HbA$_{1c}$ and Risk of Severe Hypoglycemia in Type 2 Diabetes

The Diabetes and Aging Study

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OBJECTIVE—We examined the association between HbA$_{1c}$ 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$_{1c}$ 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$_{1c}$ levels. We also tested whether the HbA$_{1c}$-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$_{1c}$ 7.5 ± 1.5%), 985 (10.8%) reported experiencing severe hypoglycemia. Across HbA$_{1c}$ levels, rates of hypoglycemia were 9.3–13.8%. Compared with those with HbA$_{1c}$ 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$_{1c}$ <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$_{1c}$-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.

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$_{1c}$ levels. Compelling evidence for this comes from the Diabetes Control and Complications Trial (DCCT), which reported an inverse relationship between HbA$_{1c}$ 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$_{1c}$ 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$_{1c}$ 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...
HbA1c levels (19), whereas others have shown increased risk of hypoglycemia at higher HbA1c levels (16,17), but none of these prior analyses were specifically designed to test the association between HbA1c 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 HbA1c 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 HbA1c levels compared with those with glycemic control similar to the standard arm in clinical trials (mean HbA1c ~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 HbA1c 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 HbA1c level, we speculated that the relationship between HbA1c 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](care.diabetesjournals.org)
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 HbA1c level collected during the preobservation period. In this way, we could study the effect of HbA1c, 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 HbA1c 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 HbA1c implemented by the National Glycohemoglobin Standardization Group.

HbA1c was categorized into five groups to facilitate detection of nonlinearity in the relationship between HbA1c 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 HbA1c 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 χ2 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 HbA1c categories with HbA1c 7–7.9% as the reference. The base model (model 1) of severe hypoglycemia included only HbA1c 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 HbA1c 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.
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.

HbA1c was measured in the preobservation period with a mean number of days between the date HbA1c 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 HbA1c 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 HbA1c 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%) HbA1c values tended to be at higher risk for hypoglycemia compared with those with HbA1c values in the 7–7.9% range (Fig. 3). However, the elevated RR was only statistically significant for those with HbA1c ≥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 (HbA1c <6 and ≥9%), the fully adjusted model showed no statistically significant differences in hypoglycemia risk between each HbA1c 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 value = 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 HbA1c and age, diabetes duration, or...
fully adjusted model, respectively.

The fully adjusted model includes age, sex, race, diabetes duration, comorbidities (including renal function), polypharmacy, prior history of hypoglycemia, and category of diabetes medications. The RR values for RR of hypoglycemia in HbA1c categories <6, 6–6.9, 7–7.9, and ≥8% 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.

The conventional wisdom that patients achieving near-normal glycemia are at highest risk for severe hypoglycemia is supported by our findings, which suggest an association between self-reported severe hypoglycemia and subsequent mortality, mean HbA1c 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 HbA1c, analysis of data from an underserved population of a large community hospital diabetes clinic showed that lower HbA1c 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 HbA1c level, the latter being more complex. In the DCCT of type 1 diabetic patients, an inverse relationship between HbA1c level and serious hypoglycemia was noted, with the number of events increasing with decreasing HbA1c (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 HbA1c level during the first 4 months of the trial was not associated with increased hypoglycemia risk. Rather, patients who started out with higher baseline HbA1c 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 HbA1c 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,
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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 HbA1c, with higher risk associated with near-normal or very poor glycemic control. Near-normal HbA1c 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 HbA1c category and hypoglycemia did not differ by category of diabetes medication. The finding that very poor glycemic control (HbA1c ≥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 HbA1c level (18) despite intensive or standard diabetes treatment experienced high rates of severe hypoglycemia.

In our study, we specifically investigated whether the relationship between HbA1c 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 at the extremes of glycemic control (compared with the HbA1c reference) was similar regardless of age, diabetes duration, or category of diabetes medication.

Current diabetes quality performance measures are predominantly based on meeting specific HbA1c target levels: the National Committee for Quality Assurance Healthcare Effectiveness Data and Information Set (HEDIS) set a goal of HbA1c <7% for people <65 years of age without cardiovascular disease or end-stage complications of diabetes, and HbA1c <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 HbA1c 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 HbA1c 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 HbA1c 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 HbA1c-hypoglycemia relationship. Finally, our analyses describe an association between HbA1c and self-reported hypoglycemia, but they were not designed to determine causal pathways between HbA1c 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 HbA1c 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.

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References

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