Hypoglycemia and Cardiovascular Risks

BRIAN M. FRIER, MD
GUNTRAM SCHERNTHANER, MD
SIMON R. HELLER, MD

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 arterial system, 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 wall (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,
Effect of experimental hypoglycemia on QT interval

Figure 1—Typical QT measurement with a screen cursor placement from a subject during eu-glycemia (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, coagula-
bility, and viscosity. Increased plasma viscosity occurs during hypoglycemia be-
cause of an increase in erythrocyte concent-
tration, 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 in-
crease in C-reactive protein and the mobil-
ization and activation of neutrophils and 
platelet activation. These changes may 
promote intravascular coagulation and 
 thrombosis and encourage the develop-
ment of tissue ischemia, with the myocar-
dium being potentially vulnerable.

HYPOGLYCEMIA-INDUCED CV EVENTS—Anecdotal case reports have indicated a temporal relationship between severe hypoglycemia, acute vas-
cular events, and sudden death (3,7).
Case reports describe angina in associa-
tion with acute hypoglycemia and acute 
coronary syndromes with typical ECG 
and enzyme changes after severe hypogly-
cemia (3). When hypoglycemia was in-
duced in six subjects with type 2 
diabetes, five developed ischemic ECG 
changes, whereas a bradyarrhythmia re-
sulted in loss of consciousness in another 
patient (12). When continuous glucose 
measurements and Holter ECG monitoring 
were performed simultaneously in pa-
tients with type 2 diabetes and known 
 ischemic heart disease, 54 episodes of hy-
pglycemia (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 dem-
onstrating that a major cardiac event has 
been provoked by acute hypoglycemia in 
any individual diabetic patient, since si-
multaneous 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 in-
vestigation of a series of deaths of young 
adults with type 1 diabetes (14). The sur-
vey 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 au-
thors 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 syn-
drome” (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 un-
disturbed 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 pre-
cisely, in conjunction with hypoglycemic 
clamps to control the depth of hypo-
glycemia, 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, mea-
sured using ambulatory ECG monitor-
ing and simultaneous measurement of blood 
glucose (by either intermittent venous 
sampling or continuous glucose monitor-
ing) (22).

Activation of the sympathoadrenal 
system probably drives these changes. 
Epinephrine infusion increases QT inter-
vals (23), and β-blocking drugs attenuate 
QT lengthening during experimental hy-
poglycemia (24). However, hypoglyce-
mia induces a fall in serum potassium 
via sympathoadrenal activation and a di-
rect effect of insulin, and hypoglycemia 
per se may have an effect by directly in-
hbiting cardiac ion channels that are re-
sponsible for potassium efflux during 
cardiac repolarization (25).

RELEVANCE OF ABNORMAL CARDIAC REPOLARIZATION AND LENGTHENED QT INTERVAL TO CARDIAC ARRYTHMIAS—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.

**POSSIBLE 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, hypoglycemia 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 HbA1c 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 HbA1c (<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 HbA1c between 6 and 7%. By contrast, diabetic patients with higher HbA1c 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 HbA1c 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 HbA1c 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 HbA1c in both cohorts. The 10% of patients who had the lowest HbA1c values (<6.7%) had a higher mortality than all other deciles with higher HbA1c values, with the exception of the 10% with the highest HbA1c values (≥9.9%). The adjusted hazard ratios (HRS) for all-cause mortality by HbA1c deciles showed a U-shaped curve, irrespective of how or when HbA1c 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 HbA1c 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 Diabetics) (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 HbA1c levels <7%. Mean HbA1c 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).

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%; ADVANCE 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 HbA1c 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

### 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/m²)      | 32.2 ± 5.5 | 28.0 ± 5.0 | 31.3 ± 3.5 |
| Duration of diabetes (years) | 10 | 8 | 11.5 |
| CVD (%)          | 39%    | 32%     | 40%  |
| Primary CVD end point | ↓10% (P = 0.16) | ↑16% (P = 0.37) | ↓13% (P = 0.12) |
| Mortality (overall) | ↑22% (P = 0.04) | ↑17% (P = NS) | ↑6.5% (P = NS) |
| CV mortality (%) | ↑35% (P = 0.02) | ↓12% (P = NS) | ↑25% (P = NS) |

**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 HbA1c targets below 7.0 or 6.5%, but without reference to specific antidiabetes treatments, diabetes duration, age of the patients, or preexisting CV disease, since there may not have been a minimum HbA1c value, especially for patients with longstanding diabetes or who have established CVD (46). Accordingly, future diabetes guidelines will have to define a minimum HbA1c 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.

Acknowledgments—No potential conflicts of interest relevant to this article were reported.

References

1. Zammitt NN, Frier BM. Hypoglycemia in type 2 diabetes: pathophysiology, frequency, and effects of different treatment modalities. Diabetes Care 2005;28:2948–2961
2. UK Hypoglycaemia Study Group. Risk of hypoglycaemia in types 1 and 2 diabetes: effects of treatment modalities and their duration. Diabetologia 2007;50:1140–1147
3. Gravelling AJ, Frier BM. Does hyperglycaemia cause cardiovascular events? Br J Diabetes Vasc Dis 2010;10:5–13
4. Gerstein HC, Miller ME, Byington RP, et al. Effects of intensive glucose lowering in type 2 diabetes. N Engl J Med 2008; 358:2543–2559
5. Patel A, MacMahon S, Chalmers J, et al. Intensive blood glucose control and vascular outcomes in patients with type 2 diabetes. N Engl J Med 2008;358:2560–2572
6. Duckworth W, Abraira C, Moritz T, et al. Glucose control and vascular complications in veterans with type 2 diabetes. N Engl J Med 2009;360:129–139
7. Wright RJ, Frier BM. Vascular disease and diabetes: is hypoglycaemia an aggravating factor? Diabetes Metab Res Rev 2008;24:353–363
8. Sommerfeldt AJ, Wilkinson IB, Webb DJ, Frier BM. Vessel wall stiffness in type 1 diabetes and the central hemodynamic effects of acute hypoglycaemia. Am J Physiol Endocrinol Metab 2007;293:E1274–E1279
9. Judson WE, Hollander W. The effects of insulin-induced hypoglycemia in patients with angina pectoris: before and after intravenous hexamethonium. Am Heart J 1956;52:198–209
10. Robinson RT, Harris ND, Ireland RH, Lee S, Newman C, Heller SR. Mechanisms of abnormal cardiac repolarisation during insulin-induced hypoglycaemia. Diabetes 2003;52:1469–1474
11. Korvicko ML, Karakas M, Salmelä PI, et al. Effects of controlled hypoglycaemia on cardiac repolarisation in patients with type 1 diabetes. Diabetologia 2008;51:426–435
12. Lindstrom T, Jorfeldt L, Tegler L, Arnqvist HJ. Hypoglycaemia and cardiac arrhythmias in patients with type 2 diabetes mellitus. Diabet Med 1992;9:536–541
13. Desouza C, Salazar H, Cheong B, Murgo J, Fonseca V. Association of hypoglycaemia and cardiac ischemia: a study based on continuous monitoring. Diabetes Care 2003;26:1485–1489
14. Tattersall RB, Gill GV. Unexplained deaths of type 1 diabetic patients. Diabet Med 1991;8:49–58
15. Campbell IW. Dead in bed syndrome: a new manifestation of nocturnal hypoglycaemia? Diabet Med 1991;8:3–4
16. Sartor G, Dahlquist G. Short-term mortality in childhood onset insulin-dependent diabetes mellitus: a high frequency of unexpected deaths in bed. Diabet Med 1995;12:607–611
17. Dahlquist G, Källén B. Mortality in childhood-onset type 1 diabetes: a population-based study. Diabetes Care 2005;28:2384–2387
18. Skriviharoug T, Bangstad HJ, Stene LC, Sandvik L, Hånsen KF, Joner G. Long-term mortality in a nationwide cohort of childhood-onset type 1 diabetic patients in Norway. Diabetologia 2006;49:298–305
19. Tu E, Twigg SM, Duflo J, Semsarian C. Causes of death in young Australians with type 1 diabetes: a review of coronal postmortem examinations. Med J Aust 2008; 188:699–702
20. Marques JLB, George E, Peacey SR, et al. Altered ventricular repolarization during hypoglycaemia in patients with diabetes. Diabet Med 1997;14:648–654
21. Landstedt-Hallin L, Englund A, Adamson U, Lins PE. Increased QT dispersion during hypoglycaemia in patients with type 2 diabetes mellitus. J Intern Med 1999;246:299–307
22. Robinson RT, Harris ND, Ireland RH, Macdonald IA, Heller SR. Changes in cardiac repolarization during clinical episodes of nocturnal hypoglycaemia in adults with type 1 diabetes. Diabetesologia 2004;47:312–315
23. Lee S, Harris ND, Robinson RT, Yeoh L, Macdonald IA, Heller SR. Effects of adrenaline and potassium on QTc interval and QT dispersion in man. Eur J Clin Invest 2003;33:93–98
24. Lee SP, Harris ND, Robinson RT, et al. Effect of atenolol on QTc interval lengthening during hypoglycaemia in type 1 diabetes. Diabetesologia 2005;48:1269–1272
25. Zhang Y, Han H, Wang J, Wang H, Yang B, Wang Z. Impairment of human ether-a-go-go-related gene (HERG) K+ channel function by hypoglycaemia and hyperglycaemia: similar phenotypes but different mechanisms. J Biol Chem 2003;278:10417–10426
26. Curran ME, Splawski I, Timothy KW, Vincent GM, Green ED, Keating MT. A molecular basis for cardiac arrhythmia: HERG mutations cause long QT syndrome. Cell 1995;80:795–803
27. Goni JM, Kadrofske MM, Schnatz S, Bastyr EJ 3rd, Vinik AI. Corrected Q-T interval prolongation as diagnostic tool for assessment of cardiac autonomic neuropathy in diabetes mellitus. Diabetes Care 1990;13:68–71
28. Adler GK, Bonyhay I, Failing H, Waring E, Dotson S, Freeman R. Antecedent hypoglycaemia impairs autonomic cardiovascular function: implications for rigorous glycemic control. Diabetes 2009;58:360–366
29. Lee SP, Yeoh L, Harris ND, et al. Influence of autonomic neuropathy on QTc interval lengthening during hypoglycaemia in type 1 diabetes. Diabetes 2004;53:1535–1542
30. Svensson AM, McGuire DK, Abrahamsson P, Dellborg M. Association between hyperand hypoglycaemia and 2 year all-cause mortality risk in diabetic patients with acute coronary events. Eur Heart J 2005;26:1255–1261
31. Kosiborod M, Inzucchi SE, Krumholz HM, et al. Glucometrics in patients hospitalized with acute myocardial infarction: defining the optimal outcomes-based measure of risk. Circulation 2008;117:1018–1027
32. Pinto DS, Kirtane AJ, Pride YB, et al. Association of blood glucose with angiographic and clinical outcomes among patients with ST-segment elevation myocardial infarction (from the CLARITY-TIMI-28 study). Am J Cardiol 2008;101:303–307
33. Ishihara M, Kojima S, Sakamoto T, et al. Comparison of blood glucose values on admission for acute myocardial infarction in patients with versus without diabetes mellitus. Am J Cardiol 2009;104:769–774
34. Kosiborod M, Inzucchi SE, Goyal A, et al. Relationship between spontaneous and iatrogenic hypoglycaemia and mortality in patients hospitalized with acute myocardial infarction. JAMA 2009;301:1556–1564
35. Finfer S, Chittock DR, Su SY, et al. Intensive versus conventional glucose control in critically ill patients. N Engl J Med 2009;360:1283–1297
36. Wiener RS, Wiener DC, Larson RJ. Benefits and risks of tight glucose control in critically ill adults: a meta-analysis. JAMA 2008;300:933–944
37. Griesdale DEG, de Souza RJ, van Dam RM, et al. Intensive insulin therapy and mortality among critically ill patients: a meta-analysis including NICE-SUGAR study data. CMAJ 2009;180:821–827
38. Ebara N, Morimoto T, Furukawa Y, et al. Effect of baseline glycemic level on long-term cardiovascular outcomes after coronary revascularization therapy in patients with type 2 diabetes mellitus treated with hypoglycemic agents. Am J Cardiol 2010;105:960–966
39. Currie CJ, Peters JR, Tynan A, et al. Survival as a function of HbA1c in people with type 2 diabetes: a retrospective cohort study. Lancet 2010;375:481–489
40. Schernthaner G. Diabetes and cardiovascular disease: is intensive glucose control beneficial or deadly? Lessons from ACCORD, ADVANCE, VADT, UKPDS, PROactive, and NICE-SUGAR. Wien Med Wochenschr 2010;160:8–19
41. Miller ME, Bonds DE, Gerstein HC, et al. The effects of baseline characteristics, glycaemia treatment approach, and glycated haemoglobin concentration on the risk of severe hypoglycaemia: post hoc epidemiological analysis of the ACCORD study. BMJ 2010;340:b5444
42. Bonds DE, Miller ME, Bergenstal RM, et al. The association between symptomatic, severe hypoglycaemia and mortality in type 2 diabetes: retrospective epidemiological analysis of the ACCORD study. BMJ 2010;340:b4909
43. Riddle MC, Ambrosius WT, Brillon DJ, et al. Epidemiologic relationships between A1C and all-cause mortality during a median 3.4-year follow-up of glycemic treatment in the ACCORD trial. Diabetes Care 2010;33:983–990
44. Pop-Busui R, Evans GW, Gerstein HC, et al. Effects of cardiac autonomic dysfunction on mortality risk in the Action to Control Cardiovascular Risk in Diabetes (ACCORD) trial. Diabetes Care 2010;33:1578–1584
45. Zoungas S, Patel A, Chalmers J, et al. Severe hypoglycaemia and risks of vascular events and death. N Engl J Med 2010;363:1410–1418
46. Schernthaner G, Barnett AH, Betteridge DJ, et al. Is the ADA/EASD algorithm for the management of type 2 diabetes (January 2009) based on evidence or opinion? A critical analysis. Diabetologica 2010;53:1258–1269
47. Turnbull FM, Abraira C, Anderson RJ, et al. Diabetic control and macrovascular outcomes in type 2 diabetes. Diabetes Care 2009;32:2288–2298