Diabetes and Cardiovascular Disease

Serious Cardiovascular Outcomes in Diabetes

The Role of Hypoglycemia

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Hypoglycemia is a well-recognized side effect of glucose-lowering therapies in patients with diabetes mellitus. The incidence of mild self-reported hypoglycemic episodes in patients with type 1 diabetes mellitus is approximately 30 episodes per patient per year, whereas the incidence of severe hypoglycemic episodes (ie, those that require third-party assistance) may be as high as 3.2 episodes per patient per year.1–3 Hypoglycemic episodes occur much less frequently in patients with type 2 diabetes mellitus, in whom the incidence of mild and severe hypoglycemic episodes is 2 to 10 per patient per year and 0.1 to 0.7 per patient per year, respectively.2

When patients are alerted to the occurrence of a hypoglycemic episode by symptoms such as tremor, diaphoresis, tachycardia, malaise, hunger, and anxiety, they can abort these episodes by consuming carbohydrates. However, if hypoglycemic episodes occur rapidly or are unrecognized and untreated, the resulting neuroglycopenia may cause confusion, seizures, accidents, angina, and, rarely, death or permanent cognitive impairment.3,4 Patients who experience frequent episodes of hypoglycemia are especially at risk of having unrecognized hypoglycemic episodes (and their sequelae), because their counterregulatory response to hypoglycemia becomes blunted. Indeed, the rare occurrence of sudden death during sleep in young patients with type 1 diabetes mellitus (the so-called dead-in-bed syndrome) has been attributed to hypoglycemia, although this cause is seldom proven.5–7

It is well known that hypoglycemic episodes are associated with a surge of sympathetic activity and a release of catecholamines.8–10 These observations have supported the suggestion that the tachycardia and the rise in blood pressure observed during a hypoglycemic episode might destabilize an atherosclerotic plaque.11 These hemodynamic changes, the increased myocardial work, and hypoglycemia-induced increases in platelet aggregation, platelet activity,12–14 and hematocrit15,16 may precipitate cardiac and cerebral ischemic events in patients at high risk of cardiovascular disease.17 Support for this possibility comes from a number of small studies and case reports. For example, continuous glucose and ECG monitoring in 19 patients with coronary artery disease and type 2 diabetes mellitus18 revealed a higher frequency of ischemic ECG changes when glucose levels fell below 3.9 mmol/L (70 mg/dL). A similar study in 24 patients with type 1 diabetes mellitus19 revealed a nocturnal increase in the corrected QT interval and some minor rhythm disturbances when nocturnal glucose levels fell below 3.5 mmol/L (63 mg/dL) that were not observed when nocturnal glucose levels were >5 mmol/L (90 mg/dL). Experimentally induced hypoglycemia prolonged the corrected QT interval and reduced potassium levels in healthy adults10 and in people with type 1 and type 2 diabetes mellitus.20,21 Finally, case reports have shown a relationship between ischemic cerebral changes and concurrent severe hypoglycemia in patients presenting with neurological deficits22,23 and between arrhythmias and concurrent low blood glucose levels that responded to glucose administration.24,25

These considerations clearly provide the basis for concerns that hypoglycemic episodes may promote cardiovascular events (myocardial infarction [MI], stroke, and cardiovascular death) and death. These concerns are magnified by the fact that hospitalized and ambulatory individuals with diabetes may have concomitant renal disease, liver disease, weight loss, or other conditions that increase the likelihood of having a hypoglycemic episode and that are themselves risk factors for serious health outcomes. If hypoglycemic episodes precipitate (rather than are simply associated with) cardiovascular events and death, then epidemiological studies would identify hypoglycemia as an independent risk factor for serious cardiovascular outcomes, and interventions that increase the risk of hypoglycemia might increase the risk of these outcomes. The recent publication of several large randomized trials and epidemiological studies that were restricted to people with diabetes and that collected and reported data regarding both hypoglycemia and serious outcomes provides an opportunity to examine this possibility. These studies are reviewed and summarized below so as to address the following questions:

1. Does an intervention that increases the risk of hypoglycemic episodes increase the risk of serious cardiovascular outcomes?
2. Are hypoglycemic episodes a risk factor for serious cardiovascular outcomes?
3. Do hypoglycemic episodes precipitate serious cardiovascular events?

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Does an Intervention That Increases the Risk of Hypoglycemic Episodes Increase the Risk of Serious Cardiovascular Outcomes?

Any effect of hypoglycemia on cardiovascular outcomes may be influenced by a patient’s age, the clinical setting, the glucose-lowering therapies that are used, and the glucose level that is achieved. Several large randomized, controlled trials have assessed the effect of a variety of glucose-lowering approaches on cardiovascular outcomes in ambulatory patients with diabetes. These trials can broadly be classified as trials in which allocation was to 2 different targeted levels of glycemic control (intensive versus standard) and trials in which allocation was to 2 different glucose-lowering strategies, in which differences in glycemic control may have been achieved but were not the focus of the intervention. Several other trials of the effect of insulin therapy on mortality in hospitalized critically ill patients with and without diabetes have also been published. Although these trials defined hypoglycemic events in a variety of ways, they all reported the effect of the allocated therapy on both hypoglycemic events and adjudicated cardiovascular outcomes. These trials therefore provide some insight into the nature of the relationship between hypoglycemia and cardiovascular events.

Trials Comparing Different Intensities of Glucose-Lowering Therapies

To date, 5 large trials allocated people to a strategy that targeted more- versus less-intensive glucose lowering. These included the Diabetes Control and Complications Trial (DCCT), which was conducted in relatively young people with type 1 diabetes mellitus, and the United Kingdom Prospective Diabetes Study (UKPDS). Action to Control Cardiovascular Risk in Diabetes (ACCORD), Veterans Affairs Diabetes Trial (VADT), and Action in Diabetes and Vascular Disease: Preterax and Diamicron Modified Release Controlled Evaluation (ADVANCE) trials, which were conducted in people with type 2 diabetes mellitus.

Type 1 Diabetes Mellitus

In the DCCT, 1441 people with a mean duration of type 1 diabetes mellitus of 5.7 years and a mean age of 27 years were randomly allocated to either intensified insulin therapy targeting a hemoglobin A1c ≤ 6.05% or conventional insulin therapy aimed at preventing symptoms of hyperglycemia or hypoglycemia. Ninety-nine percent of the participants completed the active-therapy period of the trial after a mean follow-up of 6.5 years, and 93% were passively followed up for an additional 10.5 years. At the end of the active-therapy period, the mean hemoglobin A1c levels were 7.4% and 9.1% in the treatment and control groups, respectively. During this period, severe hypoglycemic episodes requiring assistance affected approximately 27% of participants in the intensive-therapy group and 10% of participants in the conventional group annually. Moreover, a very strong inverse relationship was noted between the achieved hemoglobin A1c and the risk of severe hypoglycemia. Despite this much higher risk of severe hypoglycemia, participants who had been allocated to the intensified insulin therapy group had a nonsignificant 41% reduction in cardiovascular events at the end of the active treatment period and a significant 42% (95% confidence interval [CI] 9% to 63%) lower risk of cardiovascular disease than participants who had been allocated to the conventional insulin therapy group when evaluated after 17 years of follow-up. Furthermore, analyses suggested that the difference in hemoglobin A1c during the active treatment period accounted for this benefit. The risk of cardiovascular events among the people who experienced severe hypoglycemia was not reported. Nevertheless, these data suggest that in type 1 diabetes mellitus, a glucose-lowering therapy that dramatically increases the risk of severe hypoglycemia does not cause long-term cardiovascular harm.

Type 2 Diabetes Mellitus

The 4 trials conducted in people with type 2 diabetes mellitus differed with respect to the participants studied and the approach used (Table 1). The UKPDS was conducted in people with newly diagnosed type 2 diabetes mellitus and relatively low cardiovascular risk; only 2% had a history of preexisting cardiovascular disease. Conversely, the ACCORD, ADVANCE, and VADT were conducted in people with established diabetes of 10, 8, and 12 years duration, respectively, and with other risk factors for cardiovascular disease. Indeed, 35%, 32%, and 40% of participants in ACCORD, ADVANCE, and VADT had a previous cardiovascular event, respectively. These trials differed in the approach to glucose lowering. In the UKPDS, the 2 different fasting glucose levels were targeted by allocating people to an intensive glucose control policy that started with insulin or sulfonylurea versus a conventional control policy based on diet, whereas in the ACCORD, ADVANCE, and VADT trials, 2 different levels of hemoglobin A1c were targeted with a similar, broad menu of drugs that were added or adjusted at regular visits. These glycemia intervention strategies achieved median hemoglobin A1c levels that varied from 6.4% to 7.0% in the intensive-therapy groups and from 7.3% to 8.4% in the standard-therapy groups.

The effect of the interventions studied in these trials on the risk of severe hypoglycemia during a follow-up period ranging from 3.4 to 5.6 years was recently meta-analyzed. Overall, people who were allocated to the intensive-therapy arm were 2.5 times more likely to experience 1 or more severe hypoglycemic events (95% CI 1.9 to 3.2) than those who were allocated to the standard-therapy arm. Of note was evidence of statistical heterogeneity in the risk of severe hypoglycemia among the trials, with a 1.9-fold higher risk in the intensive- versus standard-therapy group in ADVANCE and a 3-fold higher risk in ACCORD and the UKPDS. Despite this higher risk of severe hypoglycemia in the intensive-therapy groups in all 4 studies, a meta-analysis of the effect of the intervention on cardiovascular outcomes suggested that an intensive approach modestly reduced the overall risk of the first occurrence of major cardiovascular events, comprising nonfatal MI, nonfatal stroke, or cardiovascular death (hazard ratio [HR] 0.91, 95% CI 0.84 to 0.99). This effect was reflected in a reduced risk of MI (HR 0.85, 95% CI 0.76 to 0.94) but no effect on the risk of stroke (HR 0.96, 95% CI 0.83 to 1.10) or cardiovascular death (HR 1.10,
95% CI 0.84 to 1.42). Moreover, the effect on cardiovascular death varied among studies, with evidence of statistical heterogeneity: Compared with standard therapy, intensive therapy increased the risk of cardiovascular death in the ACCORD trial and had a neutral or salutary effect in the ADVANCE and the UKPDS trials. Despite these differences, these 4 trials suggest that in people with type 2 diabetes mellitus, glucose-lowering approaches that clearly increase the risk of severe hypoglycemia reduce the risk of MI, have a neutral effect on stroke, and have an uncertain and apparently mixed effect on cardiovascular death.

**Trials Comparing Different Glucose-Lowering Regimens in Type 2 Diabetes Mellitus**

The results of 4 large outcomes trials of different glucose-lowering approaches or regimens in people with type 2 diabetes mellitus and other cardiovascular risk factors have also been reported and are summarized in Table 1. These included the Prospective Pioglitazone Clinical Trial in Macrovascular Events (PROACTIVE)34; the Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes (RECORD)35; the Hyperglycemia and Its Effect After Acute Myocardial Infarction on Cardiovascular Outcomes in Patients With Type 2 Diabetes Mellitus; and BARI 2D, Bypass Angioplasty Revascularization Investigation 2 Diabetes.

### Table 1. HR (95% CI) of Severe Hypoglycemia and Serious Clinical Outcomes in the Treatment vs Control Group in People With Type 2 Diabetes Mellitus

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Subjects</th>
<th>Treatment Groups</th>
<th>Risk (95% CI) of Severe Hypoglycemia</th>
<th>Risk (95% CI) of Serious Clinical Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td>CONTROL meta-analysis33</td>
<td>27 049</td>
<td>Intensive vs standard glucose control</td>
<td>2.48 (1.91-3.21)</td>
<td>All-Cause Death: 1.04 (0.90-1.20), CV Death: 1.10 (0.84-1.42), Fatal or Nonfatal MI: 0.85 (0.76-0.94), Fatal or Nonfatal Stroke: 0.96 (0.83-1.10)</td>
</tr>
<tr>
<td>PROACTIVE34</td>
<td>5238</td>
<td>Add-on pioglitazone vs placebo</td>
<td>1.75 (0.83-3.66)*</td>
<td>All-Cause Death: 0.96 (0.78-1.18), CV Death: 0.94 (0.75-1.19)*, Fatal or Nonfatal MI: 0.83 (0.65-1.06)†</td>
</tr>
<tr>
<td>RECORD35</td>
<td>4447</td>
<td>Rosiglitazone plus metformin or SU vs metformin and SU</td>
<td>0.67 (0.58-0.79)‡</td>
<td>All-Cause Death: 0.86 (0.68-1.08), CV Death: 0.84 (0.59-1.18), Fatal or Nonfatal MI: 1.14 (0.80-1.63), Fatal or Nonfatal Stroke: 0.72 (0.49-1.06)</td>
</tr>
<tr>
<td>HEART 2D36</td>
<td>1115</td>
<td>Prandial insulin vs basal insulin strategy</td>
<td>1.36 (0.97-1.90)*</td>
<td>All-Cause Death: 1.00 (0.68-1.48), CV Death: 1.05 (0.69-1.60), Fatal or Nonfatal MI: 1.01 (0.71-1.43), Fatal or Nonfatal Stroke: 1.20 (0.63-2.29)</td>
</tr>
<tr>
<td>BARI 2D37</td>
<td>2368</td>
<td>Insulin provision vs sensitization strategy</td>
<td>1.56 (1.16-2.09)*</td>
<td>All-Cause Death: 1.02 (0.83-1.26)<em>, CV Death: 1.06 (0.76-1.47)</em>, Fatal or Nonfatal MI: 1.14 (0.92-1.43)<em>, Fatal or Nonfatal Stroke: 1.33 (0.81-2.18)</em></td>
</tr>
</tbody>
</table>

CI indicates confidence interval; CV, cardiovascular; MI, myocardial infarction; CONTROL, Collaboration on Trials of Lowering Glucose; PROACTIVE, Prospective pioglitAzone Clinical Trial In macroVascular Events; RECORD, Rosiglitazone Evaluated for Cardiac Outcomes and Regulation of Glycaemia in Diabetes; SU, sulfonylurea; HEART 2D, Hyperglycemia and Its Effect After Acute Myocardial Infarction on Cardiovascular Outcomes in Patients With Type 2 Diabetes Mellitus; and BARI 2D, Bypass Angioplasty Revascularization Investigation 2 Diabetes.

* Relative risk (95% CI) is shown because hazard ratio was not available.
† The HR for nonfatal MI is indicated because the hazard for both fatal and nonfatal MI was not provided.
‡ The relative risk of any hypoglycemia (and not severe hypoglycemia) was provided in the publication.

**Trials of Insulin Therapy in Critically Ill Patients With Dysglycemia**

A recent meta-analysis of 26 trials of insulin therapy and mortality in hospitalized critically ill patients with and without a history of diabetes included 14 trials that provided information on hypoglycemic episodes.38 Despite an overall 6-fold higher risk of hypoglycemic episodes, there was no overall increase in mortality; indeed, studies conducted in surgical intensive care units suggested a reduced mortality. Unfortunately, the risks of hypoglycemia and mortality were not reported specifically for the subgroup of people with diabetes. Nevertheless, these data suggest that an in-hospital intervention that causes hypoglycemic episodes does not increase the risk of mortality.

**Are Hypoglycemic Episodes a Risk Factor for Serious Cardiovascular Outcomes?**

Whether hypoglycemia is a risk factor for future cardiovascular events is best assessed by comparing the incidence of serious cardiovascular outcomes in individuals who have had hypoglycemic episodes and in individuals who have not. Several such analyses of data from prospective studies have been reported recently. These analyses were based on people recruited for either epidemiological studies or clinical trials either during a hospitalization or within an ambulatory environment. These studies are consistent with the conclusion that hypoglycemia is indeed a risk factor for cardiovascular outcomes and are summarized below and in Table 2.
Risk of Cardiovascular Outcomes After an In-Hospital Hypoglycemic Episode

Epidemiological Cohort Studies
Analyses of the long-term effect of in-hospital hypoglycemic episodes have been based on data collected in single or many hospitals. In 1 study, glucose levels were abstracted from the charts of 684 (96%) of 713 consecutive patients with type 2 diabetes mellitus who were admitted to a Swedish hospital with unstable angina or an acute MI, and the subsequent 2-year mortality outcomes were obtained from the Swedish mortality registry. A total of 44 patients (6.4%) experienced at least 1 episode of hypoglycemia, which was defined as blood glucose ≤3.0 mmol/L (55 mg/dL) with or without clinical symptoms or intervention at any time during hospitalization. These patients were thinner, had a longer duration of diabetes, and were less likely to have a history of hypertension than those who had no hypoglycemic episodes. Moreover, compared with those whose lowest glucose level during the hospitalization was 3.1 to 6.5 mmol/L, they had a higher subsequent 2-year risk of death that persisted after adjustment for the confounders noted above as well as others (HR 1.93, 95% CI 1.18 to 3.17). This mortality risk was similar to that of patients whose lowest in-hospital glucose levels were >6.5 mmol/L. A similar J-shaped relationship between persistently low in-hospital glucose levels <3.9 mmol/L (70 mg/dL) and in-hospital mortality was noted in an administrative database of 16 871 people admitted to the hospital with an acute MI, as well as in the subset of people with a history of diabetes.

Epidemiological Analyses of Clinical Trials
The risk of cardiovascular outcomes after an in-hospital hypoglycemic episode has been analyzed in at least 3 large clinical trials of hospitalized patients. In the 2nd Diabetes, Glucose and Acute Myocardial Infarction (DIGAMI 2) trial, 1253 patients with either type 2 diabetes mellitus or an admission blood glucose ≥11.1 mmol/L who were hospitalized for suspected acute MI were randomized to (1) a 24-hour insulin-glucose infusion aiming at normoglycemia, followed by subcutaneous insulin-based regimen for long-term glucose control; (2) a 24-hour insulin-glucose infusion, followed by standard glycemic care; or (3) standard glycemic care. Participants were hospitalized for approximately 10 days and followed up for a median of 2.1 years after admission. A hypoglycemic episode was defined as blood glucose <3.0 mmol/L, and both symptomatic and nonsymptomatic hypoglycemic episodes were documented during hospitalization. During the first 24 hours of admission, 2.2% of all patients had symptomatic hypoglycemic episodes. Regardless of allocated group, individuals who experienced such an episode were generally older and thinner and were more likely to have comorbid conditions than those who did not experience a hypoglycemic episode. Moreover, these individuals were twice as likely to die of all causes (95% CI 1.2 to 3.3) and of cardiovascular causes (95% CI 1.2 to 3.5) during the 2-year follow-up period compared with individuals who did not experience a hypoglycemic episode. It is notable that this increased risk was significantly attenuated after accounting for differences in baseline characteristics between those who did and did not have an episode. Indeed, after adjustment for baseline confounders, the hazard ratio was no longer significant for either total mortality (HR 1.09, 95% CI 0.64 to 1.87) or cardiovascular mortality (HR 1.20, 95% CI 0.69 to 2.09). There was no evidence of an increased hazard of a composite outcome of death, stroke, and reinfarction in the hypoglycemic group in either unadjusted or adjusted analyses.

Similar findings were reported from a combined analysis of data from 2 trials comprising a total of 30 536 patients (5440 with a previous history of diabetes) who were hospitalized with an acute MI. In both of these trials, patients presenting to the hospital with acute ST-elevation MI were randomized to a high-dose glucose-insulin-potassium infusion versus standard care. This intervention was aimed at improving energy balance of the ischemic myocardium rather than at lowering plasma glucose. A hypoglycemic episode was defined as a documented glucose value ≤3.8 mmol/L (70 mg/dL) with or without symptoms of hypoglycemia, and a hyperglycemic episode was defined as a glucose level

Table 2. HR (95% CI) of Serious Clinical Outcomes After a Hypoglycemic Episode in Hospitalized Patients With Diabetes

<table>
<thead>
<tr>
<th>Study</th>
<th>No. of Subjects</th>
<th>Comparison Groups</th>
<th>Time of Outcome Analysis</th>
<th>Adjusted HR (95% CI) of Serious Clinical Outcomes</th>
</tr>
</thead>
<tbody>
<tr>
<td></td>
<td></td>
<td></td>
<td></td>
<td>All-Cause Death</td>
</tr>
<tr>
<td>Svensson et al (2005)</td>
<td>684</td>
<td>Hypoglycemia vs normoglycemia during hospitalization for acute MI</td>
<td>2 y</td>
<td>1.93 (1.18–3.17)</td>
</tr>
<tr>
<td>Kosiborod et al (2008)</td>
<td>4916</td>
<td>Mean blood glucose &lt; 3.9 mmol/L vs 5.5–6 mmol/L during hospitalization for acute MI</td>
<td>Length of hospitalization</td>
<td>6.5*</td>
</tr>
<tr>
<td>DIGAMI-2 trial</td>
<td>1253</td>
<td>Symptomatic hypoglycemia vs no hypoglycemia during the first 24 h of hospitalization for acute MI</td>
<td>2.1 y</td>
<td>1.09 (0.64–1.87)</td>
</tr>
<tr>
<td>CREATE-ECLA and OASIS-6 trials</td>
<td>5440</td>
<td>Hypoglycemia vs normoglycemia on admission for acute MI</td>
<td>30 d</td>
<td>2.13 (1.01–4.49)</td>
</tr>
<tr>
<td></td>
<td></td>
<td>Hypoglycemia vs normoglycemia during 24 h after an acute MI</td>
<td>30 d</td>
<td>1.58 (0.77–3.24)</td>
</tr>
</tbody>
</table>

HR indicates hazard ratio; CI, confidence interval; CV, cardiovascular; MI, myocardial infarction; NA, not available; DIGAMI-2, Diabetes Mellitus Insulin-Glucose Infusion in Acute Myocardial Infarction 2; CREATE-ECLA, Clinical Trial of Reviparin and Metabolic Modulation in Acute Myocardial Infarction Treatment Evaluation-Studios Cardiológicos Latinoamérica; and OASIS-6, Sixth Organization to Assess Strategies in Acute Ischemic Syndromes.

*Adjusted odds ratio in the subgroup of patients with diabetes was estimated from a graph.
and/or ≥7.1 mmol/L (140 mg/dL) without any value <3.8 mmol/L (70 mg/dL). Of the participants with a prior history of diabetes, 0.7% were hypoglycemic at the time of admission, and 2.0% had at least 1 hypoglycemic episode during the first 24 hours after admission. Compared with people whose admission glucose levels were between 3.9 and 7.0 mmol/L, patients whose admission glucose levels were ≤3.8 mmol/L (70 mg/dL) were twice as likely to die within 30 days of admission (HR 2.13, 95% CI 1.01 to 4.49) after adjustment for confounders. Conversely, hypoglycemic episodes that were detected during the first 24 hours of admission were not related to 30-day mortality after adjustment for confounders (HR 1.58, 95% CI 0.77 to 3.24). Moreover, despite the fact that postadmission hypoglycemia was twice as common in the group allocated to glucose-insulin-potassium, it was not associated with 30-day mortality in either the glucose-insulin-potassium group (adjusted HR 0.85, 95% CI 0.59 to 1.24) or the control group (adjusted HR 1.02, 95% CI 0.67 to 1.56).

The foregoing analyses therefore suggest that hypoglycemia that spontaneously occurs before hospitalization for coronary disease is a predictor of future mortality. However, they also suggest that hypoglycemia induced by therapy does not increase mortality.

**Risk of Cardiovascular Outcomes After a Hypoglycemic Episode in Ambulatory Patients**

The relationship between a low ambulatory fasting plasma glucose level and subsequent all-cause and cardiovascular mortality was analyzed in 14 670 ambulatory patients with documented coronary artery disease who were screened for a large randomized controlled trial.44 Compared with participants with a plasma glucose level of 4.4 to 6.0 mmol/L (80 to 109 mg/dL), those whose glucose levels were ≤3.8 mmol/L (69 mg/dL) had a higher 8-year adjusted risk of death and cancer-related death (HR 1.84, 95% CI 1.29 to 2.61 and HR 2.26, 95% CI 1.12 to 4.57, respectively) but not coronary artery disease–related death (HR 1.30, 95% CI 0.73 to 2.29). The effect of hypoglycemia in the subgroup of people with diabetes was not reported.

Similar findings were reported in a recent analysis of 10 194 participants with type 2 diabetes mellitus and other cardiovascular risk factors who participated in the ACCORD trial.45 In this trial, a severe hypoglycemic episode was defined as an episode requiring assistance that either responded to therapy or was associated with a glucose level <2.8 mmol/L (50 mg/dL). Participants who had such an episode after randomization had an increased risk of death after adjustment for confounders regardless of whether they were allocated to the intensive-therapy group (HR 1.41, 95% CI 1.03 to 1.93) or the standard-therapy group (HR 2.30, 95% CI 1.46 to 3.65). Similar effects were also noted when the analysis was restricted to the subset of people who required assistance from medical personnel for the hypoglycemic episode (HR 1.28, 95% CI 0.88 to 1.85 for the intensive-therapy group and HR 2.87, 95% CI 1.73 to 4.76 for the standard-therapy group; Figure). Thus, as noted in the studies of hospitalized patients, hypoglycemia within an ambulatory environment is also a risk factor for death.

**Do Hypoglycemic Episodes Precipitate Serious Cardiovascular Events?**

Analyses from both the acute MI trials and the ACCORD trial suggest that hypoglycemia that occurs as a consequence of a therapeutic intervention has a different relationship with serious cardiovascular outcomes or death than spontaneous hypoglycemia or episodes that occur as part of the routine management of diabetes. This possibility was explicitly explored in analyses of differences in the relationship between severe hypoglycemic episodes and death within the 2 ACCORD treatment groups.45 Thus, participants allocated to the intensive group who had at least 1 severe hypoglycemic episode had a lower mortality rate (2.8% per year) than those allocated to the standard group (3.7% per year). This was also noted (Figure 1) when the mortality rate in participants in the intensive-therapy group who had at least 1 severe episode that required medical assistance (2.8% per year) was compared with the rate in participants in the standard-therapy group.
(4.9% per year). Indeed, compared with standard-therapy participants who had 1 or more severe episodes that required assistance, intensive-therapy group participants were about half as likely to die during 3.5 years of follow-up (adjusted HR 0.55, 95% CI 0.31 to 0.99). Conversely, as noted in Figure 1, mortality was 25% higher in the intensive- versus the standard-therapy group among individuals who did not have such an episode (adjusted HR 1.25, 95% CI 1.03 to 1.52). Moreover, in a supplemental analysis of capillary glucose levels measured during 7 days before each study visit, there was a relationship between levels <3.3 mmol/L and death overall. In the group with a history of severe hypoglycemia that required medical assistance, however, there was a nonsignificant trend that suggested a lower risk of death in people in both the intensive- and standard-therapy groups who had greater numbers of low capillary glucose measurements (HR 0.68, 95% CI 0.36 to 1.24). A similar finding was reported in the small Steno 2 trial of 160 patients followed up for more than 13 years. In this trial, a multifactorial approach targeting many cardiovascular risk factors, including hemoglobin A1c levels, reduced both total mortality and cardiovascular outcomes. No association was noted between hypoglycemic events and mortality. Indeed, symptomatic hypoglycemic episodes were associated with a lower risk of both total and cardiovascular mortality in the conventional-therapy group and a nonsignificant trend toward a lower risk in the intensive-therapy group.

**Summary**

Hypoglycemia is the most common side effect of glucose-lowering therapies in both type 1 and type 2 diabetes mellitus. Most hypoglycemic episodes are easily self-treated, although some are severe and require the assistance of another person to treat. Data from a variety of small physiological studies and epidemiological evidence linking such episodes to serious cardiovascular outcomes and death have fueled long-standing concerns that glucose-lowering therapies that increase the risk of hypoglycemia may cause these outcomes. None of the studies discussed in this commentary provide evidence that clearly refutes this possibility, and it is certainly possible that the consequences of hypoglycemia were underestimated, because (1) many hypoglycemic episodes may not be detected or recorded (especially if mild) or (2) recording of hypoglycemic episodes may have occurred differently in each of the allocated treatment groups in nonblinded randomized trials. It is also possible that any potential cardioprotective benefits of certain drugs or therapies may mitigate the consequences of hypoglycemia, thus obscuring any harms. Moreover, people who have frequent hypoglycemic episodes might “adapt” to them, whereas the hypoglycemic episodes that are harmful are those that occur infrequently and would therefore be less likely to be detected as a risk factor. However, the studies discussed herein provide no evidence to support or refute these possibilities. Indeed, with the exception of the ACCORD trial, the significantly higher hypoglycemia rates in the intensive glucose-lowering group were clearly not associated with higher risks of serious cardiovascular outcomes or mortality in that group in the large clinical trials that compared more- versus less-intense glucose con-


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