REVIEW

The case for hypoglycaemia as a proarrhythmic event: basic and clinical evidence

C. Nordin

Abstract Recent clinical studies show that hypoglycaemia is associated with increased risk of death, especially in patients with coronary artery disease or acute myocardial infarction. This paper reviews data from cellular and clinical research supporting the hypothesis that acute hypoglycaemia increases the risk of malignant ventricular arrhythmias and death in patients with diabetes by generating the two classic abnormalities responsible for the proarrhythmic effect of medications, i.e. QT prolongation and Ca^{2+} overload. Acute hypoglycaemia causes QT prolongation and the risk of ventricular tachycardia by directly suppressing K^+ currents activated during repolarisation, a proarrhythmic effect of many medications. Since diabetes itself, myocardial infarction, hypertrophy, autonomic neuropathy and congestive heart failure also cause QT prolongation, the arrhythmogenic effect of hypoglycaemia is likely to be greatest in patients with pre-existent cardiac disease and diabetes. Furthermore, the catecholamine surge during hypoglycaemia raises intracellular Ca^{2+}, thereby increasing the risk of ventricular tachycardia and fibrillation by the same mechanism as that activated by sympathomimetic inotropic agents and digoxin. Diabetes itself may sensitise myocardium to the arrhythmogenic effect of Ca^{2+} overload. In humans, noradrenaline (norepinephrine) also lengthens action potential duration and causes further QT prolongation. Finally, both hypoglycaemia and the catecholamine response acutely lower serum K^+, which leads to QT prolongation and Ca^{2+} loading. Thus, hypoglycaemia and the subsequent catecholamine surge provoke multiple, interactive, synergistic responses that are known to be proarrhythmic when associated with medications and other electrolyte abnormalities. Patients with diabetes and pre-existing cardiac disease may therefore have increased risk of ventricular tachycardia and fibrillation during hypoglycaemic episodes.

Keywords ACCORD study · Ca^{2+} overload · Catecholamine necrosis · Dead in bed syndrome · Hypoglycaemia · Hypokalaemia · Proarrhythmia · QT prolongation · Review · Sudden death

Abbreviations

ACCORD	Action to Control Cardiovascular Risk in Diabetes
QTc	QT interval corrected for heart rate

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Introduction

With the advent of very aggressive lowering of HbA_{1c} values, patients with diabetes are at increased risk of hypoglycaemic episodes [1–3]. Several recent papers suggest that hypoglycaemia is associated with increased mortality rates [3–8], particularly in patients with pre-existent cardiac disease or acute myocardial infarction [3–5]. The Action to Control Cardiovascular Risk in Diabetes (ACCORD) Study [3] found excess mortality rates in diabetic patients under tight glycaemic control who had either multiple risk factors or known coronary artery disease, when compared with conventional glucose control.

Since over one third of excess deaths were attributed to unexpected cardiac death, i.e. possible sudden death, the ACCORD study is the first large controlled clinical trial to raise the possibility that ventricular tachycardia and fibrillation are promoted by hypoglycaemia.

These findings fit with prior studies. The modern recognition that malignant arrhythmias might be a consequence of hypoglycaemia started in Europe after the introduction of human insulin in the 1980s. Disturbing reports of deaths at night in young patients with type 1 diabetes led to the term 'dead in bed syndrome' [9–13]. Since many autopsies showed no pathological findings, several investigators speculated that hypoglycaemia increases the risk of sudden cardiac death. Pioneering clinical research by S. R. Heller and colleagues [14–21], and by others [22, 23] showed that hypoglycaemia and the associated catecholamine surge increase the QT interval, an electrocardiographic change strongly associated with sudden death in other contexts, particularly with medications.

Cellular research on ventricular myocardium in the 1980s also showed that diabetes itself increases the risk of electrical instability. Action potential prolongation, the substrate for QT prolongation on the electrocardiogram, was first reported by Fein et al. in ventricular papillary muscles from rats with streptozotocin-induced diabetes [24]. The effect is dramatically increased by the addition of hypertension [25]. Shortly thereafter, I and other members of the same research group showed that papillary muscles from this animal model of type 1 diabetes have a greater propensity than normal to develop delayed afterdepolarisations, a form of cellular electrophysiological instability associated with Ca^{2+} overload, ventricular tachycardia and sudden death [26].

Since then, many papers have been published on the cellular electrophysiological properties of ventricular muscle in animal models of cardiovascular disease and diabetes, as well as on hypoglycaemia itself. These studies show that the effect of acute hypoglycaemia, particularly in the setting of diabetes and pre-existent heart disease, is indistinguishable at a cellular level from that of medications known to be associated with arrhythmias and sudden death. Hypoglycaemia can therefore be considered a proarrhythmic event. The purpose of this paper is to review cellular and clinical research supporting the hypothesis that hypoglycaemia increases the risk of ventricular arrhythmias and sudden death.

The two proarrhythmic mechanisms and their relevance to hypoglycaemia

Proarrhythmic responses are not random. Almost all proarrhythmic medications cause one or both of the following: (1) longer action potential duration; and (2) higher myoplasmic Ca^{2+} concentration. Both of these changes convert normally quiescent cells into spontaneously active cells that have abnormal pacemaker activity; both changes are also likely to occur during hypoglycaemia.

When action potentials become too long, ventricular cells fail to repolarise and may subsequently generate recurrent spontaneous action potentials from depolarised takeoff potentials via reactivation of Ca^{2+} channels, a process called early afterdepolarisation (Fig. 1) If such non-driven action potentials propagate to normal myocardium, they cause ventricular tachycardia. Since repolarisation of ventricular action potentials causes T waves on the ECG, longer action potentials cause QT interval prolongation, which is recognised as a marker of the propensity to develop early afterdepolarisations and ventricular tachycardia, as described in a review by D. M. Roden [27].

One major way in which action potentials can be prolonged is by blocking repolarising K^+ channels that are activated during the start of the action potential; the two most important K^+ channels are I_{Kr} and I_{Ks}. Genetic mutations in the proteins involved cause congenital QT prolongation, which has a high rate of sudden death. Furthermore, given that many types of medications, including tricyclic antidepressants, antibiotics and other non-cardiac drugs, cause blockade of repolarising K^+ channels, occurrence of QT prolongation and sudden death [27] suggest that this is a fundamental pathway for electrical instability.

A second type of proarrhythmic oscillatory activity is associated with Ca^{2+} overload [28–31]. Increased intracellular Ca^{2+} concentration in myocardial muscle leads to the development of spontaneous intracellular Ca^{2+} cycling between the sarcoplasm and the myoplasm, which depolarises the membrane potential by generating electrogenic currents carried primarily by Na–Ca exchange molecules [31]. If strong enough, the oscillations, called delayed afterdepolarisations, can generate non-driven, pacemaker action potentials that can propagate as ventricular tachycardia (Fig. 1). Originally described with digitalis glycosides [28–30], delayed afterdepolarisations have been seen in multiple settings including diabetes itself [26] and beta adrenergic stimulation [32–35]. A large body of evidence links the proarrhythmic effect of inotropic agents, including catecholamines [36], to the development of Ca^{2+} overload, delayed afterdepolarisations and both ventricular tachycardia and fibrillation [37, 38].

Two important facts are crucial to an understanding of the close relationship between the basic pathophysiological processes described above and hypoglycaemia.

First, action potential prolongation and Ca^{2+} overload are final common pathways for electrical instability of ventricular muscle, the effect of which is not confined
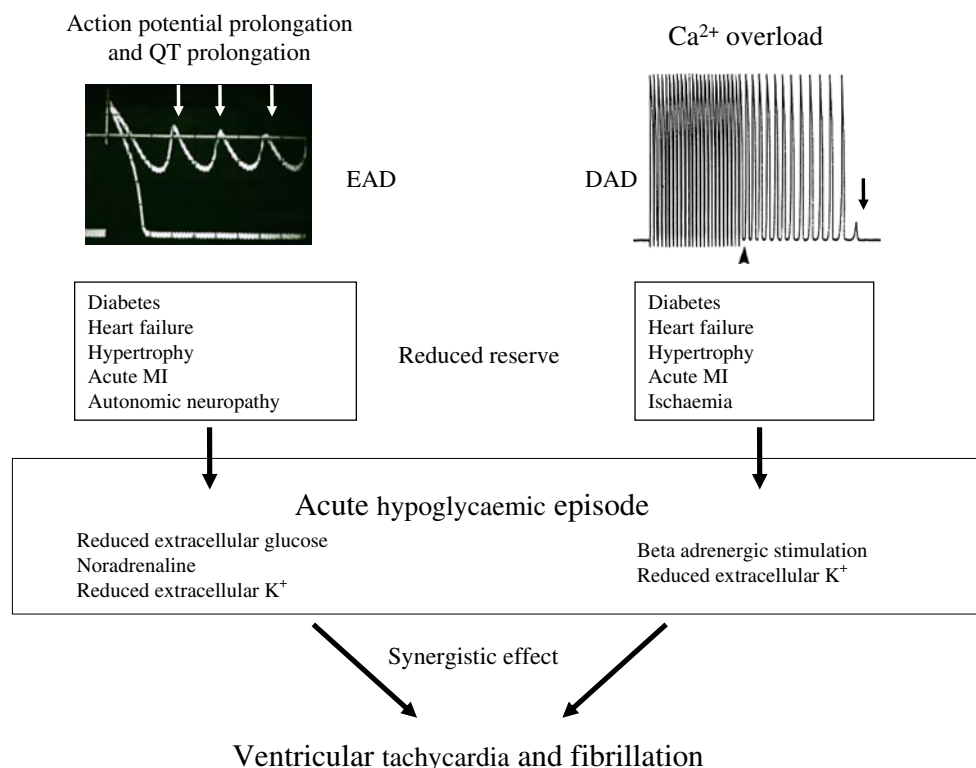
Fig. 1 Proposed mechanism of proarrhythmic events in patients with cardiovascular disease, diabetes and hypoglycaemia. The two main mechanisms for proarrhythmia involve longer action potentials, which cause QT prolongation on the ECG and lead to proarrhythmic early afterdepolarisations (EAD, arrows) and Ca^{2+} overload, which causes increased contractility and leads to proarrhythmic non-driven action potentials following rapid pacing stimulations (arrowhead) triggered by delayed afterdepolarisations (DAD, arrow). Diabetes itself increases action potential duration and the propensity to develop Ca^{2+} overload. Other conditions common to patients with cardiovascular disease do the same (small boxes). These reduce reserve for the additional proarrhythmic effects of hypoglycaemia. Acute lowering of extracellular glucose causes additional action potential prolongation, increasing the risk of early afterdepolarisations. The catecholamine surge in response to low glucose leads to longer action potentials in humans and increases the risk of developing Ca^{2+} overload. Acute reduction in extracellular K^+ seen during hypoglycaemic episodes also leads to action potential prolongation and Ca^{2+} overload. Both pathways interact synergistically to increase the risk of ventricular arrhythmias and sudden death. For details, see text. MI, myocardial infarction. Figure adapted from Nordin [41] with permission from the American Physiological Society and from Nordin and Aronson [99] with permission from Springer Science and Business Media

specifically to medications. With regard to action potential prolongation, perhaps the clearest example of this phenomenon is the fact that highly reproducible, completely reversible early afterdepolarisations can be generated simply by injecting tiny amounts of depolarising current, which do not affect any channel proteins directly, but merely delay repolarisation [39–41]. Blockade of repolarising K^+ channels is an even more specific final common pathway for electrical instability in genetic mutations and with multiple medications and other interventions [27]. Ca^{2+} overload is also a final common pathway for electrical instability. Thus delayed afterdepolarisations can be amplified simply by injecting cyclic AMP into ventricular myocytes [32]. These and other studies confirm that action potential prolongation and Ca^{2+} overload cause electrical instability due to abnormal interactions that are built into the biophysical properties of the channels themselves [40, 41]. Thus, almost any intervention that leads to action potential

prolongation or increases intracellular Ca^{2+} will be proarrhythmic.

> Action potential prolongation (which causes QT prolongation on the ECG) and Ca^{2+}overload are proarrhythmic, regardless of the cause

Second, multiple interventions that cause action potential prolongation or Ca^{2+} overload act synergistically to increase the risk of afterdepolarisations, ventricular tachycardia and sudden death. With regard to action potential prolongation, Roden has named this phenomenon 'reduced repolarisation reserve' [42]. Furthermore, Ca^{2+} overload and action potential prolongation can interact synergistically to magnify the risk of electrical instability. One highly relevant example is reduced extracellular K^+, which causes Ca^{2+} loading and longer action potentials. In this setting,

Ca^{2+} oscillations coordinate with and amplify the magnitude of early afterdepolarisations, making them more likely to propagate as ventricular tachycardia [39].

Evidence that hypoglycaemia is a proarrhythmic event in patients with diabetes and cardiovascular disease

The above concepts directly apply to hypoglycaemia in patients with diabetes and pre-existent cardiovascular disease. The evidence is summarised in Fig. 1 and the following sections.

Diabetes induces a proarrhythmic state associated with QT prolongation and increased risk of Ca^{2+} overload Diabetes was an independent risk factor for sudden death in several epidemiological studies [43–45]. In one large study [44], diabetes increased the risk of sudden death by an odds ratio of 3.8 in patients with prior history of coronary artery disease. Diabetes also adds to the risk of sudden death in patients with hypertrophy or diastolic dysfunction [46, 47], and is associated with ventricular fibrillation independently of coronary artery disease or heart failure status [48].

Diabetes causes QT prolongation [49–51]. The change in QT interval corresponds to the fact that, at a cellular level, diabetes lengthens action potentials [24, 52] and reduces repolarising of K^+ currents [52] in a way similar to proarrhythmic medications. QT prolongation predicts mortality in type 1 [53] and type 2 [54–58] diabetes. In the case of type 1 diabetes, QT prolongation conferred an odds ratio for death of 24.6 (95% CI 6.52–92.85) [53].

> Diabetes itself induces changes in action potential duration and Ca^{2+} handling that are proarrhythmic

Diabetic muscle is also more susceptible than normal to arrhythmias from Ca^{2+} overload. Exposing muscle from rats [26] or guinea-pigs [59] with streptozotocin-induced diabetes to high Ca^{2+} solutions with ouabain leads to a greater incidence of delayed afterdepolarisations than in control. This susceptibility may be related to changes in gene expression caused by hyperglycaemia. Diabetes depresses Na-K ATPase activity [60], and this digoxin-like effect reduces the ability of diabetic muscle to control intracellular $[Na^+]$ and therefore intracellular $[Ca^{2+}]$.

Many cardiovascular diseases are also associated with QT prolongation and Ca^{2+} overload, and therefore increase risk of proarrhythmic effects during hypoglycaemia In addition to the effect of diabetes itself, action potential prolongation and QT prolongation occur in a variety of other cardiac conditions commonly seen in patients with diabetes. Hypertrophy [61, 62], myocardial infarction [63, 64] and congestive heart failure [65, 66], all of which are known to increase the risk of sudden death, are also known to cause action potential and QT prolongation. Each is associated with reduction of repolarising K^+ channels [65–67]. These processes reduce repolarisation reserve in patients with cardiovascular disease and at risk of hypoglycaemia. Moreover, patients with congestive heart failure frequently have increased levels of catecholamines [68] and may be on inotropic agents, both of which cause Ca^{2+} overload and increase the risk of sudden death.

Hypoglycaemia causes QT prolongation by a cellular mechanism identical to that of proarrhythmic drugs In addition to the studies of Heller and colleagues [14–21], at least five other groups have confirmed that hypoglycaemia itself is associated with lengthening of the QT interval. [22, 23, 69–71]. Zhang et al [72] showed that hypoglycaemia inhibits current through the human ether-a-go-go related gene channel, which generates I_{Kr}, one of the main repolarising K^+ channels in human myocytes. Interestingly, the same team also showed that hyperglycaemia impairs current flow through the same channels, but by a different mechanism. These experiments directly link hypoglycaemia to the mechanism of drug-induced proarrhythmia [27]. Hypoglycaemia, moreover, has been repeatedly associated with a reduction in the serum K^+ concentration. Hypokalaemia lengthens the QT interval [73, 74] and is also associated with an increase in rates of sudden death [75].

> Hypoglyacemia causes action potential prolongation through a mechanism identical to many proarrhythmic medications

The catecholamine surge following hypoglycaemic episodes is also proarrhythmic During hypoglycaemia, the adrenal medulla secretes noradrenaline and adrenaline, and the sympathetic nervous system increases alpha and beta stimulation [76, 77]. Increased catecholamine activity, both endogenous and through medications, has long been recognised to increase cardiac death [36, 78–80]. Catecholamines cause early and delayed afterdepolarisations in myocytes from guinea pigs and dogs [33, 34]. Exposure of ventricular myoctes isolated from human end-stage failing hearts to noradrenaline also causes delayed afterdepolarisations [37], longer action potentials [81] and early afterdepolarisations [81]. Corresponding to these basic experiments, catecholamines cause longer QT intervals in humans [19, 82]. Furthermore, adrenaline infusion lowers serum K^+ [17]. The effect of adrenaline on QT interval

corrected for heart rate (QTc) is reduced by holding serum K^+ constant, but remains highly significant [17]. Thus, the catecholamine surge in hypoglycaemia is likely to be highly arrhythmogenic.

> The catecholamine surge and fall in serum K^+ associated with hypoglycaemia cause additional QT prolongation and Ca^{2+} overload

Clinical evidence that hypoglycaemia increases the risk of sudden death

No definitive clinical study has yet proved that hypoglycaemia increases the risk of arrhythmias. However, there is strong and increasing circumstantial evidence from several sources that hypoglycaemia increases the risk of cardiovascular sudden death.

First, case reports and small case series have shown that the incidence of sudden death during sleep in patients with type 1 diabetes is three to four times that of the non-diabetic population [15]. Second, several recent large studies have shown a close association between hypoglycaemia and death [6–8]. The NICE-SUGAR Study [6] demonstrated that tight control of glucose (target range 4.5–6.1 mmol/l) for patients in intensive care units led to a significantly higher death rate than in patients with more conventional control. The incidence of hypoglycaemia in the tight control group was over ten times higher than in the control group (6.8% vs 0.5%). Furthermore, death from cardiovascular causes was statistically higher in the tight control group. Two other studies have directly linked episodes of hypoglycaemia with increased risk of death in hospitalised patients with diabetes [7] and in outpatients [8]. Both studies showed that the risk of death was directly related to the severity of hypoglycaemia, suggesting a causal relationship. In addition, risk of death is increased within 24 h of a hypoglycaemic event [8], suggesting an acute event such as an arrhythmia as the cause.

A third set of studies has shown a striking risk of low serum glucose on admission to hospital affecting 30 day outcome in patients admitted for ST elevation myocardial infarction [4, 5]. In one study [4], the overall death rate was 4.6% in patients with admission glucose <4.5 mmol/l compared with 1.0% for patients with glucose between 4.5 and 7.0 mmol/l (Fig. 2). Even more striking was the rate of death in patients with glucose <4.5 mmol/l and a thrombolysis in myocardial infarction score of five or more (i.e. severe cardiac compromise), namely 22.6%. This was more than 11 times the death rate of patients with glucose values between 4.5 and 7.0 mm/l, and much higher than any other glucose level, including glucose >11 mmol/l. Low admission glucose increased mortality rates in patients with and without diabetes, suggesting the effect is unlikely to be related only to medications used to treat diabetes. These results were confirmed in a second study [5], which used a different database of patients with ST elevation myocardial infarctions. Neither study documented the mode of death. Thus there is no information to evaluate a direct relationship between hypoglycaemia on admission and sudden death. Nevertheless, other experimental evidence suggests that hypoglycaemia might exacerbate the already high probability of developing ventricular arrhythmias in a setting of reduced repolarisation reserve caused by myocardial infarction [63, 64].

> Low admission glucose is a powerful predictor of mortality in patients with ST elevation myocardial infarctions

The final source of data supporting the hypothesis that hypoglycaemia increases risk of sudden death is the
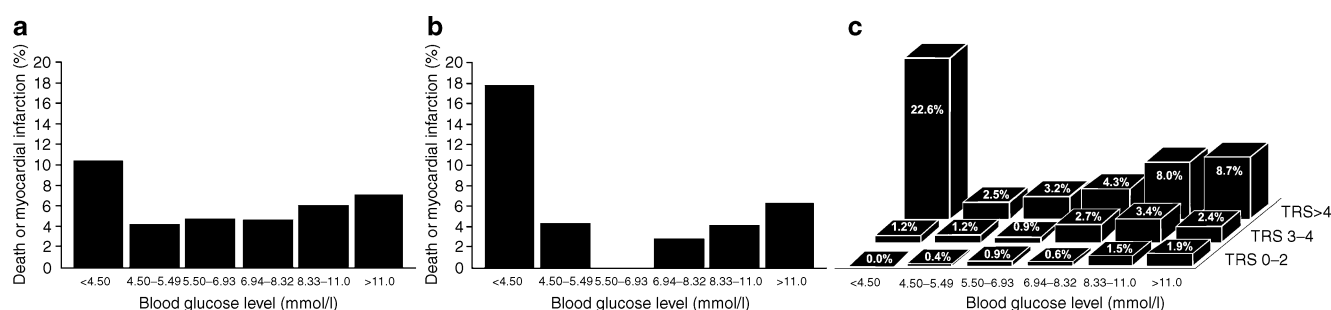

Fig. 2 Plots of death or recurrent myocardial infarction as a function of admission serum glucose value in (**a**) all patients and (**b**) diabetic patients in a study of 4,224 cases of acute ST elevation myocardial infarction [4]. In the total cohort (**a**), a U-shaped relationship can be seen, with a higher rate in patients with admission glucose <4.5 mmol/l than in those with higher values ($p<0.001$). **b** In patients with diabetes, the risk associated with low admission glucose was even more prominent ($p<0.001$). **c** Death at 30 days plotted as a function of initial glucose level and thromblysis in myocardial infarction risk score (TRS) on presentation. Higher TRS indicates more advanced cardiac disease and haemodynamic instability at the time of the myocardial infarction. The highest risk of death (22.6%) was in patients admitted with serum glucose <4.5 mmol/l and TRS >4. Figure modified from Pinto et al. [4] with permission from Elsevier

ACCORD study [3], which tested the hypothesis that cardiovascular complications of diabetes could be reduced by very aggressive lowering of HbA_{1c} levels. The study recruited over 10,000 patients, all of whom had either documentation of or multiple risk factors for coronary artery disease. The design included two groups: one that aimed to reduce HbA_{1c} values to less than 7%, and the other, a tight glycaemic control group, that aimed for a reduction to less than 6%. The ACCORD study was stopped early when a significant risk of increased death was found in the second group (tight control, with the goal of HbA_{1c} of 6%). The actual mean values of HbA_{1c} were 6.4% in the tight control group and 7.4% in the standard control group. The risk of death from cardiovascular causes was increased by 35% ($p=0.02$). The excess levels of cardiovascular deaths were spread through several categories, but 46% (19/41) were listed as unexpected cardiac deaths. No other associations in the study design (e.g. specific medications) were found to be significant. The incidence of hypoglycaemia requiring assistance was over three times higher in the tight control group. Despite the increase in hypoglycaemic episodes in the tight control group, preliminary non-prespecified exploratory analysis did not identify hypoglycaemia as the cause of increased death in the ACCORD study. However, the number of deaths was relatively small.

> 46% (19/41) of the excess cardiovascular deaths in the tight control group of ACCORD were classified as unexpected

Other recent studies have reinforced the findings of the ACCORD study. In a retrospective cohort study from the UK General Practice Research Database, Currie et al [83] showed that the adjusted hazard ratio for mortality in patients with type 2 diabetes was significantly higher in the lowest decile of HbA_{1c} (median 6.4%, 6.1–6.6) than in the decile with lowest hazard (median 7.5%, 7.5–7.6%) and higher than any other decile of HbA_{1c} below 10%. The cause of death was not determined in this study, but the authors speculated that hypoglycaemia was a likely cause. In the VADT study [84], another randomised study evaluating intensive vs conventional treatment for type 2 diabetes, subgroup analysis of the cause of death in patients in the intensive treatment arm demonstrated a strong trend towards increased rates of sudden death (1.2% vs 0.4%, $p=0.07$). In contrast, the ADVANCE study [85] did not show an increased risk of death with intensive treatment. However, the rate of hypoglycaemia was much lower than in ACCORD.

Are there possible antiarrhythmic effects of diabetes or hypoglycaemia that might ameliorate the proarrhythmic response?

From the perspective of cellular electrophysiology, the only way the multiple proarrhythmic effects of hypoglycaemia could be negated would be through equally powerful antiarrhythmic effects induced by the hypoglycaemic state.

The parasympathetic response induced by hypoglycaemia may be antiarrhythmic. Parasympathetic stimulation, by slowing heart rate, may reduce the amount of Ca^{2+} loading from the sympathetic surge of hypoglycaemia. Bradycardia has been recorded in patients during hypoglycaemic episodes [71], while studies in animal models show that direct stimulation of the vagus nerve [86] and exposure to choline [87] or pilocarpine [88] reduce ventricular arrhythmias during occlusion of the left anterior descending coronary artery. The effect may be due to a reduction in Ca^{2+} overload and delayed afterdepolarisations. However, slowing of the heart rate increases the risk of early afterdepolarisations and torsade de pointes in patients with QT prolongation [27]. Thus, the overall effect of parasympathetic stimulation is not clear.

A second possible condition that may reduce the proarrhythmic effect of hypoglycaemia is the blunting of autonomic responses seen in diabetic patients with autonomic neuropathy or following recurrent episodes of hypoglycaemia. Lee et al. [19] showed that QTc prolongation due to hypoglycaemia is reduced in patients with severe autonomic neuropathy and impaired baroreflex sensitivity, primarily due to reduced levels of adrenaline during hypoglycaemic episodes. The same basic response would apply to reduced sympathetic responses to recurrent episodes of hypoglycaemia [89, 90]. However, patients with diabetes and autonomic neuropathy have longer QT and QTc intervals than controls [57, 91], and autonomic neuropathy itself is associated with an increase in sudden cardiac death in diabetes [57]. Therefore, patients with diabetic autonomic neuropathy have less repolarisation reserve [42] and are likely to be more susceptible to other causes of QT prolongation, such as hypoglycaemia, even if the catecholamine response is blunted.

Summary and recommendations

Hypoglycaemia, particularly when seen in the setting of cardiac disease, creates multiple changes that are proarrhythmic. Diabetes [26, 49–51] and cardiovascular complications [61–68] increase the likelihood of pre-existent QT prolongation and Ca^{2+} overload, thus reducing reserve against further conditions that lead to each of these two. Hypoglycaemia [14–23] and the sympathetic response [19,

33, 34, 37, 82] create additional QT prolongation and Ca^{2+} overload. The two proarrhythmic pathways are known to interact in a synergistic way to increase the risk of arrhythmias [39, 42].

From a basic science perspective, the evidence that associates hypoglycaemia and the secondary catecholamine response with sudden death is very strong. Hypoglycaemia causes the specific changes in K^+ currents [72] and Ca^{2+} loading [26, 59] that have been repeatedly associated with the development of malignant ventricular arrhythmias and sudden death from medications [36, 78–80]. While parasympathetic activation and autonomic neuropathy may attenuate the proarrhythmic effect of hypoglycaemia by reducing the effect of the catecholamine surge [19, 86–88] both cause other changes that may themselves be proarrhythmic [27, 57, 71]. Recurrent episodes of hypoglycaemia also blunt the catecholamine response [89, 90], but multiple proarrhythmic changes are still induced by direct effects of hypoglycaemia.

No large epidemiological study has yet definitively confirmed or disproved the hypothesis that hypoglycaemia is a proarrhythmic event leading to an increase in malignant ventricular tachyarrhythmias and sudden death. However, studies have repeatedly suggested that hypoglycaemia is particularly dangerous for patients with pre-existent heart disease or other risks for sudden death [3–8], especially severe myocardial infarction [4].

Despite the association between hypoglycaemia and sudden death, there is no definitive evidence that ventricular tachycardia and fibrillation are more common in patients with hypoglycaemia. One recent study of 24 patients with type 1 diabetes [71] did show that ventricular ectopy developed during hypoglycaemic episodes, including one case of ventricular couplets in a patient whose QTc during the episode was 560 ms, considered to be dangerously long.

With regard to medications, the link between death and QT prolongation or Ca^{2+} overload has sometimes been delayed or revealed only in large epidemiological studies. This is particularly true in populations at risk of death from other causes. For example, the well recognised danger of torsade de pointes ventricular tachycardia in patients on methadone was overlooked for over 45 years because deaths were attributed to the known risk of respiratory depression and overdose [92]. In patients with cardiovascular disease, the risk of sudden death is high, and this is independent of glucose control. It is possible that the additional risk of death from hypoglycaemia has been similarly obscured. And since the effect of hypoglycaemia is evanescent, fatal arrhythmias may be even more difficult to prove than in the case of medications, where the risk is more constant.

Several papers now urge caution when lowering blood glucose in patients with known heart disease. These include recommendations made at the original press conference following the release of the ACCORD study data [93], as well as a recent position statement from the American Diabetes Association, in conjunction with the American College of Cardiology and the American Heart Association [94]. The position statement specifically recommends considering less stringent HbA_{1c} goals than 7% for patients with advanced macrovascular disease.

These recommendations, however, also emphasise that tight control of glucose is highly beneficial for patients with diabetes. Indeed, follow-up studies from long-term cohorts with type 1 [95] and type 2 [96] diabetes have demonstrated that early aggressive lowering of HbA_{1c} levels leads to a reduction of myocardial infarction and other measures of macrovascular disease 10 or more years later.

Taken together, the data suggest that it is appropriate to lower HbA_{1c} levels aggressively for patients with early diabetes and at low risk of myocardial infarction or coronary artery disease. For patients who already have structural heart disease, including hypertrophy, prior myocardial infarctions, autonomic neuropathy, systolic heart failure or QT prolongation, less tight control may be appropriate. The overall strategy should be to reach the lowest HbA_{1c} that can be achieved and maintained safely. Determining the precise values will require further research.

How can we test the hypothesis that hypoglycaemia increases the risk of sudden death? Evaluation of large databases was crucial for confirming the association between many medications and sudden death [97], as most recently shown for atypical antipsychotic medications, which cause QT prolongation [98]. Given the scope of the problem, this should be a high priority for clinical research in the future. Few questions are more important for the practice of medicine today.

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