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Death During Intensive Glycemic Therapy of Diabetes: Mechanisms and Implications*

Philip E. Cryer, M.D.

Division of Endocrinology, Metabolism and Lipid Research, Washington University in St. Louis

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Despite its documented microvascular^{1–3} and potential macrovascular^{4,5} benefits in both type 1 and type 2 diabetes mellitus, intensive glycemic therapy was not found to produce macrovascular benefits, let alone survival benefits, in three recent randomized clinical trials: Action to Control Cardiovascular Risk in Diabetes (ACCORD),⁶ Action in Diabetes and Vascular Disease: Preterax and Diamicon Modified Release Controlled Evaluation (ADVANCE),⁷ and Veterans Affairs Diabetes Trial (VADT).⁸ Similarly, it was not found to produce a survival benefit in hyperglycemic intensive care unit patients.^{9–11} Indeed, intensive glycemic therapy resulted in increased mortality in one large trial involving patients with type 2 diabetes⁶ and in another large trial involving critically ill individuals (Normoglycemia in Intensive Care—Survival Using Glucose Algorithm Regulation (NICE-SUGAR)).⁹ Regardless of the specific causative mechanisms, the latter findings are of concern. It appears that some aspect of intensive therapy increased the risk of death.

There is clear evidence that administration of insulin or of an insulin secretagogue can cause fatal hypoglycemia,^{12–15} and can do so in persons with diabetes.^{16–32} First, the Toronto investigators' insulin extract sometimes killed diabetic dogs, and they found that convulsions following insulin extract administration were associated with low blood glucose concentrations and could be prevented by intravenous glucose administration in rabbits as early as 1922.¹² Second, high mortality rates characterize experimental hypoglycemia.^{13–15} Thus, there is no doubt that hypoglycemia can kill. Third, there is a reported iatrogenic mortality rate in type 1 diabetes.^{16–21} Older estimates were that 2% to 4% of patients with type 1 diabetes die from hypoglycemia.^{16–18} More recent estimates are that 6%,¹⁹ 7%²⁰ or 10%²¹ of those with type 1 diabetes die from hypoglycemia. Fourth, continuous glucose monitoring subcutaneous glucose concentrations that fell to <10 mg/dL (0.6 mmol/L) were temporally associated with the death of a patient with type 1 diabetes.²² Fifth, an association between therapeutic insulin-induced hypoglycemia and cardiac arrhythmias has long been

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Correspondence: Philip E. Cryer, M.D., Campus Box 8127, Washington University School of Medicine, 660 South Euclid Avenue, St. Louis, MO 63110, Phone: 314-362-7635, Fax: 314-362-7989, pcrayer@wustl.edu.

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recognized,²³ and a patient with hypoglycemia who developed ventricular tachycardia that reverted to sinus rhythm after intravenous glucose administration has been reported.²⁴ Sixth, hypoglycemic deaths have been reported in many patients with type 2 diabetes.^{25–27} Indeed, an association between hypoglycemic events and acute cardiovascular events in type 2 diabetes has been noted,²⁸ a Danish survey disclosed increased cardiovascular and all cause mortality in patients treated with sulfonylureas compared with those treated with metformin²⁹ and an association between low hemoglobin A1c (A1C) levels and mortality in patients with type 2 diabetes has been reported.^{30–32} With all of this evidence, it is simply not credible to contend, or even imply, that iatrogenic hypoglycemia is never fatal.

Given the association between hypoglycemia and mortality in ACCORD⁶ and NICE-SUGAR⁹ and in other trials,^{7,8} and the fact that hypoglycemia can be fatal as just summarized,^{12–32} it is reasonable to suspect that iatrogenic hypoglycemia was a cause of excess mortality during intensive glycemic therapy in ACCORD⁶ and in NICE-SUGAR.⁹ Excessive mortality during intensive glycemic therapy of type 2 diabetes in ACCORD could have been the result of chance, a nonglycemic effect of some aspect of the intensive therapy regimen (e.g., weight gain, a side-effect of one of the several drugs used or something else) or hypoglycemia.^{33–35} The plasma glucose concentrations at the times of death are not known. Therefore, conclusions to the contrary^{36–38} notwithstanding, it is not possible to conclude with certainty whether hypoglycemia was or was not a culprit. Interestingly, mortality in the intensive therapy group was directly related to the A1C level.³³ However, that does not exclude hypoglycemia as a cause of mortality. In ACCORD there were aggressive goals for the intensive therapy group, including an A1C <6%, and a plan to add drugs or increase doses of drugs monthly if those goals were not being met. Thus, it may be that, rather than attaining an A1C <6%, striving for that A1C and failing to achieve it led to even more aggressive glycemic therapy and excess mortality in ACCORD.³⁹ Notably, the fact that there was no significant difference in all cause mortality or in severe hypoglycemia rates in the two groups after the transition to the same, less intensive, glycemic goals³⁸ further indicates that there was something about the pre-transition intensive glycemic therapy regimen that led to excess mortality.

Based on their finding not only of an association between severe hypoglycemia and cardiovascular death but also associations between severe hypoglycemia and nonvascular outcomes in type 2 diabetes, Zoungas and colleagues⁴⁰ suggested that severe hypoglycemia might be a direct cause of death or it might be a marker of vulnerability to another cause of death. The latter is the tack pursued by Boucai and colleagues⁴¹ in this issue of the journal. However, it is not clear how such a nonvascular cause of death would lead to severe hypoglycemia, the putative marker. One can only speculate that it might have been malnutrition leading to both severe hypoglycemia and death. Furthermore, the lack of a temporal relationship between an episode of recognized severe hypoglycemia and death is not a compelling argument since it is conceivable that hypoglycemic episodes, including one at the time of death, were not recognized. Finally, it does not follow that a person with a co-morbidity, for example ischemic heart disease, cannot die from hypoglycemia because he or she has that co-morbidity. Indeed, for reasons developed later it is probable that such an individual would be more likely to suffer a fatal event, for example a ventricular arrhythmia, during a hypoglycemic episode.

The finding of excess mortality or cardiovascular events in patients with type 2 diabetes with A1C levels in the lower, as well the higher, ranges^{30–32} would seem to imply a direct effect of hypoglycemia. In the UK General Practice Research Database³⁰ mortality of patients with type 2 diabetes and A1C levels in the lower deciles was increased in those treated with a sulfonylurea and, to a greater extent, in those treated with insulin, drugs that can cause hypoglycemia. In the Kaiser Permanente Southern California database³¹ the risk

of a cardiovascular event (nonfatal myocardial infarction or stroke or cardiovascular death) was increased in patients with type 2 diabetes and an A1C $\geq 6\%$. The risk was increased in those treated with a sulfonylurea and to a greater extent in those treated with insulin—drugs that can cause hypoglycemia—but not in those treated with metformin. An association between A1C levels $<6\%$ and mortality has also been reported in older patients with type 2 diabetes.³² (A report of increased mortality of initially nondiabetic individuals with low A1C levels⁴² was not confirmed.⁴³ In the latter data set the hazard ratio for all cause mortality in nondiabetic individuals was virtually constant across the low A1C range.)

Prolonged, profound hypoglycemia can cause brain death.^{13–15,44,45} The mechanism is thought to be sustained increased glutamate release and receptor activation when plasma glucose concentrations are less than 18 mg/dL (1.0 mmol/L), the electroencephalogram is isoelectric and brain glucose and glycogen levels are unmeasurably low. Fortunately, those conditions occur very rarely in persons with diabetes. Thus, most fatal hypoglycemic episodes are the result of other mechanisms, presumably cardiac arrhythmias.⁴⁵ The mechanisms of fatal hypoglycemia-induced ventricular arrhythmias have been reviewed.^{46,47} One mechanism is impaired ventricular repolarization, reflected in a prolonged corrected QT (QTc) interval in the electrocardiogram. A prolonged QTc interval is known to be associated with lethal ventricular arrhythmias. Pathogenic factors include, but are not limited to, sympathoadrenal activation and hypokalemia during hypoglycemia. QTc interval prolongation occurs during experimental and clinical hypoglycemia in patients with type 1 diabetes.^{48–50}

Iatrogenic hypoglycemia in diabetes is the result of the interplay of absolute or relative therapeutic hyperinsulinemia and compromised defenses against the resulting falling plasma glucose concentrations.⁵¹ The compromised defenses include absent decrements in insulin, absent increments in glucagon and attenuated increments in epinephrine causing the syndrome of defective glucose counterregulation and attenuated increments in sympathoadrenal activity causing the syndrome of hypoglycemia unawareness. Because of the key roles of attenuated adrenomedullary and sympathetic neural responses in these syndromes, defective glucose counterregulation and hypoglycemia unawareness are conceptualized as components of hypoglycemia-associated autonomic failure (HAAF) in diabetes.⁵¹ HAAF is typically caused by recent antecedent iatrogenic hypoglycemia. It is now recognized that recent antecedent hypoglycemia also reduces baroreflex sensitivity.⁵² That cardiovascular HAAF is entirely analogous to metabolic HAAF.⁵¹ Thus, the construct of hypoglycemic mortality shown in the Figure is plausible. First, recent antecedent hypoglycemia causes cardiovascular HAAF including reduced baroreflex sensitivity and the resulting increased vulnerability to a ventricular arrhythmia. Second, recent antecedent hypoglycemia causes metabolic HAAF with an increased risk for an episode of iatrogenic hypoglycemia with sympathoadrenal activation that, through an array of mechanisms including abnormal cardiac repolarization, could trigger a ventricular arrhythmia and sudden death.

Iatrogenic hypoglycemia is the limiting factor in the glycemetic management of diabetes.⁵¹ It causes recurrent morbidity in most people with type 1 diabetes and many with advanced type 2 diabetes, and, as summarized here, is sometimes fatal. It generally precludes maintenance of euglycemia over a lifetime of diabetes and, thus, full realization of the benefits of glycemetic control. It impairs defenses against subsequent falling plasma glucose concentrations and therefore causes a vicious cycle of recurrent hypoglycemia. Clearly, there are many compelling reasons to minimize the risk of hypoglycemia in persons with diabetes.

Consideration of diabetes trials^{2,3,6-8} has prompted some to reconsider glycemic goals for persons with diabetes.⁵³⁻⁵⁶ Accepting the premise of individualized glycemic goals and since the barrier to glycemic control is hypoglycemia,⁵¹ it would seem that the glycemic goal for a given individual at a given point in the progression of his or her diabetes should be based on the drug regimen and the risk of hypoglycemia. A reasonable generic glycemic goal is the lowest A1C that does not cause severe hypoglycemia (that requiring the assistance of another person), preserves awareness of hypoglycemia and causes, at worst, an acceptable number of documented episodes of symptomatic hypoglycemia.⁵⁷ Absent these conditions, the regimen needs to be adjusted to eliminate the problem⁵¹ or, if serious efforts at that are not effective, the glycemic goal needs to be raised. During effective therapy of early type 2 diabetes with lifestyle changes or with pharmacological glucose-lowering agents other than a sulfonylurea, a glinide or insulin, a reasonable glycemic goal might be a normal A1C since such patients are not at risk for hypoglycemia during treatment with currently approved glucose-lowering medications.⁵¹ That might well be beneficial over a substantial portion of the course of type 2 diabetes. But, such therapies are seldom effective over a lifetime of type 2 diabetes and are not effective in type 1 diabetes. During therapy of type 2 diabetes with a sulfonylurea, a glinide or insulin or of type 1 diabetes with insulin, the glycemic goal might be an A1C <7%.^{53,58} That sometimes can be accomplished safely with a sulfonylurea or even with insulin shortly after oral agent failure in type 2 diabetes⁵⁹ and with insulin very shortly after the diagnosis of type 1 diabetes (i.e., in the “honeymoon” period). If such an A1C is not achievable safely, there is demonstrable benefit from reducing the A1C level from high to lower, albeit still above optimal, levels.⁶⁰ Indeed, a mean A1C of 7.5% was associated with an all cause mortality risk ratio of 1.0 in the UK General Practice Research Database.³⁰ Finally, glucose levels low enough to prevent symptoms of hyperglycemia become an appropriate goal in individuals with a limited life expectancy or functional capacity in whom glycemic control is unlikely to be beneficial.

Glycemic control is, of course, only one aspect of the management of diabetes. Interventions aimed at multiple risk factors – advice concerning diet, exercise and smoking cessation, blood pressure control and blood lipid control, along with glycemic control – produce both microvascular and macrovascular benefits.⁶¹

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Sudden Death in Diabetes

Figure.

Potential mechanism of iatrogenic hypoglycemia-induced hypoglycemia-associated autonomic failure (HAAF) mediated sudden death in diabetes: cardiovascular HAAF causing reduced baroreceptor sensitivity and metabolic HAAF leading to an episode of hypoglycemia that increases sympathoadrenal system activity which triggers a fatal ventricular arrhythmia in the setting of reduced baroreflex sensitivity.