Poor Cognitive Function and Risk of Severe Hypoglycemia in Type 2 Diabetes

Post hoc epidemiologic analysis of the ACCORD trial

OBJECTIVE—Self-management of type 2 diabetes including avoidance of hypoglycemia is complex, but the impact of cognition on safe self-management is not well understood. This study aimed to assess the effect of baseline cognitive function and cognitive decline on subsequent risk of severe hypoglycemia and to assess the effect of different glycemic strategies on these relationships.

RESEARCH DESIGN AND METHODS—Prospective cohort analysis of data from the ACCORD trial included 2,956 adults aged ≥55 years with type 2 diabetes and additional cardiovascular risk factors. Cognitive tests (Digit Symbol Substitution Test [DSST], Rey Auditory Verbal Learning Test, Stroop Test, and Mini Mental Status Examination) were conducted at baseline and 20 months. Study outcomes were incident confirmed severe hypoglycemia requiring medical assistance (HMA) and hypoglycemia requiring any assistance (HAA).

RESULTS—After a median 3.25-year follow-up, a 5-point-poorer baseline score on the DSST was predictive of a first episode of HMA (hazard ratio 1.13 [95% CI 1.08–1.18]). Analyses of the other cognitive tests and of HAA were consistent with the DSST results. Cognitive decline over 20 months increased the risk of subsequent hypoglycemia to a greater extent in those with lower baseline cognitive function (Pinteraction = 0.037). Randomization to an intensive versus standard glycemic strategy had no impact on the relationship between cognitive function and the risk of severe hypoglycemia.

CONCLUSIONS—Poor cognitive function increases the risk of severe hypoglycemia in patients with type 2 diabetes. Clinicians should consider cognitive function in assessing and guiding their patients regarding safe diabetes self-management regardless of their glycemic targets.

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*A complete list of the ACCORD Group of Investigators and the ACCORD-MIND Investigators can be found in the Supplementary Data.

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type 2 diabetes is an increasingly common disease. Its optimal management requires the active participation of affected patients, who must perform home glucose monitoring and adjust glucose-lowering medication and insulin, in anticipation and avoidance of hypoglycemia (1–3). The complexity of many diabetes treatment regimens requires good cognitive function. Therefore, cognitive function may be an important determinant of the risk for treatment-related adverse events such as severe hypoglycemia. Prospective studies suggest that cognitive status may affect the functional ability of patients with type 2 diabetes (4), and patients with dementia are less likely to be involved in diabetes self-care (5). However, it has not been shown that cognitive impairment leads to a greater risk of severe hypoglycemia. Improved understanding of this relationship may assist providers, caregivers, and patients in developing new treatment and education guidelines for diabetes management for people with cognitive impairment.

The ACCORD (Action to Control Cardiovascular Risk in Diabetes) trial assessed the effects of two different glycemic control strategies among individuals with type 2 diabetes at high risk for cardiovascular disease. ACCORD prospectively and systematically ascertained all severe hypoglycemic episodes. In addition, the ACCORD-MIND (Memory IN Diabetes) study assessed several domains of cognition among a subset of ACCORD participants. Thus, ACCORD-MIND provides a unique opportunity to assess the effect of baseline cognitive function on subsequent risk of severe hypoglycemia, as well as the effect of declines in cognitive function on the ongoing risk for severe hypoglycemia, and whether intensive versus standard glycemic control strategies affect these relationships.

RESEARCH DESIGN AND METHODS

Study design and eligibility

The design of ACCORD has previously been described (6,7). In brief, from 2001 to 2005, participants aged 40–79 years...
with type 2 diabetes and an A1C ≥ 7.5% and who had characteristics putting them at high risk of cardiovascular disease were recruited from 77 sites in the U.S. and Canada. Individuals were excluded if they had had frequent or serious hypoglycemia in the previous year or were unwilling to do home glucose monitoring. All 10,251 participants were randomized either to comprehensive intensive glycemic therapy targeting A1C ≤ 6.0% or to standard glycemic therapy targeting A1C 7.0–7.9%. In a double 2 × 2 factorial design, 4,733 of the participants were enrolled in a blood pressure–lowering trial, and 5,518 participants were enrolled in a lipid therapy trial. In December 2007, after a mean 3.5 year follow-up, the independent data and safety monitoring board recommended discontinuation of the intensive glycemia intervention due to excess mortality, after which point all participants were managed using the standard glycemic strategy. This report describes events occurring during the active glycemia intervention period.

All participants were provided with glucose-lowering medications prescribed by the investigators, glucose-monitoring equipment, educational materials, and counseling regarding diabetes care. Intensive group participants were asked about experiences of “low blood sugar” including therapy and consequences. A diagnosis of severe hypoglycemia required documentation of a plasma glucose <50 mg/dL (2.8 mmol/L) or symptoms that promptly resolved with oral carbohydrate, intravenous glucose, or parenteral glucagon. Episodes requiring hospitalization or care in an emergency department or from emergency personnel were identified as “hypoglycemia requiring medical assistance” (HMA). The primary outcome for this report is time from randomization until the first episode of HMA. HMA is a more specific measure of severe hypoglycemia and is more likely to be well documented than episodes of “hypoglycemia requiring any third-party assistance” (HAA) from a medical or any nonmedical person. For assessment of the effect on people who experience recurrent severe hypoglycemia, time to the second episode of HMA was also reported. Time to first and second episodes of HAA was also reported.

**Definitions of severe hypoglycemia**

At every visit, participants were asked about experiences of “low blood sugar” and consequences. A diagnosis of severe hypoglycemia required documentation of a plasma glucose <50 mg/dL (2.8 mmol/L) or symptoms that promptly resolved with oral carbohydrate, intravenous glucose, or parenteral glucagon. Episodes requiring hospitalization or care in an emergency department or from emergency personnel were identified as “hypoglycemia requiring medical assistance” (HMA). The primary outcome for this report is time from randomization until the first episode of HMA. HMA is a more specific measure of severe hypoglycemia and is more likely to be well documented than episodes of “hypoglycemia requiring any third-party assistance” (HAA) from a medical or any nonmedical person. For assessment of the effect on people who experience recurrent severe hypoglycemia, time to the second episode of HMA was also reported. Time to first and second episodes of HAA was also reported.

**Cognitive tests**

The ACCORD-MIND battery, described elsewhere (8), was chosen because of its sensitivity to cognitive changes arising from both cerebrovascular and neurodegenerative etiologies.

The primary cognitive measure for this study was the Digit Symbol Substitution Test (DSST), which is a subset of the Wechsler Adult Intelligence Scale (WAIS-III). It assesses a wide variety of executive functions that may be relevant to recognition and rapid treatment of hypoglycemia, including visual motor speed, learning capacity, sustained attention, and working memory. It has been used in cognitively intact individuals, and it has been shown to predict cognitive decline, physical disability (2% over 8.4 years for a one-point-lower score) (9), and mortality (0.2–0.7% per year for a one-point-lower score) (9–11). Scores of 0 (worst) to 133 (best) are possible. Across the range of normal cognition, six points on the DSST is approximately equivalent to one point on the Mini-Mental Status Exam (MMSE), with which clinicians may be more familiar (12). The DSST is the cognitive test of greatest interest in this study, since it provides a broad assessment of cognition (12).

The Rey Auditory Verbal Learning Test (RAVLT), a test of verbal memory, assesses registration and recall of words. It is a sensitive tool for neurologic impairment in a variety of patients and has been used extensively in epidemiologic research. Higher scores indicate better performance (13).

The MMSE assesses global mental status and is used clinically to screen for possible cognitive impairment, which may require more in-depth evaluation. It is mainly used in elderly populations. Scores of 0 (worst) to 30 (best) are possible (15).

**Statistical methods**

All analyses were conducted using SAS software, version 9.1 (SAS Institute). Baseline characteristics and 20-month change in cognitive test scores (20-month score minus baseline score) of participants with or without HMA were compared by t tests or X² tests. Baseline characteristics of interest were those that have previously been associated with cognitive status and/or hypoglycemia (16,17). Pearson correlations between baseline cognitive test scores were calculated.

Unadjusted annualized incidence rates of hypoglycemia for groups of individuals divided by tertiles of baseline cognitive test score were calculated by dividing the number of individuals with events by the total number of person-years until the time of the first event or last contact. Time to first episode of severe hypoglycemia was compared between these three cognitive groups using Kaplan-Meier curves and log-rank tests. Hazard ratios (HRs) and 95% CIs were calculated by Cox models for each of the upper two groups compared with the group in the lowest...
third of cognitive test scores after controlling for variables used to stratify randomization.

Cox models were also used to calculate HRs and 95% CIs of a five-point-worse DSST test score for severe hypoglycemia among all participants and separately for intensive and standard group participants. Assumptions of linearity (P = 0.26) and proportional hazards (P = 0.11) were not rejected and therefore were considered valid. The interaction between baseline cognitive scores and the glycemia intervention group was used to determine whether the effect of baseline cognitive status on the risk of hypoglycemia differed in the intensive versus the standard group. Three sets of models were fit: model 1 includes variables used to stratify randomization (second tertile of cognitive test scores after con-

### RESULTS

#### Participant characteristics

ACCORD-MIND enrolled 2,977 participants. We excluded 20 individuals who did not complete baseline cognitive assessments and 1 who experienced severe hypoglycemia between randomization and the baseline cognitive assessment. Of the remaining 2,956 participants followed for a median of 3.25 years, 160 reported one or more HMA episodes, including 36 who reported at least two HMA episodes. Sixty-eight people who had no HMA episodes before the 20-month assessment reported one or more HMA episodes occurring after the 20-month cognitive assessment, nine of whom reported at least two HMA episodes after this time. In total, 238 of the 2,956 participants reported at least one HAA, and 73 reported at least two HAAs. Of those who had no HAAs before 20 months, 99 reported at least two HAAs and 18 reported at least two HAAs after the 20-month assessment.

Compared with those who never had an HMA episode, participants who experienced at least one HMA episode were more likely to be female, older, African American, and less educated; more likely to have less-well controlled diabetes of longer duration with more albuminuria, neuropathy, and cardiovascular disease; and more likely to have been randomized to intensive glycemic therapy and also had significantly worse baseline scores on all cognitive tests (Table 1). The absolute value of Pearson correlation coefficients between pairs of the four cognitive tests were similar between intensive and standard glycemia intervention groups.

#### Table 1—Baseline characteristics of participants

<table>
<thead>
<tr>
<th>Variable</th>
<th>All</th>
<th>At least one HMA</th>
<th>No HMA</th>
<th>P</th>
</tr>
</thead>
<tbody>
<tr>
<td>N</td>
<td>2,956</td>
<td>160</td>
<td>2,796</td>
<td></td>
</tr>
<tr>
<td>Age (years)</td>
<td>62.49 ± 5.82</td>
<td>63.91 ± 6.41</td>
<td>62.41 ± 5.77</td>
<td>0.002</td>
</tr>
<tr>
<td>Female</td>
<td>1,378 (46.6)</td>
<td>89 (55.6)</td>
<td>1,289 (46.1)</td>
<td>0.019</td>
</tr>
<tr>
<td>Race</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>Non-Hispanic white</td>
<td>2,078 (70.3)</td>
<td>96 (60.0)</td>
<td>1,982 (70.9)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>African American</td>
<td>479 (16.2)</td>
<td>48 (30.0)</td>
<td>431 (15.4)</td>
<td></td>
</tr>
<tr>
<td>Hispanic</td>
<td>209 (7.1)</td>
<td>10 (6.3)</td>
<td>199 (7.1)</td>
<td></td>
</tr>
<tr>
<td>Other</td>
<td>190 (6.4)</td>
<td>6 (3.8)</td>
<td>184 (6.6)</td>
<td></td>
</tr>
<tr>
<td>Education</td>
<td></td>
<td></td>
<td></td>
<td>0.010</td>
</tr>
<tr>
<td>Less than high school</td>
<td>385 (13.0)</td>
<td>26 (16.3)</td>
<td>359 (12.8)</td>
<td></td>
</tr>
<tr>
<td>High school graduate</td>
<td>761 (25.7)</td>
<td>56 (35.0)</td>
<td>705 (25.2)</td>
<td></td>
</tr>
<tr>
<td>Some college</td>
<td>1,023 (34.6)</td>
<td>43 (26.9)</td>
<td>980 (35.1)</td>
<td></td>
</tr>
<tr>
<td>College graduate or more</td>
<td>787 (26.6)</td>
<td>35 (21.9)</td>
<td>752 (26.9)</td>
<td></td>
</tr>
<tr>
<td>BMI (kg/m²)</td>
<td>32.98 ± 5.35</td>
<td>32.08 ± 5.64</td>
<td>33.03 ± 5.33</td>
<td>0.029</td>
</tr>
<tr>
<td>Diabetes duration (years)</td>
<td>10.39 ± 7.36</td>
<td>14.13 ± 8.74</td>
<td>10.18 ± 7.22</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>A1C (%)</td>
<td>8.28 ± 1.05</td>
<td>8.46 ± 1.06</td>
<td>8.27 ± 1.05</td>
<td>0.021</td>
</tr>
<tr>
<td>Any insulin use</td>
<td>1,015 (34.3)</td>
<td>104 (65.0)</td>
<td>911 (32.6)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>History of depression</td>
<td>776 (26.3)</td>
<td>45 (28.1)</td>
<td>731 (26.1)</td>
<td>0.58</td>
</tr>
<tr>
<td>History of stroke</td>
<td>147 (5.0)</td>
<td>18 (11.3)</td>
<td>129 (4.6)</td>
<td>0.0002</td>
</tr>
<tr>
<td>History of cardiovascular disease</td>
<td>860 (29.1)</td>
<td>67 (41.9)</td>
<td>793 (28.4)</td>
<td>0.0003</td>
</tr>
<tr>
<td>Neuropathy score</td>
<td>0.46 ± 0.50</td>
<td>0.53 ± 0.50</td>
<td>0.45 ± 0.50</td>
<td>0.049</td>
</tr>
<tr>
<td>Urine albumin-to-creatinine (mg/mmol)</td>
<td></td>
<td></td>
<td></td>
<td></td>
</tr>
<tr>
<td>&lt;30</td>
<td>2,105 (71.7)</td>
<td>94 (58.8)</td>
<td>2,011 (72.4)</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>30–300</td>
<td>651 (22.2)</td>
<td>44 (27.5)</td>
<td>607 (21.9)</td>
<td></td>
</tr>
<tr>
<td>&gt;300</td>
<td>180 (6.1)</td>
<td>22 (13.8)</td>
<td>158 (5.7)</td>
<td></td>
</tr>
<tr>
<td>Glycemia intervention group</td>
<td></td>
<td></td>
<td></td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>Intensive</td>
<td>1,459 (49.4)</td>
<td>118 (73.8)</td>
<td>1,341 (48.0)</td>
<td></td>
</tr>
<tr>
<td>Standard</td>
<td>1,497 (50.6)</td>
<td>42 (26.3)</td>
<td>1,455 (52.0)</td>
<td></td>
</tr>
<tr>
<td>DSST score</td>
<td>52.55 ± 15.89</td>
<td>46.45 ± 17.01</td>
<td>52.89 ± 15.76</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>RAVLT score</td>
<td>7.52 ± 2.54</td>
<td>6.90 ± 2.72</td>
<td>7.55 ± 2.53</td>
<td>0.002</td>
</tr>
<tr>
<td>Stoop score</td>
<td>31.99 ± 16.66</td>
<td>37.69 ± 22.02</td>
<td>31.66 ± 16.25</td>
<td>&lt;0.0001</td>
</tr>
<tr>
<td>MMSE score</td>
<td>27.42 ± 2.51</td>
<td>26.83 ± 2.80</td>
<td>27.45 ± 2.49</td>
<td>0.002</td>
</tr>
</tbody>
</table>

Data are means ± SD or n (%) unless otherwise indicated.
at baseline ranged from 0.29 to 0.47 (all P values <0.0001).

**Effect of baseline cognitive status on risk of hypoglycemia**

Lower baseline DSST score was associated with an increased risk for first episode of HMA (Fig. 1) (P < 0.0001 by log-rank test). The crude rate of HMA within the lowest third of baseline DSST score was 2.90% per year (95% CI 2.34–3.59), whereas rates were progressively lower within the middle (1.42% per year [95% CI 1.05–1.93]) and upper third (1.21% per year [0.87–1.67]). There was a 50% (95% CI 27–65) lower risk in the middle third compared with the lowest third and a 57% (36–71) lower risk in the highest third compared with the lowest third after adjustment for randomization stratification variables.

In the setting of model 1, a five-point-lower DSST score increased the risk of HMA by 13% (95% CI 8–18) and HAA by 11% (7–15). Similar results were seen for recurrent hypoglycemia and after adjustment for model 2 variables (Table 2). Even after adjustment for all the variables in model 3, a five-point-lower DSST score increased the risk of HMA by 10% (0–22) and HAA by 7% (2–13). The risk of hypoglycemia due to poor cognition was not statistically different between the two intervention groups (Table 2).

Consistent with the results of the DSST, a one-point difference in the direction of poorer cognitive function in the baseline scores of the other cognitive tests was also predictive of a first episode of HMA after adjustment for stratification variables (model 1): RAVLT HR 1.10 (95% CI 1.03–1.17; P = 0.0023); Stroop 1.01 (1.007–1.02; P = 0.001); and MMSE 1.09 (1.03–1.15; P = 0.0014).

**Effect of cognitive decline on risk of hypoglycemia**

A total of 2,665 participants completed baseline and 20-month DSST assessments and did not have any hypoglycemia before the 20-month assessment. Among these participants, the changes in cognitive test scores from baseline to the 20-month assessment (20-month score minus baseline score mean ± SD) were not significantly different for those who did (n = 68) versus those who did not (n = 2,597) experience subsequent HMA (DSST −0.30 ± 7.33 vs. −1.39 ± 8.14, P = 0.58; RAVLT −0.03 ± 1.95 vs. 0.36 ± 1.75, P = 0.11; Stroop 0.94 ± 19.83 vs. −1.00 ± 13.52, P = 0.43; and MMSE 0.43 ± 2.49 vs. −0.10 ± 1.97, P = 0.28).

However, with use of Cox analysis, cognitive decline over 20 months, assessed by the DSST, was associated with an increased risk of hypoglycemia thereafter among those with lower baseline cognitive status, whereas this relationship was not present for those with better baseline cognitive status (interaction between baseline value and change score treated as continuous variables: Pinteraction = 0.037 for HMA.

![Figure 1](https://example.com/figure1.png)

**Figure 1**—Kaplan-Meier curves for HMA according to baseline thirds of the DSST score. Crude incidence rates and 95% CIs are shown for each group. Log-rank test P < 0.0001. HRs for the middle- and highest-score groups are with reference to the lowest–DSST score group.
and \( P_{\text{interaction}} = 0.029 \) for HAA) after adjustment for the covariates in model 1. The relationship did not differ between standard and intensive glycemic intervention groups (\( P = 0.13 \) for HMA and \( P = 0.32 \) for HAA; data not shown). The dependence on baseline cognitive status of the relationship between change in DSST score and HMA incidence is illustrated by arbitrarily dividing participants into thirds of baseline DSST and change in DSST. As noted in Fig. 2, the pattern of increased incidence of HMA being associated with larger declines in cognition is not apparent in the group with the highest baseline scores.

CONCLUSIONS—Severe hypoglycemia requiring assistance occurs in 0.4–1.5% of patients treated with standard type 2 diabetes therapy every year (18,19). The association between hypoglycemia and poor cognitive function is well described, but it is most often used to infer that cognitive decline is a consequence of hypoglycemia (20). The current study shows that cognitive function is a significant determinant of hypoglycemia, an important consideration in safe self-management of type 2 diabetes. The risk of developing severe hypoglycemia was significantly higher for patients with deficits in cognitive status. A DSST score in the lowest third increased the rate of HMA twofold. This is considerable, given that antecedent HMA (generally considered a strong risk factor) increased the risk of HMA fourfold. A five-point-lower DSST score increased the risk of HMA by 13% and recurrent HMA to an even greater degree after considering other factors. To put this in context, ~40 g alcohol (3–4 standard drinks) will acutely lower an individual’s DSST score by approximately five points (21–23), and among people in the same age range as those in ACCORD-MIND, a one-point difference in DSST score is consistent with the difference in cognition seen between two people differing in age by 1–2 years (24–28), differing in formal education experience by ~4 years (26) and, among people with type 2 diabetes, differing in A1C by 0.57% (16). Thus, even small differences in cognition can have an impact on hypoglycemia risk.

These findings are supported by observations from a study with very similar patients. The ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) study found an increased risk of severe hypoglycemia among those with worse MMSE scores (29). In addition to corroborating the findings based on the MMSE, our study extends the relationship to a variety of cognitive domains assessed by the DSST, RAVLT, and Stroop test. Given that these tests assess somewhat overlapping but largely distinct domains (\(|r| = 0.29–0.47\)), it seems that the risk of severe hypoglycemia is related to a core cognitive construct or an interrelation of several cognitive domains.
Cognitive deficit increases hypoglycemia risk

The relationship between poor cognitive status or cognitive decline and severe hypoglycemia was not different between the intensive versus standard glycemic therapy groups, consistent with the ADVANCE findings (29). These results suggest that clinicians should be alert to the increased risk of hypoglycemia in patients with poor cognitive status regardless of their current glycemic targets.

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Z.P., M.E.M., and H.C.G. researched data, contributed to discussion, wrote the manuscript, and reviewed and edited the manuscript. L.J.L., J.D.W., E.R.S., and R.M.B. researched data, contributed to discussion, and reviewed and edited the manuscript. R.M.L. and F.I.-B. contributed to discussion and reviewed and edited the manuscript. T.C.-Y. and M.D.S. researched data and reviewed and edited the manuscript. L.C.L. reviewed and edited the manuscript. Z.P. 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.

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