of hypoglycemia across HbA<sub>1c</sub> categories with HbA<sub>1c</sub> 7–7.9% as the reference. The base model (model 1) of severe hypoglycemia included only HbA<sub>1c</sub> category as the independent variable. We further adjusted the base model by adding demographic variables (age, sex, and race) (model 2) and clinical factors (diabetes duration, comorbidities, polypharmacy, prior history of hypoglycemia, and baseline diabetes medications) (model 3). We tested interactions by adding cross-product terms between each category of HbA<sub>1c</sub> and the potential effect modifiers in unadjusted and fully adjusted models. All analyses were performed using SAS 9.3 (SAS Institute, Cary, NC). *P* values



**Figure 2**—Timing of the DISTANCE survey, occurrence of hypoglycemia, and collection of key variables for the study.

## HbA<sub>1c</sub> and severe hypoglycemia

of <0.05 were considered statistically significant.

**RESULTS**—Among the 9,094 study participants, 985 (10.8%) reported experiencing severe hypoglycemia in the previous year (Table 1). Among those

reporting hypoglycemia, 752 (76.3%) reported 1–3 events, 152 (15.4%) reported 4–6 events, 44 (4.5%) reported 7–11 events, and 37 (3.8%) reported 12 or more events. Patients who reported hypoglycemia were more likely to be women; to have a longer duration of diabetes,

a prior history of hypoglycemia, and multiple comorbidities; to use more than four medications for chronic conditions (polypharmacy); or to use either insulin or a secretagogue in the preobservation period.

HbA<sub>1c</sub> was measured in the preobservation period with a mean number of days between the date HbA<sub>1c</sub> was obtained and the start of the observation period of 116 days (SD 89). Nearly half (48.9%) of the values were obtained within 3 months of the observation period. Hypoglycemia was reported by 11.5, 9.3, 10.6, 11.5, and 13.8% of patients in HbA<sub>1c</sub> categories <6, 6–6.9, 7–7.9, 8–8.9, and ≥9%, respectively (*P* value <0.01), suggestive of a U-shaped relationship. Moreover, the mean HbA<sub>1c</sub> was higher among those who reported hypoglycemia (7.7 ± 1.6%) compared with those who did not (7.5% ± 1.5%, *P* < 0.01).

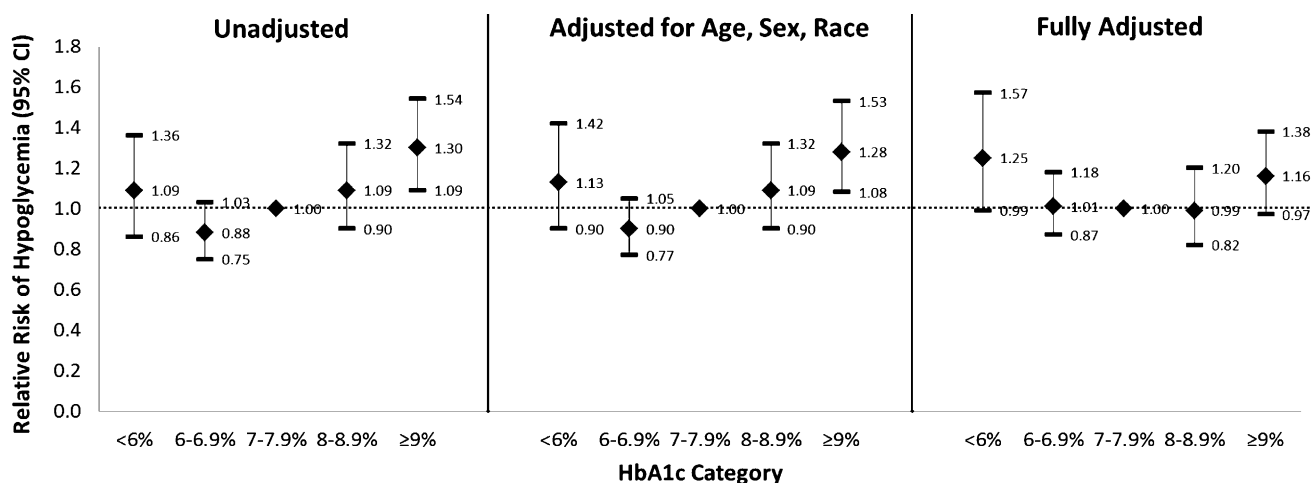
The unadjusted Poisson regression models indicated that patients with the lowest (<6%) and highest (≥9%) HbA<sub>1c</sub> values tended to be at higher risk for hypoglycemia compared with those with HbA<sub>1c</sub> values in the 7–7.9% range (Fig. 3). However, the elevated RR was only statistically significant for those with HbA<sub>1c</sub> ≥9%. Adjustment for demographic variables did not alter the shape of this relationship. Although the point estimates for hypoglycemia risk remained higher at the two extremes of glycemic control (HbA<sub>1c</sub> <6 and ≥9%), the fully adjusted model showed no statistically significant differences in hypoglycemia risk between each HbA<sub>1c</sub> category and the reference group.

We then examined the prevalence of hypoglycemia across categories of the three potential effect modifiers. A similar percentage of patients in each age-group reported hypoglycemia (10.8% of <50 years of age, 10.6% of 50–59 years of age, 11.3% of 60–69 years of age, and 10.4% of 70–79 years of age; *P* = 0.78). Patients with diabetes duration >10 years were more likely to report hypoglycemia (13.9%) compared with those with shorter diabetes duration (8.3%, *P* < 0.01). Hypoglycemia was most common among patients using insulin therapy (19.0%), less common in those using secretagogues (9.6%), and least common in those using other glucose-lowering medications (5.8%) (*P* < 0.01). Despite these differences in prevalence of hypoglycemia across these categories, we found no significant differences in the relationship between HbA<sub>1c</sub> and age, diabetes duration, or

**Table 1—Characteristics of type 2 diabetic participants by self-report of severe hypoglycemia**

	All participants (n = 9,094)	Reported no hypoglycemia (n = 8,109)	Reported hypoglycemia (n = 985)
Age, mean (years)	59.5 (9.8)	59.5 (9.8)	59.6 (9.7)
Age category (years)			
<50	1,465 (16.1)	1,307 (16.1)	158 (16.0)
50–59	2,926 (32.2)	2,616 (32.3)	310 (31.5)
60–69	3,065 (33.7)	2,719 (33.5)	346 (35.1)
70–77	1,638 (18.0)	1,467 (18.1)	171 (17.4)
Female	4,544 (50.0)	3,998 (49.3)	546 (55.4)
Race			
Asian	1,118 (12.3)	1,036 (12.8)	82 (8.3)
Black	1,601 (17.6)	1,440 (17.8)	161 (16.4)
Filipino	1,022 (11.2)	899 (11.1)	123 (12.5)
Latino	1,607 (17.7)	1,381 (17.0)	226 (22.9)
White	2,334 (25.7)	2,114 (26.1)	220 (22.3)
Multiracial/other/missing	1,412 (15.5)	1,239 (15.3)	173 (17.6)
Last HbA <sub>1c</sub> , mean (%)	7.5 (1.5)	7.5 (1.5)	7.7 (1.6)
HbA <sub>1c</sub> category			
<6%	747 (8.2)	661 (8.2)	86 (8.7)
6–6.9%	3,145 (34.6)	2,852 (35.2)	293 (29.8)
7–7.9%	2,612 (28.7)	2,335 (28.8)	277 (28.1)
8–8.9%	1,232 (13.6)	1,090 (13.4)	142 (14.4)
≥9%	1,358 (14.9)	1,171 (14.4)	187 (19.0)
Diabetes duration >10 years	4,035 (44.6)	3,473 (43.0)	562 (57.4)
Diabetes duration, mean (years)	10.6 (8.4)	10.3 (8.3)	12.8 (9.2)
Polypharmacy (more than four medications)	5,960 (65.5)	5,261 (64.9)	699 (71.0)
Prior hypoglycemia	76 (0.8)	42 (0.5)	34 (3.5)
Diabetes medications			
Any insulin	2,041 (22.4)	1,653 (20.4)	388 (39.4)
Secretagogues	4,982 (54.8)	4,506 (55.6)	476 (48.3)
Other	2,071 (22.8)	1,950 (24.0)	121 (12.3)
Comorbidities			
Chronic kidney disease	1,456 (16.0)	1,222 (15.1)	234 (23.8)
Myocardial infarction	539 (5.9)	447 (5.5)	92 (9.3)
Congestive heart failure	612 (6.7)	479 (5.9)	133 (13.5)
Cerebrovascular disease	445 (4.9)	361 (4.5)	84 (8.5)
Chronic lung disease	1,388 (15.3)	1,187 (14.6)	201 (20.4)
Depression	2,025 (22.3)	1,704 (21.0)	321 (32.6)
eGFR category* (mL/min/1.73 m <sup>2</sup> )			
≥90	3,025 (33.3)	2,728 (33.6)	297 (30.2)
60–89	3,585 (39.4)	3,227 (39.8)	358 (36.3)
30–59	1,245 (13.7)	1,064 (13.1)	181 (18.4)
15–29	129 (1.4)	97 (1.2)	32 (3.2)
<15	82 (0.9)	61 (0.8)	21 (2.1)

Data presented as number or mean (% or SD). *P* value <0.01 comparing those who did and did not report hypoglycemia for all categories, except for mean age and age-groups. \*eGFR category was calculated for 1,028 persons with nonmissing creatinine values and not on dialysis.



**Figure 3**—RR of hypoglycemia in unadjusted, demographically adjusted, and fully adjusted modified Poisson models (reference: HbA<sub>1c</sub> 7–7.9%). The fully adjusted model includes age, sex, race, diabetes duration, comorbidities (including renal function), polypharmacy, prior history of hypoglycemia, and category of diabetes medications. P values for RR of hypoglycemia in HbA<sub>1c</sub> categories <6, 6–6.9, 8–8.9, and ≥9% were 0.48, 0.10, 0.39, and 0.003 in the unadjusted model; 0.31, 0.16, 0.38, and 0.005 in the demographically adjusted model; and 0.06, 0.88, 0.94, and 0.10 in the fully adjusted model, respectively.

category of diabetes medication (i.e., no significant interactions).

**CONCLUSIONS**—Self-reported severe hypoglycemia was common (10.8%) among type 2 diabetic patients treated with glucose-lowering therapy within a large, integrated healthcare system. Among patients with severe hypoglycemia, nearly one in four people reported frequent episodes (more than three over the past year). Intensive glucose control strategies have been previously shown to increase the risk of hypoglycemia in clinical trials, but we did not find an inverse relationship between HbA<sub>1c</sub> level and hypoglycemia. Instead, in our study, hypoglycemia was common at all levels of glycemic control. Patients achieving near-normal glycemia (<6%) and those who were poorly controlled (≥9%) appeared to be at the highest risk for severe hypoglycemia. The conventional wisdom that patients with lowest HbA<sub>1c</sub> levels are at highest risk of hypoglycemia was not supported by our findings.

Our study expands prior research by examining the occurrence of hypoglycemia across multiple HbA<sub>1c</sub> categories and by using an outcome of self-reported severe hypoglycemia. Previous observational studies have yielded inconsistent findings with regard to the relationship between glucose control and hypoglycemic events. In the Fremantle longitudinal cohort study, HbA<sub>1c</sub> was dichotomized, and the level of ≥7% was associated with an

increased crude hazard of hypoglycemia requiring ambulance, emergency department, or hospital visit among community-dwelling type 2 diabetic patients (31). In adjusted analyses, HbA<sub>1c</sub> ≥7% was no longer independently associated with hypoglycemia; however, each 1% increase in HbA<sub>1c</sub> was significantly associated with a higher frequency of hypoglycemic events. In the Tayside population study of type 1 and 2 diabetic patients, higher HbA<sub>1c</sub> level was similarly associated with hypoglycemia requiring emergency medical assistance (32). Finally, in a recent study that assessed the association between self-reported severe hypoglycemia and subsequent mortality, mean HbA<sub>1c</sub> was higher among patients who reported hypoglycemia compared with those who did not (17). In contrast to these findings, which suggest an association between hypoglycemia and higher HbA<sub>1c</sub>, analysis of data from an underserved population of a large community hospital diabetes clinic showed that lower HbA<sub>1c</sub> was associated with higher odds of reported hypoglycemia, which was subsequently confirmed with a capillary blood glucose (19).

Clinical trial data consistently show that assignment to intensive glucose control strategy is associated with a higher risk of hypoglycemia compared with standard care (1–5). However, the relationship between hypoglycemia risk and treatment intensity differs substantively from the relationship between hypoglycemia risk and achieved HbA<sub>1c</sub> level, the

latter being more complex. In the DCCT of type 1 diabetic patients, an inverse relationship between HbA<sub>1c</sub> level and serious hypoglycemia was noted, with the number of events increasing with decreasing HbA<sub>1c</sub> (4). In contrast, detailed post hoc analyses of ACCORD participants showed that type 2 diabetic patients with poorer glycemic control had a higher risk of hypoglycemia irrespective of treatment assignment (18). In fact, a greater drop in HbA<sub>1c</sub> level during the first 4 months of the trial was not associated with increased hypoglycemia risk. Rather, patients who started out with higher baseline HbA<sub>1c</sub> levels and were unable to reduce their blood glucose levels appeared to be at the highest risk of hypoglycemic events. Moreover, participants with persistently elevated HbA<sub>1c</sub> levels (≥7%) after initiation of the intensive strategy had a higher mortality risk than those achieving lower glycemic levels (<7%) (33). What is actually mediating the higher risk of hypoglycemia and mortality and how they may be linked is unclear, but the findings suggest that intensive glucose-lowering efforts in patients who remain hyperglycemic may confer a higher risk for subsequent hypoglycemia and death.

The majority of the prior literature was based on hypoglycemia identified via emergency visits or hospitalizations and thus may miss events that are handled outside of the clinical setting (34). Given the high out-of-pocket cost of an ambulance response or emergency room visit,

patients or family members who assist may self-select whether to seek medical assistance. Accordingly, research based on self-reported hypoglycemia offers a different and complementary understanding of this serious public health concern compared with inquiries based solely on administrative data sources.

Our study results demonstrate that hypoglycemia occurs across all levels of HbA<sub>1c</sub>, with higher risk associated with near-normal or very poor glycemic control. Near-normal HbA<sub>1c</sub> levels (<6%) may denote overly intensive glucose control efforts that raise the risk of hypoglycemia. Since all of the patients in our study were receiving antihyperglycemic agents, these levels of glycemic control should not reflect mild, new-onset diabetes. Moreover, the relationship between HbA<sub>1c</sub> category and hypoglycemia did not differ by category of diabetes medication. The finding that very poor glycemic control (HbA<sub>1c</sub> ≥9%) was associated with a higher risk of hypoglycemia seems counterintuitive given the consistent association between intensive glucose strategies and hypoglycemia in clinical trials. However, poor glucose control may occur in patients who are “resistant” to glucose lowering despite exposure to an intensive antihyperglycemic effort. These findings are consistent with those reported for the ACCORD trial, in which participants who failed to achieve a drop in their HbA<sub>1c</sub> level (18) despite intensive or standard diabetes treatment experienced high rates of severe hypoglycemia.

In our study, we specifically investigated whether the relationship between HbA<sub>1c</sub> and hypoglycemia differs by age, duration of diabetes, or category of diabetes medication. We hypothesized that in older patients with longer duration of the disease and with the use of insulin, the RR of hypoglycemia may be much higher at low HbA<sub>1c</sub> levels (<6%) compared with reference (7–7.9%) than in younger patients with shorter diabetes duration or with the use of noninsulin-based therapies, in whom the RR of hypoglycemia may vary less by HbA<sub>1c</sub> level. Indeed, the current standards of diabetes care specifically recommend less intensive glycemic targets in older patients with longstanding diabetes who may be at risk for hypoglycemia (20). However, we found that none of these factors significantly modified the relationship between HbA<sub>1c</sub> and hypoglycemia. Although the absolute risk of hypoglycemia was higher in patients with longer duration of

diabetes and in those who used insulin, the RR of hypoglycemia at the extremes of glycemic control (compared with the HbA<sub>1c</sub> reference) was similar regardless of age, diabetes duration, or category of diabetes medication.

Current diabetes quality performance measures are predominantly based on meeting specific HbA<sub>1c</sub> target levels: the National Committee for Quality Assurance Healthcare Effectiveness Data and Information Set (HEDIS) set a goal of HbA<sub>1c</sub> <7% for people <65 years of age without cardiovascular disease or end-stage complications of diabetes, and HbA<sub>1c</sub> <8% for people 65–74 years of age. These measures do not adequately account for adverse effects associated with treatment efforts, such as hypoglycemia, and are not consistent with individualized approaches to glucose lowering. As one solution, Pogach and Aron (35) recently suggested a quality indicator for overtreatment of diabetes, and proposed to use an HbA<sub>1c</sub> of <7% in older people (>65 years of age) at high risk for hypoglycemia as a warning signal to physicians to reevaluate the appropriateness of glycemic treatment. Although such efforts have the potential to limit adverse effects of overtreatment and to improve patient outcomes, our study results suggest that future efforts should also consider the safety of the various glucose-lowering therapies in patients with higher HbA<sub>1c</sub> levels. Poorly controlled diabetes appears to be associated with both higher risk of diabetes complications and higher risk of treatment-related hypoglycemia. Therefore, quality improvement efforts must balance the need to improve glucose levels with safety of antihyperglycemic therapy in this group.

Our study does have several limitations. Hypoglycemia was not confirmed with laboratory values. It is possible that patients, particularly those with uncontrolled diabetes, may experience hypoglycemic symptoms when blood glucose values are actually normal. However, these symptoms typically do not require assistance from others nor do they result in unconsciousness. Some patients may have blunted hypoglycemic awareness and may under-report the frequency of events because they do not consistently experience the symptoms typically associated with hypoglycemia. Nonetheless, self-reported severe hypoglycemia that does not come to medical attention remains associated with adverse outcomes (17). Our hypoglycemia measure was

based upon a survey question regarding events occurring within the past year, so the exact timing of event(s) was not available. We used a retrospective cohort design where the timing of hypoglycemic events lagged with respect to the occurrence of clinical and laboratory variables to overcome this limitation. However, changes in glucose-lowering therapies or HbA<sub>1c</sub> values may have occurred between the start of the observation period and the occurrence of the event. The DISTANCE survey was conducted among members 30–77 years of age, limiting our ability to apply the findings to elderly patients with diabetes. Although patterns of antihyperglycemic use have changed since the 2005–2006 survey (with substantial decreases in sulfonylurea use) (36), we did not find significant interactions between type of medication and the HbA<sub>1c</sub>-hypoglycemia relationship. Finally, our analyses describe an association between HbA<sub>1c</sub> and self-reported hypoglycemia, but they were not designed to determine causal pathways between HbA<sub>1c</sub> and hypoglycemia.

In conclusion, self-reported severe hypoglycemia is common among patients with type 2 diabetes. Contrary to conventional wisdom, hypoglycemia occurs just as frequently among those with poor glycemic control as it does in those achieving near-normal glycemia. The relationship between HbA<sub>1c</sub> category and hypoglycemia did not differ by age, duration of diabetes, or category of diabetes medication. Recent clinical trials have raised questions about the benefits of intensive glucose lowering and the risks associated with tight control. Our results from the community setting suggest that efforts to improve the safety of glucose-lowering therapies need to be directed not only to patients achieving near-normal glycemia but also to patients with poorly controlled disease. Future analyses are needed to identify management strategies and treatment factors that may mitigate hypoglycemia risk.

---

**Acknowledgments**—This study was funded by R01-DK-081796, R01-DK-080726, R01-DK-065664, R01-HD-46113, P30-DK-092924, and P30 DK092949. K.J.L. is funded by T32-AG-019134 from the National Institute on Aging and H.M.K. is funded by Grant 1U01-HL-105270-03 (Center for Cardiovascular Outcomes Research at Yale University) from the National Heart, Lung, and Blood Institute.

S.E.I. has been a consultant to Merck, Boehringer Ingelheim, Janssen, Novo Nordisk,

and Bristol-Myers Squibb. No other potential conflicts of interest relevant to this article were reported.

K.J.L. researched data and wrote, reviewed, and edited the manuscript. E.M.W. analyzed data, reviewed and edited the manuscript, and contributed to discussion. E.S.H. and A.J.K. reviewed and edited the manuscript, contributed to discussion, and obtained funding. H.H.M., S.E.I., and H.M.K. reviewed and edited the manuscript and contributed to discussion. A.J.K. is the guarantor of this work and, as such, had full access to all the data in the study and takes responsibility for the integrity of the data and the accuracy of the data analysis.

This study was presented in abstract form at the 73rd Scientific Sessions of the American Diabetes Association, Chicago, Illinois, 21–25 June 2013.

## References

- Duckworth W, Abraira C, Moritz T, et al.; VADT Investigators. Glucose control and vascular complications in veterans with type 2 diabetes. *N Engl J Med* 2009;360:129–139
- 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
- Patel A, MacMahon S, Chalmers J, et al.; ADVANCE Collaborative Group. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. *N Engl J Med* 2008;358:2560–2572
- The Diabetes Control and Complications Trial Research Group. The effect of intensive treatment of diabetes on the development and progression of long-term complications in insulin-dependent diabetes mellitus. *N Engl J Med* 1993;329:977–986
- UK Prospective Diabetes Study (UKPDS) Group. Intensive blood-glucose control with sulphonylureas or insulin compared with conventional treatment and risk of complications in patients with type 2 diabetes (UKPDS 33). *Lancet* 1998;352:837–853
- 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
- Kirkman MS, Briscoe VJ, Clark N, et al. Diabetes in older adults. *Diabetes Care* 2012;35:2650–2664
- Greenfield S, Billimek J, Pellegrini F, et al. Comorbidity affects the relationship between glycemic control and cardiovascular outcomes in diabetes: a cohort study. *Ann Intern Med* 2009;151:854–860
- Huang ES, Liu JY, Moffet HH, John PM, Karter AJ. Glycemic control, complications, and death in older diabetic patients: the diabetes and aging study. *Diabetes Care* 2011;34:1329–1336
- Whitmer RA, Karter AJ, Yaffe K, Quesenberry CP Jr, Selby JV. Hypoglycemic episodes and risk of dementia in older patients with type 2 diabetes mellitus. *JAMA* 2009;301:1565–1572
- Schwartz AV, Vittinghoff E, Sellmeyer DE, et al.; Health, Aging, and Body Composition Study. Diabetes-related complications, glycemic control, and falls in older adults. *Diabetes Care* 2008;31:391–396
- Johnston SS, Conner C, Aagren M, Ruiz K, Bouchard J. Association between hypoglycaemic events and fall-related fractures in Medicare-covered patients with type 2 diabetes. *Diabetes Obes Metab* 2012;14:634–643
- Johnston SS, Conner C, Aagren M, Smith DM, Bouchard J, Brett J. Evidence linking hypoglycemic events to an increased risk of acute cardiovascular events in patients with type 2 diabetes. *Diabetes Care* 2011;34:1164–1170
- 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
- Green AJ, Fox KM, Grandy S; SHIELD Study Group. Self-reported hypoglycemia and impact on quality of life and depression among adults with type 2 diabetes mellitus. *Diabetes Res Clin Pract* 2012;96:313–318
- Laiteerapong N, Karter AJ, Liu JY, et al. Correlates of quality of life in older adults with diabetes: the diabetes & aging study. *Diabetes Care* 2011;34:1749–1753
- McCoy RG, Van Houten HK, Ziegenfuss JY, Shah ND, Wermers RA, Smith SA. Increased mortality of patients with diabetes reporting severe hypoglycemia. *Diabetes Care* 2012;35:1897–1901
- Miller ME, Bonds DE, Gerstein HC, et al.; ACCORD Investigators. The effects of baseline characteristics, glycaemia treatment approach, and glycated haemoglobin concentration on the risk of severe hypoglycaemia: post hoc epidemiological analysis of the ACCORD study. *BMJ* 2010;340:b5444
- Miller CD, Phillips LS, Ziemer DC, Gallina DL, Cook CB, El-Kebbi IM. Hypoglycemia in patients with type 2 diabetes mellitus. *Arch Intern Med* 2001;161:1653–1659
- Hemmingsen B, Christensen LL, Wetterslev J, et al. Comparison of metformin and insulin versus insulin alone for type 2 diabetes: systematic review of randomised clinical trials with meta-analyses and trial sequential analyses. *BMJ* 2012;344:e1771
- Karter AJ, Schillinger D, Adams AS, et al. Elevated rates of diabetes in Pacific Islanders and Asian subgroups: the Diabetes Study of Northern California (DISTANCE). *Diabetes Care* 2013;36:574–579
- Karter AJ, Ferrara A, Liu JY, Moffet HH, Ackerson LM, Selby JV. Ethnic disparities in diabetic complications in an insured population. *JAMA* 2002;287:2519–2527
- Moffet HH, Adler N, Schillinger D, et al. Cohort profile: the Diabetes Study of Northern California (DISTANCE)—objectives and design of a survey follow-up study of social health disparities in a managed care population. *Int J Epidemiol* 2009;38:38–47
- Karter AJ, Ackerson LM, Darbinian JA, et al. Self-monitoring of blood glucose levels and glycemic control: the Northern California Kaiser Permanente Diabetes Registry. *Am J Med* 2001;111:1–9
- Steinman MA, Landefeld CS, Rosenthal GE, Berthenthal D, Sen S, Kaboli PJ. Polypharmacy and prescribing quality in older people. *J Am Geriatr Soc* 2006;54:1516–1523
- Huang ES, Karter AJ, Danielson KK, Warton EM, Ahmed AT. The association between the number of prescription medications and incident falls in a multi-ethnic population of adult type-2 diabetes patients: the diabetes and aging study. *J Gen Intern Med* 2010;25:141–146
- Shorr RI, Ray WA, Daugherty JR, Griffin MR. Incidence and risk factors for serious hypoglycemia in older persons using insulin or sulfonylureas. *Arch Intern Med* 1997;157:1681–1686
- Matsushita K, Mahmoodi BK, Woodward M, et al.; Chronic Kidney Disease Prognosis Consortium. Comparison of risk prediction using the CKD-EPI equation and the MDRD study equation for estimated glomerular filtration rate. *JAMA* 2012;307:1941–1951
- Ginde AA, Blanc PG, Lieberman RM, Camargo CA Jr. Validation of ICD-9-CM coding algorithm for improved identification of hypoglycemia visits. *BMC Endocr Disord* 2008;8:4
- Zou G. A modified Poisson regression approach to prospective studies with binary data. *Am J Epidemiol* 2004;159:702–706
- Davis TM, Brown SG, Jacobs IG, Bulsara M, Bruce DG, Davis WA. Determinants of severe hypoglycemia complicating type 2 diabetes: the Fremantle Diabetes Study. *J Clin Endocrinol Metab* 2010;95:2240–2247
- Leese GP, Wang J, Broomhall J, et al.; DARTS/MEMO Collaboration. Frequency of severe hypoglycemia requiring emergency treatment in type 1 and type 2 diabetes: a population-based study of health service resource use. *Diabetes Care* 2003;26:1176–1180

## *HbA<sub>1c</sub> and severe hypoglycemia*

33. Riddle MC, Ambrosius WT, Brillon DJ, et al.; Action to Control Cardiovascular Risk in Diabetes Investigators. Epidemiologic relationships between A1C and all-cause mortality during a median 3.4-year follow-up of glycemic treatment in the ACCORD trial. *Diabetes Care* 2010;33:983–990
34. Cain E, Ackroyd-Stolarz S, Alexiadis P, Murray D. Prehospital hypoglycemia: the safety of not transporting treated patients. *Prehosp Emerg Care* 2003;7:458–465
35. Pogach L, Aron D. The other side of quality improvement in diabetes for seniors: a proposal for an overtreatment glycemic measure. *Arch Intern Med* 2012; 172:1510–1512
36. Alexander GC, Sehgal NL, Moloney RM, Stafford RS. National trends in treatment of type 2 diabetes mellitus, 1994–2007. *Arch Intern Med* 2008;168: 2088–2094