# Hypoglycemia and Cardiovascular Risks

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Although hypoglycemia is the most common side effect of insulin therapy in diabetes and its morbidity is well known, for many years, the potentially life-threatening effects of hypoglycemia on the cardiovascular (CV) system have either been overlooked or have been dismissed as inconsequential to people with insulin-treated type 2 diabetes. This scenario may possibly be a consequence of the persisting misconception that this population is seldom exposed to severe hypoglycemia, defined as any episode that requires external assistance for recovery, whereas self-treated events are classified as "mild" (1). This myth was firmly repudiated by the findings of the large prospective study by the U.K. Hypoglycemia Study Group (2), which demonstrated that severe hypoglycemia is a common problem in insulin-treated type 2 diabetes and that the incidence increases with duration of insulin therapy. However, evidence for CV morbidity associated with hypoglycemia has been predominantly hypothetical and anecdotal (1,3). The potential dangers of intensive treatment regimens and strict glycemic control in people with type 2 diabetes who have CV disease (CVD) have now been highlighted by the disconcerting outcomes of recent studies (4–6), in which hypoglycemia was implicated in the excess mortality that was observed in some of these trials. It is therefore timely to review the effects of hypoglycemia on the CV system, how this major metabolic stress could precipitate major vascular events such as myocardial infarction and stroke, and its potential role in these recent clinical studies.

## PHYSIOLOGICAL EFFECTS OF HYPOGLYCEMIA

—In the adult human, acute hypoglycemia causes pronounced physiological responses as a consequence of autonomic activation, principally of the sympatho-adrenal system, and results in end-organ stimulation and a profuse release of epinephrine (adrenaline). This profound autonomic stimulus provokes hemodynamic changes, the important consequences of which are to maintain the supply of glucose to the brain and promote the hepatic production of glucose. Blood flow is therefore increased to the myocardium, the splanchnic circulation (to provide precursors of gluconeogenesis to the liver), and the brain. The hemodynamic changes associated with hypoglycemia include an increase in heart rate and peripheral systolic blood pressure, a fall in central blood pressure, reduced peripheral arterial resistance (causing a widening of pulse pressure), and increased myocardial contractility, stroke volume, and cardiac output (7). The workload of the heart is therefore temporarily but markedly increased. This transient cardiac stress is unlikely to be of serious functional importance in healthy young people who have a normal CV system, but may have dangerous consequences in many older people with diabetes, especially individuals with type 2 diabetes, many of whom have coronary heart disease.

In nondiabetic people, the arteries become more elastic during acute hypoglycemia with a decline in arterial wall stiffness, but in people with type 1 diabetes of >15 years' duration, arterial wall stiffness per se is greater and arteries are less elastic in response to hypoglycemia, manifesting in a lesser fall in central arterial pressure (8). Normal elasticity of the arterial wall ensures that the reflected pressure wave from the high-pressure arterioles, generated during each myocardial contraction, returns to the heart during early diastole, so enhancing coronary arterial perfusion, which occurs mainly during diastole. However, progressive stiffening of the arterial walls (as occurs in most people with longstanding diabetes) accelerates the return of the reflected wave causing its earlier arrival during late systole. This pathophysiological effect may interfere with coronary arterial perfusion and promote myocardial ischemia.

Hypoglycemia has long been known to affect the electrocardiogram (ECG) (9), causing ST wave changes with lengthening of the QT interval (10) and cardiac repolarization (11). Both experimentally induced and spontaneous clinical hypoglycemic episodes prolong cardiac repolarization, the process whereby the heart prepares for coordinated contraction during diastole and where abnormalities in other conditions can increase the risk of cardiac arrhythmias. These changes are reflected by changes in the T wave of the electrocardiogram (Fig. 1). Hypoglycemia leads to reduction in its amplitude with flattening and lengthening of the T wave (3), which is quantified by measuring the length of the QT interval (mathematically corrected for the prevailing heart rate [QTc]). Electrophysiological changes are related to hypokalemia, which is a consequence of the profuse secretion of catecholamines. These changes may increase the risk of cardiac arrhythmia; various abnormal heart rhythms, including ventricular tachycardia and atrial fibrillation, have been reported during hypoglycemia. This phenomenon and its contribution to causing sudden death after hypoglycemia are discussed in detail below.

The increased sympathetic activity and concurrent secretion during hypoglycemia of other hormones and peptides such as the potent vasoconstrictor,

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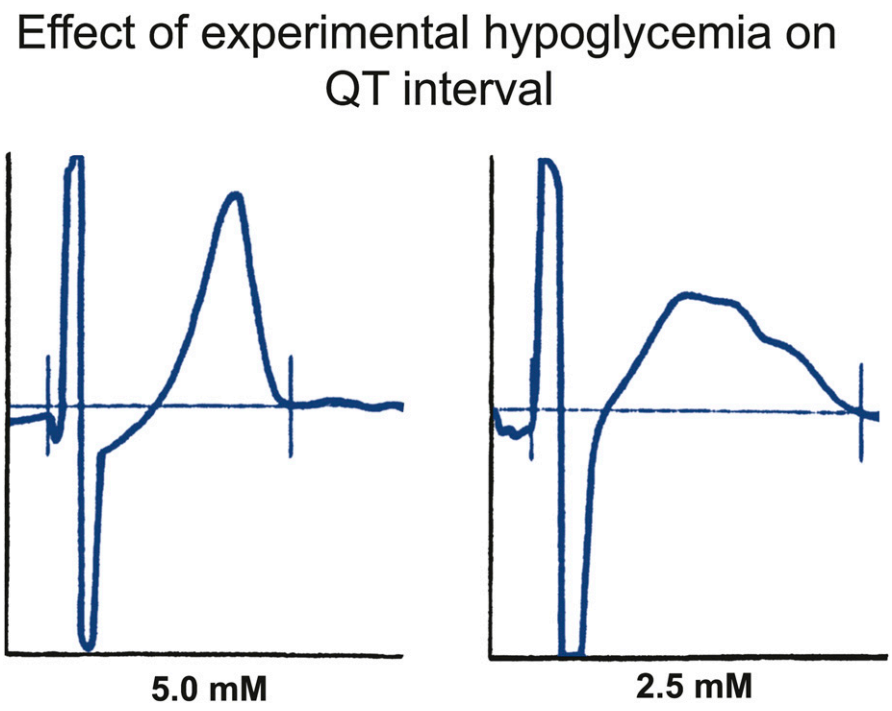


**Figure 1**—*Typical QT measurement with a screen cursor placement from a subject during euglycemia* (left panel)*, showing a clearly defined T wave, and hypoglycemia* (right panel)*, showing prolonged repolarization and a prominent U wave. Reproduced from Marques et al. (20) with permission from John Wiley & Sons.*

endothelin, also have pronounced effects on intravascular hemorheology, coagulability, and viscosity. Increased plasma viscosity occurs during hypoglycemia because of an increase in erythrocyte concentration, whereas coagulation is promoted by platelet activation and an increment in factor VIII and von Willebrand factor (7). Endothelial function may be compromised during hypoglycemia because of an increase in C-reactive protein and the mobilization and activation of neutrophils and platelet activation. These changes may promote intravascular coagulation and thrombosis and encourage the development of tissue ischemia, with the myocardium being potentially vulnerable.

## HYPOGLYCEMIA-INDUCED CV EVENTS

—Anecdotal case reports have indicated a temporal relationship between severe hypoglycemia, acute vascular events, and sudden death (3,7). Case reports describe angina in association with acute hypoglycemia and acute coronary syndromes with typical ECG and enzyme changes after severe hypoglycemia (3). When hypoglycemia was induced in six subjects with type 2 diabetes, five developed ischemic ECG changes, whereas a bradyarrhythmia resulted in loss of consciousness in another patient (12). When continuous glucose measurements and Holter ECG monitoring were performed simultaneously in patients with type 2 diabetes and known ischemic heart disease, 54 episodes of hypoglycemia (blood glucose level <3.9 mmol/L [70 mg/dL]) were identified, 10 of which were accompanied by chest pain (13). This illustrates the difficulty of demonstrating that a major cardiac event has been provoked by acute hypoglycemia in any individual diabetic patient, since simultaneous glucose and ECG monitoring is rarely possible in clinical practice.

## SUDDEN DEATH IN YOUNG PEOPLE WITH TYPE 1 DIABETES

—A link between hypoglycemia and sudden death was raised in the 1960s, but the first detailed description appeared in 1991 after investigation of a series of deaths of young adults with type 1 diabetes (14). The survey was commissioned by the British Diabetic Association after concern that insulin of human origin might cause fatal hypoglycemia. After deaths from definite causes were excluded, the authors identified 22 individuals with type 1 diabetes aged <50 years, who despite being previously well had a very similar manner of death. Most were found lying in an undisturbed bed, a scenario that prompted the label "dead in bed syndrome" (15). These observations have been followed by several epidemiological surveys that have confirmed both the mode of death and its increased frequency in individuals with type 1 diabetes (16–18). An autopsy study from Australia (19) suggested that sudden unexpected deaths are four times more frequent than in a comparable nondiabetic population and, of these, many are found dead in an undisturbed bed.

## HYPOGLYCEMIA AS A POTENTIAL RISK FACTOR FOR SUDDEN DEATH IN DIABETES

—Cumulating clinical and experimental evidence has shown that hypoglycemia can cause abnormal electrical activity in the heart and has strengthened the premise that hypoglycemia can provoke sudden death. High-resolution electrocardiography, which measures the QT interval precisely, in conjunction with hypoglycemic clamps to control the depth of hypoglycemia, has demonstrated lengthening of the QT interval both in diabetic and nondiabetic individuals (20,21). Clinical episodes of hypoglycemia have been shown to cause QT lengthening, measured using ambulatory ECG monitoring and simultaneous measurement of blood glucose (by either intermittent venous sampling or continuous glucose monitoring) (22).

Activation of the sympathoadrenal system probably drives these changes. Epinephrine infusion increases QT intervals (23), and β-blocking drugs attenuate QT lengthening during experimental hypoglycemia (24). However, hypoglycemia induces a fall in serum potassium via sympathoadrenal activation and a direct effect of insulin, and hypoglycemia per se may have an effect by directly inhibiting cardiac ion channels that are responsible for potassium efflux during cardiac repolarization (25).

## RELEVANCE OF ABNORMAL CARDIAC REPOLARIZATION AND LENGTHENED QT INTERVAL TO CARDIAC ARRHYTHMIAS

—In other situations, lengthening of the QT interval is a strong predictor of sudden death. The long QT syndrome is a congenital condition caused by mutations within the genes that code for proteins comprising the voltage-gated ion channels contributing to the cardiac action

potential. Those affected have abnormal cardiac repolarization represented by prolonged QT on their electrocardiograms and an increased risk of sudden death due to cardiac arrhythmias (26). QT lengthening caused by certain therapeutic agents including antihistamines or antibiotics in susceptible individuals can also cause sudden cardiac death. Because hypoglycemia is common and sudden death is rare, abnormal cardiac repolarization alone cannot explain why hypoglycemia might lead to sudden death. Other factors that might contribute include inherited mutations or polymorphisms of genes involved in cardiac electrical activity and acquired abnormalities of other potentially relevant pathological mechanisms such as autonomic neuropathy.

**POTENTIAL ROLE OF CARDIAC AUTONOMIC NEUROPATHY**—It is possible that an interaction between hypoglycemia-induced abnormalities of cardiac repolarization and autonomic neuropathy contributes to the risk of sudden death in individuals with diabetes. Diabetic autonomic neuropathy is known to be associated with an increased mortality, and resting QT intervals are generally longer in patients with autonomic neuropathy than in patients without (27). The recent demonstration that brief periods of experimental hypoglycemia impair CV autonomic function for up to 16 h is additional evidence for a clinically relevant interaction (28).

However, not all data are supportive, since individuals with diabetic autonomic neuropathy actually have smaller increments in QT intervals during experimental hypoglycemia than individuals without (29). The apparent paradox relates to the diminished sympathoadrenal responses that are observed both in patients with neuropathy (in part related to a long duration of diabetes) and after repeated episodes of hypoglycemia. Thus, on the one hand, a combination of autonomic neuropathy (aggravated by antecedent hypoglycemia) and then a severe episode leading to a powerful sympathoadrenal response might substantially increase the risk of arrhythmia-provoked sudden death, whereas on the other hand, repeated hypoglycemia in a person with impaired sympathoadrenal responses and longstanding diabetes might be protective. The way in which these different factors interact to confer risk is poorly understood and requires further experimental work.

**CASE REPORTS OF HYPOGLYCEMIA-ASSOCIATED ARRHYTHMIA**—The numerous case reports of cardiac arrhythmias provoked by spontaneous hypoglycemia (7) emphasize the clinical relevance of the association, particularly since ethical considerations limit experimental studies in this area. Those reported range from severe sinus bradycardia (which might progress to asystole) and atrial fibrillation to ventricular tachycardia.

**RISKS OF HYPOGLYCEMIA IN CRITICAL ILLNESS**—Evidence has emerged from other clinical studies of people with serious illness to support the premise that exposure to hypoglycemia carries inherent CV risks. The mortality rate of patients with diabetes, who were exposed to severe hypoglycemia after admission to hospital with an acute coronary syndrome, was twice that of those who did not experience hypoglycemia (30). This effect persisted after adjustment was made for potential confounding factors (31). In patients with ST-elevation acute coronary syndrome, the 30-day mortality was greater in patients at the upper and lower (<4.5 mmol/L [81 mg/dL]) extremes of blood glucose measured on admission to hospitals, showing a U-shaped curve (32). A similar pattern was observed in patients with diabetes in the Japanese Acute Coronary Syndrome Study, but not in their nondiabetic group (33). In another study, nondiabetic patients who developed spontaneous hypoglycemia while in hospital had a poorer outcome and a higher mortality than patients with insulin-treated diabetes exposed to iatrogenic hypoglycemia (34). Although the development of hypoglycemia in this situation may be a surrogate marker for the severity of illness, it may also directly contribute to a fatal outcome. The susceptibility of those patients to a cardiac arrhythmia may be increased by preceding exposure to low blood glucose. Antecedent hypoglycemia diminishes the cardiac vagal baroreflex sensitivity and the sympathetic response to drug-induced hypotension, thus attenuating the autonomic responses to CV stress for up to 16 h (28). This result may be a mechanism for inducing arrhythmias, making the heart susceptible to recurring hypoglycemia.

In a large multicenter randomized controlled trial in Australia (NICE-SUGAR) (35), the relationship of glycemic control to outcome from critical illness was examined in patients being treated in intensive care units. Strict control of blood glucose (4.5–6.0 mmol/L) was compared with standard control (<10.0 mmol/L). Mortality was higher in patients who maintained strict glycemic control, in whom severe hypoglycemia (defined as blood glucose <2.2 mmol/L) was much more common (6.8 vs. 0.5%; $P < 0.001$). A subgroup analysis suggested that no difference in 90-day mortality existed between individuals with diabetes (~20%) and individuals without diabetes (~80%). Potential weaknesses of this study limit interpretation. Unfortunately, the protocol permitted a reduction in the frequency of blood glucose measurements to four hourly tests when blood glucose was considered to be "stable," which was then inadequate to assess glycemic control. In addition, neuroglycopenia may be more difficult to detect in an unconscious patient under sedation and may not therefore be identified. Two meta-analyses (36,37) have shown that strict glycemic control in seriously ill patients does not improve overall survival but reduces the risk of septicemia in surgical intensive care units at the expense of a fivefold higher incidence of hypoglycemia (13.7 vs. 2.5%).

Alarming results have been reported recently from a large multicenter registry of 3,571 Japanese patients undergoing first elective coronary revascularization (38) when a potential association was examined between preoperative $HbA_{1c}$ levels and the CV outcome. Of the 3,571 patients, 1,504 had type 2 diabetes; the outcome in patients with type 2 diabetes was analyzed according to four categories of $HbA_{1c}$: <6%, 6 to <7%, 7 to < 8%, and >8%. Freedom from composite events of CVD death, myocardial infarction, and stroke after coronary revascularization was similar in nondiabetic patients and in those diabetic patients presenting with an $HbA_{1c}$ between 6 and 7%. By contrast, diabetic patients with higher $HbA_{1c}$ values (7–8 and >8%) had a significantly higher rate of the composite end point versus nondiabetic subjects ($P < 0.0005$), but the composite end point of CVD death, myocardial infarction, and stroke after coronary revascularization was similar or even higher in diabetic patients who had the lowest $HbA_{1c}$ values (<6.0%) compared with those patients with the poorest glycemic control.

**GLYCEMIC CONTROL AND LONG-TERM SURVIVAL**—Outside the hospital setting, circumstantial

evidence suggests that strict glycemic control, with its greater risk of severe hypoglycemia, may carry a potential risk to long-term survival. A study using the large U.K. General Practice Research Database (39) examined the relationship between $HbA_{1c}$ and survival using data collected for >20 years from 48,000 patients with type 2 diabetes. One cohort ($n$ = 27,965) had been changed from oral monotherapy to a combination of oral medications, whereas the other cohort ($n$ = 20,005) had commenced regimens that included insulin. The primary outcome measure of all-cause mortality was examined for each decile of $HbA_{1c}$ in both cohorts. The 10% of patients who had the lowest $HbA_{1c}$ values (<6.7%) had a higher mortality than all other deciles with higher $HbA_{1c}$ values, with the exception of the 10% with the highest $HbA_{1c}$ values (≥9.9%). The adjusted hazard ratios (HRs) for all-cause mortality by $HbA_{1c}$ deciles showed a U-shaped curve, irrespective of how or when $HbA_{1c}$ was measured. This study was criticized in that the patients in the second cohort were older and the causes of death were unknown. Also, the frequency of hypoglycemia could not be determined in this retrospective analysis. Nevertheless, the greatest risk of death and of cardiac events was associated with the lowest and highest $HbA_{1c}$ values. Although this evidence for a CV risk of hypoglycemia is much more circumstantial, this study supports the recommendation that glycemic control must be tailored to the age of the individual patient and in particular should address his or her existing comorbidities and the type of treatment to be used.

**HYPOGLYCEMIA IN ACCORD, ADVANCE, AND VADT**—CVD is the predominant cause of death in patients with type 2 diabetes, and reducing the risk of CVD has recently been the focus of three large glucose-lowering trials: ACCORD (Action to Control Cardiovascular Risk in Diabetes) (4), ADVANCE (Action in Diabetes and Vascular Disease: Preterax and Diamicron MR Controlled Evaluation) (5), and VADT (Veterans Affairs Diabetes Trial) (6) (Table 1). These three studies randomized almost 24,000 patients with longstanding high-risk type 2 diabetes to standard or intensive glycemic control for up to 5 years, ensuring $HbA_{1c}$ levels <7%. Mean $HbA_{1c}$ levels in the intensive arms of ACCORD, ADVANCE, and VADT were 6.4, 6.5, and 6.9% in contrast to 7.5, 7.3, and 8.5% in the standard arms. Unfortunately, strict glycemic control in these three studies did not incur a significant CV benefit, and none of the trials demonstrated any positive effect on CV events or mortality (Table 1). Even worse, the ACCORD study was prematurely interrupted because of an excess mortality among intensively treated patients. The rate of death from CV causes was higher in the intensive therapy group than in the standard therapy group (2.6 vs. 1.8%; HR 1.35; 95% CI 1.04–1.76; $P$ = 0.02). Similarly, the rate of death from any cause was also significantly higher in the intensive therapy group than in the standard therapy group (5.0 vs. 4.0%; HR 1.22; 95% CI 1.01–1.46; $P$ = 0.04).

**Table 1—*Clinical characteristics and effects of intensive glucose lowering vs. standard therapy on primary CV end point, total mortality, and CV mortality in ACCORD, ADVANCE, and VADT***

| | ACCORD | ADVANCE | VADT |
|---|---|---|---|
| $n$ | 10,251 | 11,140 | 1,791 |
| Age (years) | 62 | 66 | 60 |
| Men/women (%) | 61/39 | 58/42 | 97/3 |
| Duration of study (years) | 3.5 | 5.0 | 5.6 |
| BMI (kg/m$^2$) | 32.2 ± 5.5 | 28.0 ± 5.0 | 31.3 ± 3.5 |
| Duration of diabetes (years) | 10 | 8 | 11.5 |
| CVD | 35% | 32% | 40% |
| Primary CVD end point | ↓10% ($P$ = 0.16) | ↓6% ($P$ = 0.37) | ↓13% ($P$ = 0.12) |
| Mortality (overall) | ↑22% ($P$ = 0.04) | ↓7% ($P$ = NS) | ↑6.5% ($P$ = NS) |
| CV mortality | ↑35% ($P$ = 0.02) | ↓12% ($P$ = NS) | ↑25% ($P$ = NS) |

In all three trials, severe hypoglycemia was significantly higher in the intensive glucose-lowering arms compared with the standard arms: ACCORD 16.2 vs. 5.1%; VADT 21.2 vs. 9.9%; ADVANCE 2.7 vs. 1.5% (Fig. 2). The much lower risk for severe hypoglycemia in ADVANCE may be explained by the fact that the patients in that trial appeared to have earlier or less advanced diabetes, with a shorter duration by 2–3 years and lower $HbA_{1c}$ at entry despite very little use of insulin at baseline (40). In addition, the need for insulin treatment in the intensive arm of ADVANCE was much lower compared with that in the intensive arms of the other two trials (Fig. 1).

Several post hoc analyses (41–44) have now been reported by the ACCORD investigators, who were unable to ascertain the underlying causes of the higher mortality rate associated with strict glycemic control. Symptomatic severe hypoglycemia was associated with an increased risk of death within each study arm. Unadjusted annual mortality among patients in the intensive glucose control arm was

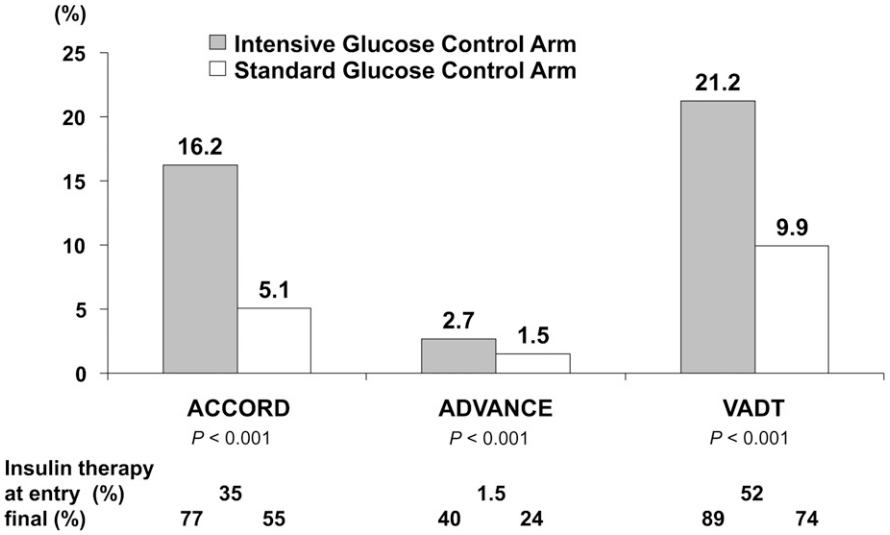


**Figure 2—*Percentage of severe hypoglycemic events in ACCORD, ADVANCE, and VADT.***

2.8% in patients who had one or more episodes of hypoglycemia requiring any assistance compared with 1.2% for individuals with no episodes (53 deaths per 1,924 person-years and 201 deaths per 16,315 person-years, respectively; adjusted HR 1.41, 95% CI 1.03–1.93). A similar pattern was seen among participants in the standard glucose control arm (3.7% [21 deaths per 564 person-years] vs. 1.0% [176 deaths per 17,297 person-years]; adjusted HR 2.30, 95% CI 1.46–3.65). However, among participants who experienced at least one episode of hypoglycemia, the risk of death was lower in participants in the intensive arm than in the standard arm. Thus, the ACCORD investigators concluded that symptomatic severe hypoglycemia does not appear to account for the difference in mortality between the two arms of the study up to the time when the ACCORD intensive glycemia arm was discontinued (43).

Nevertheless, it remains biologically plausible that severe hypoglycemia could increase the risk of CV death in participants with high underlying CVD. This risk might be further confounded by the development of impaired awareness of hypoglycemia, particularly in patients with coexisting CV autonomic neuropathy, a strong risk factor for sudden death. A recent analysis from ACCORD (44) confirmed that patients with baseline cardiac autonomic neuropathy were about twice as likely to die as patients without cardiac autonomic neuropathy. The contribution of hypoglycemia to the increased mortality in the intensive study arm might be difficult to identify in large studies such as ACCORD. Death from a hypoglycemic event may be mistakenly ascribed to coronary heart disease, since there may not have been a preceding blood glucose measurement and since hypoglycemia cannot be detected postmortem.

In contrast to the ACCORD study, in VADT, a recent severe hypoglycemic event was an important predictor for CV death (HR 3.72; 95% CI 1.34–10.4; $P < 0.01$) and all-cause mortality (HR 6.37; 95% CI 2.57–15.8; $P = 0.0001$) as reported by Dr. William Duckworth and colleagues at the American Diabetes Association Scientific Sessions in 2009 in New Orleans, Louisiana. By contrast, in the ADVANCE study (5), in which the overall occurrence of severe hypoglycemia was much lower than in ACCORD, no increase in all-cause or CV mortality was observed in patients randomized to the intensive arm. Nevertheless, severe hypoglycemia was strongly associated with increased risks of various adverse clinical outcomes (45), and the authors suggested that whereas severe hypoglycemia may contribute to these outcomes, it may alternatively be a marker of vulnerability to these events.

Many patients with advanced diabetes and CVD undergo coronary revascularization. Detailed findings about the impact of glycemic control on the outcome of the patients in that situation have not yet been reported in any of the three studies. Most guidelines recommend $HbA_{1c}$ targets below 7.0 or 6.5%, but without reference to specific antidiabetes treatments, diabetes duration, age of the patients, or preexisting CVD (46). Because, according to a recent meta-analysis, the beneficial effect of strict glycemic control on CV events (47) seems to be limited for patients who are free from CVD, a less stringent glycemic target should be recommended for diabetic patients with longer duration of the disease, shorter life expectancy, advanced macrovascular complications, and chronic kidney disease and patients who are prone to hypoglycemia (46,47). Accordingly, future diabetes guidelines will have to define a minimum $HbA_{1c}$ value, especially for patients with longstanding diabetes or who have established CVD (46). Indiscriminate application of intensive glucose-lowering therapy that could provoke dangerous hypoglycemia in frail elderly people with type 2 diabetes, or in patients with overt CVD, should be avoided.

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