ORIGINAL ARTICLE

Hypoglycemia, Diabetes, and Cardiovascular Disease

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Abstract

Cardiovascular disease (CVD) remains the leading cause of death in people with diabetes, and the risk of CVD for adults with diabetes is at least two to four times the risk in adults without diabetes. Complications of diabetes, including not only CVD but also microvascular diseases such as retinopathy and nephropathy, are a major health and financial burden. Diabetes is a disease of glucose intolerance, and so much of the research on complications has focused on the role of hyperglycemia. Clinical trials have clearly demonstrated the role of hyperglycemia in microvascular complications of diabetes, but there appears to be less evidence for as strong of a relationship between hyperglycemia and CVD in people with diabetes. Hypoglycemia has become a more pressing health concern as intensive glycemic control has become the standard of care in diabetes. Clinical trials of intensive glucose lowering in both type 1 and type 2 diabetes populations has resulted in significantly increased hypoglycemia, with no decrease in CVD during the trial period, although several studies have shown a reduction in CVD with extended follow-up. There is evidence that hypoglycemia may adversely affect cardiovascular risk in patients with diabetes, and this is one potential explanation for the lack of CVD prevention in trials of intensive glycemic control. Hypoglycemia causes a cascade of physiologic effects and may induce oxidative stress and cardiac arrhythmias, contribute to sudden cardiac death, and cause ischemic cerebral damage, presenting several potential mechanisms through which acute and chronic episodes of hypoglycemia may increase CVD risk. In this review, we examine the risk factors and prevalence of hypoglycemia in diabetes, review the evidence for an association of both acute and chronic hypoglycemia with CVD in adults with diabetes, and discuss potential mechanisms through which hypoglycemia may adversely affect cardiovascular risk.

Introduction

CARDIOVASCULAR (CV) DISEASE (CVD) remains the leading cause of death in people with diabetes,^{1,2} and the risk of CVD for adults with diabetes is at least two to four times the risk in adults without diabetes.³ Complications of diabetes, including not only CVD but also microvascular diseases such as retinopathy and nephropathy, are a major health and financial burden.

Diabetes is a disease of glucose intolerance, and so much of the research on complications has focused on the role of hyperglycemia. Clinical trials have clearly demonstrated the role of hyperglycemia in microvascular complications of diabetes,⁴ but there appears to be less evidence for as strong of a relationship between hyperglycemia and CVD in people with diabetes.⁵

More recently, it has come to the attention of clinicians and researchers that hypoglycemia may also have CV effects,^{6,7} and some studies have suggested a link between hypoglycemic excursions and CVD in people with diabetes.^{6,8} Hypoglycemia causes a cascade of physiologic effects and may induce oxidative stress,⁹ induce cardiac arrhythmias,¹⁰ contribute to sudden cardiac death,¹⁰ and cause ischemic ce-

rebral damage,^{7,11} presenting several potential mechanisms through which acute and chronic episodes of hypoglycemia may increase CVD risk.

In this review, we examine the evidence for an association of both acute and chronic hypoglycemia with CVD in adults with diabetes and discuss potential mechanisms.

Physiologic Effects of Hypoglycemia

The acute physiologic effects of hypoglycemia have been studied in order to determine mechanisms through which hypoglycemia may adversely impact CVD risk and to determine the importance of blood glucose levels during hospitalization for both in-hospital outcomes and longer-term prognosis.

Acutely, hypoglycemia stimulates the autonomic system, resulting in a cascade of actions including the release of epinephrine, glucagon secretion, increased blood flow to the brain to prevent neuroglycopenia, and increased gluconeogenesis in the liver to restore blood glucose levels.¹⁰ The physiologic effects depend on the blood glucose level, with blood glucose levels in the normally asymptomatic mild hypoglycemic range (approximately 58–69 mg/dL) stimulating

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counterregulatory hormones (glucagon and epinephrine) to increase glucose production. Once blood glucose falls lower than this, symptoms usually appear as the autonomic system is stimulated and neuroglycopenia affects the brain. Further drops in blood glucose to approximately 43–54 mg/dL result in decreased evoked responses and electroencephalographic changes and noticeable degradation in cognitive function. Severe hypoglycemia, generally glucose levels below about 27 mg/dL, is accompanied by convulsions, loss of consciousness, and coma.¹⁰

During acute hypoglycemia, heart rate and systolic blood pressure increase, blood flow increases in the myocardium, and cardiac output, stroke volume, and myocardial contractility increase, adding stress to the CV system at least temporarily. Below, we will discuss the tissue-specific effects of the hemodynamic changes that occur during acute hypoglycemia.

Effects of hypoglycemia in the heart

Adequate myocardial perfusion is normally maintained by the return of the reflected blood pressure wave during diastole, but in people with diabetes, arteriosclerosis leads to faster wave reflection, and so the reflected wave can instead return during systole, augmenting systolic blood pressure and reducing diastolic blood pressure, therefore widening the pulse pressure and decreasing the perfusion of the myocardium during diastole.¹⁰ Particularly among older adults with diabetes, the presence of coronary artery disease can lead to myocardial ischemia during hypoglycemia.

In addition to reducing myocardial perfusion, hypoglycemia can induce changes in the electrical system in the heart, including lengthening the QT interval,^{12,13} lengthening repolarization, and causing ST wave changes.¹⁰ These electrocardiographic changes are due to the effect of hypokalemia, which results due to the catecholamine release triggered by hypoglycemia. Cardiac arrhythmias may result, leading to the well-recognized complication of sudden cardiac death during hypoglycemia.¹⁴ Studies in both adults and youth with type 1 diabetes (T1D) have observed longer QTc intervals and cardiac rhythm disturbances during observed and induced hypoglycemia.^{13,15,16} In 2009, Gill et al.¹³ used continuous glucose monitoring (CGM) and continuous electrocardiography in 25 patients with T1D, 20–50 years old, to document longer QTc intervals during nocturnal hypoglycemia as well as cardiac rate and rhythm disturbances associated with 62% of 13 nocturnal hypoglycemia episodes. Current data suggest no association between normoglycemic QTc interval and prolongation of the QTc during hypoglycemia, and therefore some have suggested evaluation of the electrocardiogram (ECG) during induced, controlled hypoglycemia to assess the risk for arrhythmia with nocturnal hypoglycemia.¹⁵ Increased use of CGM to decrease the frequency and duration of hypoglycemia in T1D patients could also potentially decrease the incidence of nocturnal hypoglycemia-related arrhythmias in this population.

Effects of hypoglycemia in the brain

Ischemic stroke risk is increased two- to fourfold among people who have diabetes, particularly among those with type 2 diabetes (T2D).^{17,18} In addition to higher incidence, strokes in patients with diabetes tend to be more severe, with

greater cerebral ischemic damage, lower survival rates, and delayed recovery, and these patients tend to have hyperglycemia. In an elegant review by Radermecker and Scheen,¹⁹ the fine balancing act required between hyperglycemia and hypoglycemia in stroke patients was discussed, noting that hyperglycemia has detrimental effects on stroke outcomes and is a common complication in these patients, but efforts to reduce hyperglycemia can result in hypoglycemia, further damaging cerebral tissues.

In animal studies, rats treated with insulin and exposed to recurrent hypoglycemic episodes experienced a 44% increase in neuronal death compared with rats similarly treated with insulin but not exposed to hypoglycemia,¹¹ demonstrating that recurrent hypoglycemia can lead to more extensive cerebral ischemic damage. Decreased cognitive function can also lead to an increased risk of both hypoglycemia and CV events and mortality.²⁰ In a study examining magnetic resonance imaging of the brain in a cohort of 22 patients with T1D, brain lesions were more common in patients with T1D who had a history of repeated (five or more) hypoglycemic episodes.²¹ In some of the strongest evidence to date of the detrimental effects of hypoglycemia on cognitive function, Whitmer et al.²² at Kaiser Permanente in Northern California investigated the association of hospitalization or emergency department visits for hypoglycemia and the development of dementia in older adults with T2D and reported a dose-response relationship between the number of episodes of hypoglycemia and the risk for developing dementia.

Vascular Disease and Hypoglycemia

Although it has clearly been established that hyperglycemia increases the risk of diabetes complications, less is understood regarding the potential role of hypoglycemia in the development of these complications. In recent years, evidence has grown that hypoglycemia can affect the CV system and the brain, increasing the risk of CVD and dementia.

Acutely, hypoglycemia triggers a series of events designed to restore normal blood glucose levels and to preserve glucose delivery to the brain. When hypoglycemia is detected, the sympathetic system is activated, and counterregulatory hormones are released, resulting in transient changes in metabolism and CV function. In healthy individuals, there is likely no longer-term effects of hypoglycemia, but among patients with diabetes who already suffer from vascular damage, acute hypoglycemia may lead to acute vascular events, including acute myocardial infarction and ischemic stroke.⁷ In addition, patients with T1D who have repeated hypoglycemic episodes may exhibit greater endothelial dysfunction as measured by flow-mediated dilatation and increased carotid intima-media thickness (cIMT), a marker of subclinical atherosclerosis.²³ In a small, hypothesis-generating study design combining CGM and cIMT in individuals without diabetes, more than half with impaired glucose tolerance, the number of minutes per day spent in hypoglycemia was significantly positively correlated with cIMT.²⁴ The long-term sequelae of hypoglycemia on subclinical atherosclerosis and endothelial function are still unclear, and further studies in this area are needed.

Diabetes accelerates the aging of the vascular system, and so increasing duration of diabetes is associated with a greater

risk of vascular damage. As shown in Figure 1,⁷ it is theorized that recurrent hypoglycemia may pose the greatest CVD risk among patients who have already sustained at least a decade of vascular damage due to diabetes. Therefore, efforts to achieve very low levels of glycosylated hemoglobin (HbA1c) may be focused on younger people with shorter disease duration, rather than on people with a long duration of diabetes.

Hypoglycemia in T2D

Although lowering HbA1c has been shown to significantly decrease the risk of microvascular and macrovascular complications even decades later,²⁵ reducing hyperglycemia is also associated with an increased risk of hypoglycemic events.^{10,26} Hypoglycemia not only can be uncomfortable because of symptoms, but is also a source of anxiety due to concerns about hypoglycemia occurring at night or during activities such as driving. Furthermore, recurrent episodes of hypoglycemia can cause reduced awareness of symptoms, therefore leading to increased number and severity of episodes in the future.²³ Therefore, there is increasing recognition of the importance of personalizing treatment and balancing the need for adequate glycemic control while also minimizing hypoglycemia.²⁷

Hypoglycemia is a concern not limited to patients on intensive treatment, as severe hypoglycemia may also occur among patients with inconsistent treatment regimens or poor compliance with blood glucose self-monitoring. As a result, hypoglycemia needs to be considered for both patients on intensive therapy as well as for poorly controlled or non-compliant patients with diabetes.

Patients with T2D may be treated by a wide array of lifestyle and pharmaceutical methods, including oral medications and insulin injections. Among users of oral medications, hypoglycemia is particularly an issue among patients receiving sulfonylureas or meglitinides, as these treatments increase insulin secretion.²⁶ Among patients with insufficient residual β -cell

function, insulin treatment is required and can also cause hypoglycemia due to excessive dosing, insufficient food intake, or factors such as exercise that increase insulin sensitivity.

Prevalence of hypoglycemia in T2D

The prevalence of hypoglycemia in T2D has been underappreciated, as it has long been thought that patients with T2D do not experience significant hypoglycemia. Hypoglycemic episodes are classified as mild, which are able to be self-treated, and severe, which require assistance from another individual and/or medical treatment.⁷ The American Diabetes Association defines hypoglycemia as plasma glucose <70 mg/dL requiring carbohydrate or glucose ingestion and severe hypoglycemia as low blood sugar requiring the assistance of another person and that cannot be treated with oral carbohydrate.

In a study of 719 T2D patients 20 years of age or older using sulfonylureas, there were 605 people with hypoglycemic episodes over 34,052 person-years, resulting in an annual rate of 1.8%.²⁸ The annual risk of hypoglycemia was higher in patients ≥ 65 years of age (2%) than among younger patients (1.4%).²⁸ In the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial, participants randomized to the intensive control group averaged 1.06 hypoglycemic episodes (self-monitored blood glucose <70 mg/dL) per week, whereas the prevalence in the standard control group was 0.29 episodes per week.²⁹ Over a median 5 years of follow-up in the Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE) study, Zoungas et al.³⁰ reported that the prevalence of severe hypoglycemia was 2.1%, with at least one episode occurring in 231 of the 11,140 patients followed. Severe hypoglycemia occurred in 1.5% of patients on standard treatment, compared with 2.7% of patients in the intensive treatment group, and minor hypoglycemia was reported by over half of intensively treated patients (52%) compared with 37% of patients on standard treatment.³⁰

Maintenance of adequate glycemic control during hospitalization is also an important treatment goal, as blood sugar levels may influence the outcome and prognosis. In a study of 44 hospitals across the United States, patients with T2D who were hospitalized experienced significant hyperglycemia with over 90% of patients with diabetes having at least one blood glucose level over 200 mg/dL, but in addition, 15% of T2D patients treated with insulin and 28% of diabetes patients treated in Veterans Administration hospitals experienced at least one episode of hypoglycemia.³¹

Although these rates are lower than those in adults with T1D, nevertheless they demonstrate that hypoglycemia is a common complication of some of the most common therapeutic agents used in patients with T2D.

Risk factors for hypoglycemia in T2D

Risk factors for hypoglycemia include advanced age, combination therapy, treatment with insulin or insulin secretagogues, and the presence of co-morbid conditions such as renal complications or liver disease.²⁷

Treatment-related hypoglycemia. There are a wide variety of treatments available for patients with T2D, including combination therapies. Several factors may influence the

FIG. 1. Risks of hypoglycemia on the vasculature: theoretical model of the increasing impact of hypoglycemia once vascular complications have developed.⁷ Reproduced with permission from John Wiley and Sons.

choice of treatment, including patient characteristics such as age and compliance, monetary factors including insurance coverage and costs, and safety concerns regarding side effects, sometimes prompted by media reports regarding adverse clinical trial findings.

Treatment with thiazolidinediones carries a low risk of hypoglycemia,²⁷ but their use has been tempered by concerns over increased risks of hepatotoxicity with troglitazone, which was removed from the market in 2000, concerns over potential CV risks associated with rosiglitazone,^{32,33} and a 2011 report from the Food and Drug Administration linking long-term pioglitazone use with bladder cancer.³³ Metformin reduces blood glucose levels through inhibiting hepatic gluconeogenesis and does not carry a high risk of hypoglycemia. Newer treatment options include incretins, such as dipeptidyl peptidase-4 inhibitors and glucagon-like peptide-1 agonists, which suppress postprandial glucagon. The risk of hypoglycemia with incretins appears to be relatively low.²⁶ Long-acting glucagon-like peptide-1 agonists liraglutide and exenatide long-acting release (once weekly) reduce HbA1c the most, followed by similar reductions by short-acting glucagon-like peptide-1 agonist exenatide twice a day and dipeptidyl peptidase-4 inhibitors.³⁴ As a result, the use of incretins may present an opportunity to achieve lower HbA1c without the increased risk for hypoglycemia.

The two treatments most associated with hypoglycemia are sulfonylureas and insulin. The risk of hypoglycemia with sulfonylureas is reported to be increased by 4–9% when compared with patients treated with other oral hypoglycemic agents,²⁷ and severe hypoglycemic episodes are estimated to occur at a rate of over 2,400 per 100,000 person-years.²⁷ Sulfonylureas increase insulin secretion from the pancreas, which can result in hyperinsulinemia when glucose levels are not sufficient. Similarly, insulin treatment is associated with hypoglycemia when insulin levels exceed the amount needed for the blood glucose level, whether because of an excessive dose, reduced food intake, exercise, or any other factors influencing insulin sensitivity and blood glucose levels. The use of a combination of sulfonylureas with insulin decreases the risk of hypoglycemia when compared with insulin treatment alone, as the use of oral hypoglycemics reduces the amount of insulin needed.^{35,36}

Age and diabetes duration. Older age is associated with higher risk of hypoglycemia, with the elderly particularly at risk.³⁷ Patients with T2D often exhaust the pancreatic β -cells with increasing duration of diabetes, resulting in a switch to insulin alone, rather than sulfonylureas either alone or in combination with insulin. As noted previously, insulin monotherapy is associated with a higher risk of hypoglycemia than combination treatment with sulfonylureas.²⁶

Other co-morbid conditions. Additional risk factors for hypoglycemia include the presence of renal or liver disease, recent hospitalization, and alcohol intake. Furthermore, hypoglycemia risk is increased by the use of concomitant treatment with several other classes of drugs, including salicylates, monoamine oxidase inhibitors, clofibrate, chloramphenicol, pyrazolone derivatives, sulfonamides, and coumarin anticoagulants.²⁸ In addition, patients who are not compliant with home blood glucose testing are at higher risk for severe hypoglycemia.³⁷

Hypoglycemia in T1D

Although the association of hyperglycemia with CVD has been documented,⁵ less is known about the long-term relationship of hypoglycemia with coronary disease and stroke in T1D. However, the relationship of hypoglycemia with acute arrhythmia in T1D has been studied in more depth. Tattersall and Gill³⁸ first defined the “dead in bed” syndrome in 1991, and others have reported similar episodes of sudden nocturnal death, which is now thought to be related to cardiac arrhythmias associated with nocturnal hypoglycemia.^{39,40}

With the advent of intensive insulin therapy in T1D has come an increased risk for hypoglycemia. This increased risk was noted in the Diabetes Control and Complications Trial (DCCT), which randomized people with T1D to receive intensive or standard therapy. Early on in the DCCT, after only 21 months of study, 216 of 817 subjects had already experienced a severe hypoglycemic episode, with the majority (549) occurring in the intensively treated group.⁴¹ Fortunately, in this trial the episodes of hypoglycemia did not appear to lead to cognitive defects over the long term.⁴²

Hypoglycemic excursions and chronic hypoglycemia in T1D

Acute hypoglycemic and hyperglycemic excursions are common in patients with T1D, even among people with excellent control. Although many clinicians and patients have attempted to maintain glycemic control levels as similar to levels in people without diabetes as possible in an effort to prevent complications, the reduction in hyperglycemia is often accompanied by significant hypoglycemia. This fact has become increasingly clear with the advent of CGM, which allows for detection of asymptomatic episodes of hypoglycemia, which may particularly occur overnight and not be detected by self-monitored blood glucose. As shown in Figure 2, a patient with T1D and an HbA1c of 5.6%, which is firmly in the range of non-diabetes values, nevertheless experiences significant glycemic excursions. This patient had an average of 22% of values hypoglycemic (<70 mg/dL) over a 7-day period, recorded using a DexCom (San Diego, CA) Seven[®] Plus system. In a study among young patients with T1D, CGM has revealed that there are an average of 0.9 hypoglycemic (<65 mg/dL) episodes daily per patient,⁴³ and another study found that T1D patients experience hypoglycemia (≤ 70 mg/dL) for an average of 60–89 min/day, or 4–6% of the time.⁴⁴

Acute hypoglycemia invokes a cascade of physiologic responses, including the activation of inflammatory pathways, release of counterregulatory hormones including epinephrine, and reduced blood flow to the myocardium. Of further concern is that a hypoglycemic episode decreases the response to a later hypoglycemic event, often leading to a vicious cycle of recurrent hypoglycemia and hypoglycemic unawareness. Therefore, despite achieving current HbA1c targets, the patient whose CGM tracing is shown in Figure 2 may be at increased risk for CVD.^{13,15,16}

Epidemiologic studies have suggested that better glycemic control is associated with lower risk of CVD, but observational studies cannot prove causality, and therefore several clinical trials have sought to answer the question of whether improving glycemic control can prevent or reduce

FIG. 2. Example of a diabetes subjects with normal glycosylated hemoglobin (5.6%) but significant glycemic excursions and hypoglycemic (time spent hypoglycemic [<70 mg/dL] = 22%).

complications, including CVD. Table 1 summarizes the major clinical trials to test the effects of glucose lowering on CVD complications in patients with diabetes. The DCCT randomized subjects with T1D to receive either intensive therapy (multiple daily injections or a pump) versus standard therapy, and there was no reported decrease in CVD events during the trial⁴⁹ but a threefold increase in hypoglycemia. However, in the long-term follow-up study, the Epidemiology of Diabetes Interventions and Complications, a significant reduction in CVD events was reported.⁵ Similarly, the United Kingdom Prospective Diabetes Study randomized patients with newly diagnosed T2D to intensive treatment, with two treatment arms (insulin and sulfonylurea vs. metformin) and a conventional treatment arm, and there was no significant re-

duction in CVD events during the trial.^{50,51} However, during the 10-year long-term follow-up, significant but modest reductions in CVD events were observed.²⁵

The results of these first two randomized clinical trials demonstrated that glucose lowering may modestly decrease macrovascular complications, but over a longer period of time than the much greater reductions observed in microvascular complications. More recently, three randomized clinical trials have been conducted to test whether lowering blood glucose to normal levels ($<6\%$) or near-normal levels ($\leq 6.5\%$) reduced CVD and mortality among patients with T2D. The criteria for the ACCORD study are outlined in Table 1. Patients were randomized to intensive versus standard therapy, and the study's primary outcome was non-fatal myocardial

TABLE 1. DATA ON HYPOGLYCEMIA AND CARDIOVASCULAR DISEASE FROM CLINICAL TRIALS

<i>Study</i>	<i>Description</i>	<i>Population</i>	<i>Treatments</i>	<i>Outcome</i>
DCCT/ EDIC ⁵	Effect of intensive vs. conventional treatment on micro- and macrovascular complications	1,441 T1D adolescents and adults (13–39 years old) with diabetes duration of 1–15 years	Intensive treatment (multiple injections or pump) vs. standard therapy	Reduced CVD by 54%, but only evident after long-term (>12 -year) follow-up
UKPDS ⁴⁵	Randomized control trial of intensive therapy to reduce complications of T2D	5,102 newly diagnosed T2D adults	Two intensive treatment arms (insulin/sulfonylurea or metformin) vs. conventional therapy	No difference in CVD outcomes after trial, but 10-year follow-up revealed a modest reduction in CVD
ACCORD ⁴⁶	Randomized control trial of excellent HbA1c ($<6\%$) vs. 7.0–7.9%	10,251 T2D patients, 40–79 years of age with CVD or 55–79 years of age with atherosclerosis or $\geq$ two risk factors	Combinations of all available treatments to achieve goal HbA1c	Study stopped 3.5 years early because of increased overall and CVD mortality
ADVANCE ⁴⁷	Test if glucose lowering decreased risk of CVD in T2D patients with at least one risk factor	11,140 patients with T2D in 20 countries, ≥ 55 years of age and ≥ 30 years of age at diagnosis	Intensive glucose lowering ($\leq 6.5\%$) vs. standard treatment	No difference in CVD end point by treatment group
VADT ⁴⁸	Determine effect of intensive glycemic control on CVD risk	1,791 patients with T2D on insulin or maximal-dose oral agents	Intensive treatment ($<6.0\%$) vs. standard treatment	No difference in CVD end point by treatment group

ACCORD, Action to Control Cardiovascular Risk in Diabetes; ADVANCE, Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation; CVD, cardiovascular disease; DCCT, Diabetes Control and Complications Trial; EDIC, Epidemiology of Diabetes Interventions and Complications; HbA1c, glycosylated hemoglobin; T1D, type 1 diabetes; T2D, type 2 diabetes; UKPDS, United Kingdom Prospective Diabetes Study.

infarction or stroke, or CVD death, and secondary outcomes were all-cause mortality, microvascular disease, hypoglycemia, cognitive function, and quality of life.^{52,53} The ADVANCE study was a multicountry trial of over 11,000 people with T2D, meeting diabetes duration and age criteria as outlined in Table 1. Study subjects were randomized to intensive therapy (goal HbA1c $\leq 6.5\%$) or standard treatment. The third long-term trial was the Veterans Administration Diabetes Trial (VADT), which studied 1,791 T2D patients who had failed insulin or maximal-dose oral hypoglycemic agents and were randomized to intensive (HbA1c target $< 6\%$) versus standard glucose control arms.⁴⁸

All three trials achieved improved glycemic control, with the VADT planning at least a 1.5% separation in HbA1c between the trial arms and achieving a 1.6% separation, ACCORD ending with HbA1c significantly different in the intensive (6.4%) versus the conventional arm (7.5%) ($P=0.001$), and ADVANCE achieving an HbA1c of 6.5% in the intensive arm versus 7.3% in the conventional arm ($P=0.001$).⁵⁴ Despite achieving glycemic treatment goals, none of the trials reported a significant reduction in CVD outcomes, and the ACCORD trial was stopped early because of increased total and CVD mortality.⁵⁴

Severe hypoglycemia was clearly increased among intensively treated patients in all three studies,¹⁰ and it has been hypothesized that this increase in hypoglycemia may be one explanation for the findings because adverse effects of hypoglycemia in the heart and blood vessels could have counteracted any treatment benefits.

A post hoc analysis of severe hypoglycemia, defined as blood glucose < 50 mg/dL or symptoms of hypoglycemia without other cause, and vascular outcomes was conducted in the ADVANCE trial by Zoungas et al.³⁰ Despite increased hypoglycemia in the intensively treated group in the ADVANCE trial, there was no increased risk for mortality associated with intensive treatment. However, severe hypoglycemia was associated with an over threefold increased risk for a macrovascular event and a similar increase in mortality risk.³⁰ However, it is unclear whether there is a causal relationship between severe hypoglycemia and vascular disease, and a lack of a temporal or dose-response relationship between hypoglycemia and outcomes suggests that severe hypoglycemia was a marker of overall increased susceptibility to adverse outcomes.

In the ACCORD trial, additional post hoc analyses have also been conducted to examine a potential role for hypoglycemia in the excess mortality among intensively treated patients. Episodes of hypoglycemia were defined as a self-monitored blood glucose < 70 mg/dL, and there were 1.06 episodes reported in the week prior to the study visit among intensively treated subjects, compared with 0.29 episodes in the week prior to the study visit among patients receiving standard therapy.²⁹ Unrecognized hypoglycemia was reported for 5.8% of the intensively treated subjects and 2.6% of the standard groups at visits, but the hazard ratios for associations between hypoglycemic episodes and mortality were either protective (hazard ratio 0.93, 95% confidence interval 0.9–0.97, $P<0.001$ in the intensive group) or nonsignificant (hazard ratio 0.98, 95% confidence interval 0.91–1.06, $P=0.615$ for the standard group).²⁹ In an additional post hoc analysis, Riddle et al.⁵⁵ reported that mortality was highest among patients with the highest HbA1c while on treatment, sug-

gesting that the risk of death was greatest in individuals with persistent hyperglycemia, not among those subjects among whom the HbA1c was successfully decreased to target (HbA1c $< 6.0\%$). Therefore, it appears that hypoglycemia due to aggressively lowered HbA1c does not account for the increased mortality observed in the intensively treated subjects in the ACCORD trial.

Conclusions

In conclusion, hypoglycemia is a common effect of treatment for diabetes and is prevalent among both T1D and T2D patients. Hypoglycemia may acutely increase the risk of CV complications, because of reduced blood flow in the heart and electrical disturbances leading to arrhythmia and prolonged QT interval. In addition, chronic hypoglycemia may accelerate the development of subclinical CVD and atherosclerosis and may exacerbate ischemia in the brain, increasing risks for dementia and stroke.

Risk factors for hypoglycemia include advanced age, treatment with sulfonylureas or insulin, and co-morbid conditions such as renal disease. Although improved glycemic control definitively decreases the risk for microvascular diabetes complications, several recent clinical trials have either failed to demonstrate a benefit of glucose lowering on CVD risk or have even suggested an increased CVD risk with very tight glycemic control.

As a result of these clinical trials, the treatment of diabetes is recommended to be individualized in order to balance the goals of achieving adequate glycemic control in order to prevent microvascular complications, while also avoiding hypoglycemia and related complications. More aggressive glycemic control should therefore be a goal among younger patients without substantial CVD in order to prevent later microvascular complications, and older patients and those with co-morbid conditions such as coronary artery disease, dementia, cerebrovascular disease, and renal disease should maintain the best glycemic control possible while also preventing significant hypoglycemia.

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