**Hypoglycaemia and cardiovascular disease in diabetes:  Epidemiology, pathogenesis and management**

**The International Hypoglycaemia Study Group**

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*Abstract (150 words)*

Hypoglycaemia has long been recognised as a dangerous side effect of treatment of diabetes with insulin or insulin secretagogues, its potential to disrupt cerebral function having major effects on peoples’ lives. Recent studies have suggested that hypoglycaemia is associated with an increased risk of cardiovascular events and mortality.

Different mechanisms by which hypoglycaemia might provoke cardiovascular events have been identified in experimental studies. Clinical studies have described cardiac arrhythmias induced by hypoglycaemia, with one report describing sudden death during a severe episode.

Emerging evidence indicates the association is likely to be multi-factorial. It is probably in part due to confounding, with hypoglycaemia occurring more frequently in those with co-morbidities who are also those more likely to die. However, individuals with either type 1 or type 2 diabetes also appear at risk of hypoglycaemia-induced cardiovascular effects. This should be recognised by clinicians when agreeing glycaemic goals with patients and choosing appropriate glucose lowering therapy.

*Introduction*

Hypoglycaemia is associated with a number of negative life consequences ranging from disruption of daily activities to psychosocial problems for patients and family members. Beyond this, the possibility that hypoglycaemia might directly increase mortality has been recognised since the discovery of insulin. Fatal brain injury from profound neuroglycopenia is relatively rare but following the premature termination of the ACCORD trial because of increased mortality in those treated intensively1, there has been major interest in the association between fatal cardiovascular events and hypoglycaemia. The increased mortality observed in ACCORD provoked considerable controversy as to its underlying cause. Some believe that the cardiovascular consequences of hypoglycaemia may explain why intensive glycaemic control has generally failed to lower the risk of cardiovascular events. Others remain sceptical, believing that the association can be explained by confounding, with hypoglycaemic episodes identifying vulnerable individuals with co-morbidities that render them prone to adverse outcomes and who therefore are more likely to have experienced hypoglycaemia during treatment. This review explores the epidemiology, identifies potential mechanisms, explains the competing hypotheses, considers what additional research is required and suggests how the issue may be approached clinically.

*Search strategy and selection criteria*

References for this review were identified through searches of PubMed for articles published from January, 1971, to August 2018, by use of the terms “hypoglycaemia”, “fear of hypoglycaemia”, “pregnancy”, “cardiovascular mortality”, “cardiovascular disease”, “low glucose”, “myocardial infarction”, “stroke”, “insulin treatment”, and “intensive insulin therapy” in combination with the term “diabetes”. Relevant articles were identified through searches in the authors’ personal files, in Google Scholar, and Springer Online Archives Collection. Articles resulting from these searches and relevant references cited in those articles were reviewed. Articles published in English alone were included.

*Mortality and cardiovascular disease*

That hypoglycaemia could be fatal was recognised soon after the discovery of insulin during animal experiments and its early clinical use soon led to reports of deaths in individuals with diabetes.2 A relatively early epidemiological study reported hypoglycaemia as causing 4% of deaths3 of all people with diabetes under the age of 50. This may have underestimated the number of deaths from hypoglycaemia since this report also included deaths from myocardial infarction and other causes that may have resulted from hypoglycaemia induced cardiac arrhythmias. More recent studies have recorded a higher prevalence of deaths directly due to hypoglycaemia with more than 8% reported in people with type 1 diabetes under 56 years of age in a Norwegian study.4 While this may reflect greater precision in identifying the cause of death, an alternative explanation is that it represents an increased frequency of hypoglycaemia and associated mortality.

*Epidemiology*

The publication in 1998 of the UKPDS, a randomised controlled trial confirming that intensive glycaemic control could reduce microvascular disease in newly diagnosed type 2 diabetes also resulted in an observational analysis suggesting that such an approach had the potential to prevent macrovascular events.5 Indeed, extended follow-up for the 10 years following the end of the trial, showed significant reductions in rates of myocardial infarction and cardiovascular mortality. Three randomised clinical trials subsequently tested the hypothesis, comparing the effect of more versus less intensive glycaemic control among individuals with established type 2 diabetes at increased cardiovascular risk, but all three failed to demonstrate significant reductions in cardiovascular events or mortality.1,6,7 In fact, mortality in one of these trials, ACCORD, actually increased.1 While there are other potential causes of increased mortality such as weight gain, use of certain medications or even chance alone, it is noteworthy that compared to the ADVANCE trial,7 which showed no increase in mortality, the frequency of severe hypoglycaemia in ACCORD was 4 to 5 times higher. The VADT, which was conducted over the same period was underpowered to measure the impact on mortality.6 All three studies however demonstrated a significant association between severe hypoglycaemia and mortality, and in VADT and ADVANCE, severe hypoglycaemia predicted mortality, not at the time of the episode of hypoglycaemia but downstream of the event; in ADVANCE this occurred over 11 months later on average. The difference in diabetes duration between these later studies and UKPDS may be relevant to their different outcomes.

What remains uncertain is to what extent the association in these later trials is causal or due to confounding. It has been argued that confounding may explain the association between hypoglycaemia and mortality, i.e., that comorbidities (such as renal or liver disease, malignancy, weight loss or cognitive impairment) confer an increased risk of hypoglycaemia as well as of cardiovascular events and mortality. Zoungas et al attributed at least some of the association between mortality and severe hypoglycaemia observed in ADVANCE to confounding.8 (Figure 1) This was based on the increased hazard ratio of non-cardiovascular events in those experiencing severe hypoglycaemia compared to those without; it was reasoned that events associated with respiratory or gastrointestinal diseases were most unlikely to have been caused by hypoglycaemia.

These concerns have resulted in additional cohort studies (both clinical trial and epidemiological) in individuals with diabetes (see Table 1). Collectively, these studies have included tens of thousands of patients with types 1 or 2 diabetes from different regions of the world and health care settings. They have demonstrated an approximately 1.5 to 6-fold increased risk of cardiovascular events and mortality among those who experienced hypoglycaemia compared to those who did not. This increased risk appears to be shared by people with type 1 and type 2 diabetes,9 although the magnitude of the risks varies with diabetes type, background cardiovascular risk, presence of comorbidities, severity of hypoglycaemia, temporality of hypoglycaemia to the event, length of follow up and level of adjustment for potential confounders. The association is not confined to hypoglycaemia induced by insulin, with a recent observational study reporting a similar association of hypoglycaemia induced by sulphonylureas.10 Additional post-hoc analyses in other cardiovascular outcomes trials have also raised the likely contribution of confounding as an explanation for the association.11,12

The observational nature of many of the analyses and inability to capture all hypoglycaemia episodes (particularly milder or asymptomatic episodes which might contribute to cardiovascular events) have made it difficult to confirm or refute causality, particularly in relation to cardiovascular events. Nevertheless, some studies report an association between cardiovascular events (particularly myocardial infarction) and hypoglycaemia13; the evidence appears less consistent regarding the association between hypoglycaemia and stroke.14 For this reason, much of the review concerns studies which report relationships between mortality and severe hypoglycaemia (defined in most studies as episodes which require the assistance of another person to recover). However, where reliable studies reporting cardiovascular events were available, these are included.

The debate may also be framed by asking whether hypoglycaemia should be considered a risk factor for CVD or merely a risk marker. Chronic hyperglycaemia leads to increased rates of cardiovascular disease and so is considered a risk factor. If hypoglycaemic episodes identify patients at greater risk of severe hypoglycaemia and mortality due to confounding, hypoglycaemia would be considered a risk marker. Alternatively, if hypoglycaemia, particularly repeated episodes and not necessarily severe, activate physiological responses which accelerate cardiovascular disease, hypoglycaemia could be a regarded as a risk factor.

A definitive trial to prove causality in which severe hypoglycaemia is deliberately induced in one arm and not the other and mortality compared in both is not clearly not possible for ethical and practical reasons. The conclusion that a causal association exists between hypoglycaemia and cardiovascular events is however, supported by two systematic reviews which used the statistical technique of bias analysis in meta-analyses of large numbers studied in observational studies.15,16 The authors concluded that comorbid severe illness alone could not explain these associations, since the prevalence of comorbidity would have had to be far higher than it was to explain the association. Furthermore, Yeh et al reported a dose response relationship (ie, severe hypoglycaemia showed a stronger association than less severe episodes).16 The authors also highlighted the many plausible pathophysiological mechanisms which might contribute to increased cardiovascular events. These are described below.

Additional recent evidence supports the hypothesis that hypoglycaemia may oppose the benefits of strict glycaemic control and that hypoglycaemia is indeed a risk factor for cardiovascular disease and mortality. The study used meta-regression analysis to compare the relationship between reduction of haemoglobin A1c (HbA1c) and the risk of major adverse cardiovascular events in trials of medication which did not increase hypoglycaemia.17 The authors showed that lowering HbA1c in these trials conferred a significant risk reduction for MACE while no such association was observed in trials involving traditional therapy (whose side-effects included hypoglycaemia).

*Hypoglycaemia and CVD in specific populations*

Elderly and those with comorbidities

Many clinical practice guidelines recommend avoidance of strict glycaemic control in elderly people with diabetes, and those with complex, intermediate or poor health including frailty, impaired cognitive function and end-stage chronic illness. Benefits of strict control in this population have not been demonstrated and potential harm is increased, largely related to hypoglycaemia. Despite this, recent studies demonstrate that overtreatment is common in these individuals, particularly with insulin or sulphonylureas.18 As expected, this increases the risk of hypoglycaemia associated with increasing age per se, a high burden of comorbidities, diminished cognitive ability and diminished renal function.19 Paradoxically, poorer glycaemic control is also associated with hypoglycaemia in this population.20 Observational studies have identified an association between hypoglycaemia and mortality in older people,21,22 but its association with cardiovascular disease has not been properly assessed and has to be extrapolated from studies of younger populations.

Pregnancy

The overall rate of acute myocardial infarction (AMI) is increased in pregnancy by 3 to 4-fold, particularly in women with pre-existing diabetes, and the risk of mortality is high in patients with diabetes and myocardial infarction.23 An interaction between hypoglycaemia and ischaemic heart disease during pregnancy has not been reported to our knowledge, but severe hypoglycaemia is very frequent in pregnant women with diabetes treated with insulin, particularly in the first trimester. In one study of 972 women with type 1 diabetes during pregnancy, two of four maternal deaths that occurred were attributed to the hypoglycaemia-induced ‘Dead in Bed syndrome’.24. This cannot be used as an argument against intensive glycaemic management around pregnancy, because of its very clear benefits, but does argue for greater attention to be paid to achieving normoglycaemia without excess hypoglycaemia.

Children and Adolescents

Data regarding the cardiovascular consequences of hypoglycaemia in children with diabetes are sparse. Although speculative, the most likely impact of hypoglycaemia on the cardiovascular system in this age group is sudden unexpected death in bed (“dead in bed syndrome”), which is discussed in detail below. Mortality data are limited to children on contemporary insulin therapy but mortality in childhood compared to the age matched background population is significantly higher.4,25,26 It is probable that under-reporting of diabetes-related death is less likely to occur in children because of the lower rates of comorbid disease. Most reports describe a 2 to 4-fold increase in standardised mortality; diabetic ketoacidosis is the most frequently described cause of death but hypoglycaemia and dead in bed syndrome also feature in most surveys. Death associated with hypoglycaemia in children may follow a seizure, or be the result of an accident or drowning, and may not invoke a cardiovascular cause.

Cardiovascular effects of hypoglycaemia (Figure 2)

There is accumulating evidence that hypoglycaemia can cause cardiac dysfunction and sudden death. This includes case reports of various cardiac arrhythmias induced by hypoglycaemia and studies reporting abnormal cardiac repolarisation, which are described in more detail below. Most of the clinical studies have been conducted in either non-diabetic subjects or individuals with type 1 diabetes. The relatively few studies involving patients with type 2 diabetes are highlighted.

Hypoglycaemia activates the sympatho-adrenal system causing profuse secretion of catecholamines that exert profound haemodynamic and haemorrheological effects. Sympathetic stimulation causes a rapid increase in heart rate, myocardial contractility and cardiac output, and central systolic pressure falls secondary to increased elasticity of large vessels.27,28 Plasma potassium rapidly declines,29 inducing electrophysiological and electrocardiographic changes, which may provoke abnormal cardiac conduction and repolarisation.30 In addition to this, acute changes occur in blood coagulability, cell adhesion, endothelial dysfunction and inflammatory markers in response to hypoglycaemia. These have the potential to compromise endothelial function, blood flow and tissue perfusion, risking intravascular coagulation and thrombosis.31

Antecedent hypoglycaemia blunts the autonomic responses to cardiac stress for several hours in non-diabetic individuals32 and this transient impairment of autonomic cardiac reflexes could influence cardiac vulnerability to a subsequent stress. The haemorrheological and inflammatory responses to hypoglycaemia persist for several days in patients with type 2 diabetes.33 Functional abnormalities that persist long after restoration of normoglycaemia could create an intravascular milieu that is conducive to a thrombotic event.34 Paradoxically, greater hypoglycaemia–associated cardiovascular mortality has been observed in patients on conventional therapy with poorer glycaemic control. It is unclear whether frequent exposure to hypoglycaemia increases the risk of a cardiovascular event, or whether it might even have a protective effect through a diminished sympatho-adrenal response due to repeated hypoglycaemia.

In people with type 2 diabetes, many of whom have premature cardiovascular disease, the transient haemodynamic changes associated with hypoglycaemia may provoke acute cardiovascular (CV) events such as myocardial ischaemia and infarction, cardiac failure, and cardiac arrhythmias. Anecdotal cases have been described of acute CV events being precipitated by hypoglycaemia, and ischaemic ECG changes have been observed, with and without the development of angina.35

*Potential Mechanisms*

The body responds to the systemic challenge of hypoglycaemia by initiating a counterregulatory defence response that involves multiple stress pathways as well as activation of the sympathetic nervous system. Insulin-induced hypoglycaemia is a profound systemic stress and this has marked haemodynamic, pro-inflammatory and pro-athero-thrombotic effects as well as increasing the potential for cardiac arrhythmias as described above.

Hypoglycaemia also stimulates an increase in plasma aldosterone via activation of the renin angiotensin system, which through activation of the mineralocorticoid receptor may exacerbate endothelial dysfunction.36 Increased cardiac workload during acute hypoglycaemia is accompanied by changes in vascular haemorrheology with increased platelet activation, diminished fibrinolytic balance and elevated haemostasis.37 However, recurrent hypoglycaemia leads to a marked suppression of the sympathoadrenal response to hypoglycaemia38 as well as reduced β-adrenergic sensitivity.39 Thus, the haemodynamic effects of hypoglycaemia may be paradoxically less profound in those individuals at greatest risk of severe hypoglycaemia.

Acute hypoglycaemia also evokes a pro-inflammatory response which may contribute to endothelial dysfunction and be pro-atherogenic. In individuals with and without diabetes, hypoglycaemia increased CD40 expression on monocytes and plasma sCD40L concentrations, as well as increases in ICAM, VCAM, E-Selectin, VGEF and the cytokines IL-6, IL-8 and TNF-alpha. This pro-inflammatory response may exacerbate the chronic inflammation and endothelial dysfunction that is common in diabetes. Certainly, endothelial dysfunction with impaired NO-mediated vasodilation is evident during hypoglycaemia and exacerbated after two episodes of hypoglycaemia.37 Repeated hypoglycaemia in type 1 diabetes is also associated with flow-mediated endothelial dysfunction and increased intima-media thickness.40 In non-diabetic rodents, the cytokine profile following 4-weeks of recurrent hypoglycaemia is very different and more anti-inflammatory in nature, reflecting a reduced sympatho-adrenal response to hypoglycaemia.41

Ratter et al have shown in non-diabetic individuals and those with type 1 diabetes, that hypoglycaemia promoted mobilisation of specific leukocyte subsets from the marginal pool and induced pro-inflammatory changes in immune cells with exaggerated cytokine responses to microbial stimulation.42 However, while hypoglycaemia can activate multiple pathways that potentially lead to endothelial dysfunction, a similar response to acute hypoglycaemia in terms of inflammatory cytokine and selectin release is seen with acute exercise in non-diabetic subjects with and without coronary artery disease and exercise is generally considered to be cardioprotective.

It is important to recognise that hypoglycaemia in both types 1 and 2 diabetes occurs on the background of chronic exposure to high glucose concentrations, and (over)treatment of hypoglycaemia often results in rebound hyperglycaemia. This increased glucose variability may induce an additional inflammatory stimulus. Rebound hyperglycaemia following hypoglycaemia has a greater effect in impairing endothelial function and activating thrombosis than hypoglycaemia alone.43 Pre-existing diabetes also worsens cardiac outcomes in a rodent model of exposure to very severe hypoglycaemia.44 These observations suggest that the ability of the host’s defences to cope with the stress of hypoglycaemia is impaired by pre-existing diabetes and that the inflammatory response to hypoglycaemia may be amplified by rebound hyperglycaemia on recovery.

Clinical episodes of hypoglycaemia have been reported to cause atrial fibrillation, multiple ventricular ectopics and ventricular tachycardia. A seminal paper by Gill and Tattersall in 1991 presented strong circumstantial evidence that hypoglycaemia was implicated in the sudden overnight death of young people with type 1 diabetes.45 This mode of death, described above as ‘the Dead in Bed syndrome’ has since been reported in a series of epidemiological studies with a recent paper calculating a tenfold increase in the rate of sudden death in young people with type 1 diabetes compared to the non-diabetic population46 and the circumstances of the death make an arrhythmia a likely agonal event.

An example of sudden death occurring during profound hypoglycaemia was captured in a case of a young man with type 1 diabetes, in which the continuous glucose monitoring trace demonstrated the low glucose at the time of death.(Figure 3) With no other cause found at autopsy in an apparently healthy individual, the likely cause of death would appear to have been a cardiac arrhythmia.47 Experimentally-induced hypoglycaemia in people with types 1 and type 2 diabetes48,49 show that hypoglycaemia results in pro-arrhythmogenic cardiac repolarisation with marked prolongation of the QT interval corrected for heart rate (Figure 4). It has been hypothesised that people with underlying polymorphisms of the ion channels, which contribute to the cardiac conduction system, may be particularly vulnerable.50 Other experimental and observational studies have demonstrated marked abnormalities of cardiac repolarisation along with profound bradycardia in some susceptible individuals with type 1 diabetes51 but what confers susceptibility or triggers the fatal event remains unknown.

Profound hypoglycaemia (glucose <1.0 mmol/L) in rodent models leads to QT prolongation, ventricular ectopy and high degree heart block dependent on duration and severity of hypoglycaemia.52 Interestingly, mortality in this rodent model of profound hypoglycaemia was exacerbated by diabetes but in the most part reversed by preceding exposure to recurrent hypoglycaemia and potassium replacement, while intra-cerebroventricular glucose infusion or beta-adrenergic blockade reduced severe hypoglycaemia-induced arrhythmias and overall mortality.44

Hypoglycaemia-induced arrhythmias are also a potential contributor to the increased cardiac mortality seen in the ACCORD trial.1 Studies in an ambulatory setting combining Holter monitoring and continuous interstitial glucose measurement have documented relative increases in the frequencies of bradycardia and atrial ectopic activity during hypoglycaemia.53 In a more detailed study of the arrhythmic effects of hypoglycaemia in type 2 diabetes performed using a hypoglycaemic clamp, Chow et al54 showed that an initial vagal withdrawal during hypoglycaemia resulted in an increase in heart rate, but with more prolonged hypoglycaemia, vagal reactivation then resulted in relative bradycardia, consistent with earlier observations.55 Non-diabetic subjects in contrast had a persistent increase in heart rate during hypoglycaemia in this study, implying continued vagal withdrawal. Chow et al also noted that people with type 2 diabetes had a higher heart rate and lower heart rate variability at baseline and had greater changes in the duration and heterogeneity of repolarisation abnormalities during hypoglycaemia. Why people with type 2 diabetes respond differently to hypoglycaemia in this context is not known, but hypoglycaemia has been shown to reduce baroreflex sensitivity, shift the blood pressure thresholds for baroreflex activation and reduce the range of R-R interval responses.56 Thus, pre-existing abnormalities in autonomic function may contribute to an increased propensity to cardiac arrhythmias.

**Clinical Approaches**

*Dealing with psychological issues*

Because of the negative consequences, ranging from unpleasant symptoms to potentially dangerous situations, patients and family members often develop fear of hypoglycaemia (FoH). Numerous studies have documented the detrimental impact of FoH on quality of life across different countries and cultures.57,58 Overall, high levels of FoH are most commonly associated with a history of episodes of severe hypoglycaemia, especially those episodes resulting in cognitive disorientation, social embarrassment, loss of consciousness, accidents and physical injury. People with impaired awareness of hypoglycaemia, who are at higher risk of severe hypoglycaemia, often have significant FoH, although about one third of them paradoxically have low scores.59 Parents of children with type 1 diabetes are particularly vulnerable to high levels of fear of hypoglycaemia, including anxiety related to nocturnal episodes of hypoglycaemia, which is a major source of emotional stress60,61.

FoH may also have significant implications for diabetes management and control. Some patients may cope with their fear and try to mitigate the threat of hypoglycaemia by maintaining their BG levels in a higher range, leading to more time spent in hyperglycaemia. Several studies have found that higher levels of FoH are associated with poorer metabolic control, including more frequent hyperglycaemic BG readings and higher HbA1c levels.62 Since patients may be reluctant to report episodes of severe hypoglycaemia to their health care practitioners, it is critical to assess these in clinical settings. In addition to assessing factors such as causes, frequency and severity, it is important to ask patients and family members about aspects of the episode likely to be associated with psychological impact. These include situational characteristics (e.g. in a public setting as opposed to occurring while alone), social implications (e.g. in front of friends or colleagues), and emotional consequences (level of fearfulness or perceived danger) of the episode. Changes that patients or relatives have made in diabetes management behaviours and routine in response to an episode of hypoglycaemia should also be carefully assessed.

The rare but well recognised “dead in bed syndrome” presents a special problem and an ethical dilemma for health care practitioners with regard to patient and family education about hypoglycaemia. To our knowledge no studies have specifically explored the potential or impact of mortality secondary to hypoglycaemia on the family of those affected. However many patients and their families are concerned that severe hypoglycaemia overnight might be fatal, particularly if they have witnessed a hypoglycaemic seizure.63 Although there has been no apparent research in this area, it would appear that most clinicians do not raise the issue of fatal cardiac arrhythmias caused by hypoglycaemia in discussions with patients and family members. While nocturnal hypoglycaemia is common, fatal episodes are extremely rare. Thus, presenting it as a possible outcome may produce unwarranted high levels of anxiety. More research is required to understand the risk factors and mechanisms associated with fatal nocturnal hypoglycaemia which would help guide the development of appropriate patient education and recommendations.

*Basic clinical approaches*

Clinicians prescribing insulin and sulphonylureas must prepare patients for hypoglycaemia that may occur when these medications are used. In a busy practice setting, such patients should be referred to diabetes education for comprehensive instruction on recognising, anticipating, and treating hypoglycaemia. Learning to identify people with impaired awareness of hypoglycaemia is an important clinical skill for all practitioners. They may consider utilising the questionnaires developed by the American Diabetes Association’s Hypoglycaemia Working Group64 to ensure a systematic assessment is done at each visit. Clinician and patient educational materials have also been developed by the International Hypoglycemia Study Group65 to enhance understanding of this complication of diabetes treatment.

Recent advances in diabetes care have provided new approaches that reduce the risk of hypoglycaemia in patients with diabetes.66 Insulin-requiring patients with both types of diabetes may find they have less hypoglycaemia if they use a long-acting basal insulin, such as insulin degludec which has been shown to reduce rates of severe hypoglycaemia in both type 1 and type 2 diabetes compared to insulin glargine U100.67–69 Individuals with type 1 diabetes at increased hypoglycaemic risk may benefit from an insulin pump70 and the addition of a real time continuous glucose monitor to an existing insulin regimen has also been shown to reduce hypoglycaemia.71 Use of a threshold suspend pump72 or a hybrid closed loop pump73 can lower rates of hypoglycaemia in patients with type 1 diabetes without jeopardising glycaemic control. Patients with impaired awareness of hypoglycaemia and repeated episodes of severe hypoglycaemia despite ongoing efforts to avoid it may be eligible for islet transplantation, when available.74

*Reducing hypoglycaemia in patients at high cardiovascular risk*

The American Diabetes Association Standards of Care recommends that glycaemic targets be changed in patients who have clinically significant hypoglycaemia or impaired awareness of hypoglycaemia.75 For those on insulin or sulphonylureas, there should be a stronger emphasis on cardiovascular co-morbidities, with glucose targets shifted upwards and A1c targets increased to 55 mmol/mol (7.5%) if necessary to help vulnerable patients avoid hypoglycaemia. In patients with type 2 diabetes, reduction in hypoglycaemia risk may be accomplished by switching to a regimen that does not include insulin or a sulphonylurea. This may also allow the benefits of a lower HbA1c to be achieved.

Although the use of new technologies including pumps, CGM and insulin analogues may reduce the incidence of hypoglycaemia, there is no evidence to date that this translates into lower cardiovascular disease risk or better survival in people with diabetes, perhaps due to the short duration of the trials and the low baseline CV risk of study participants. The study that has come closest to finding such an effect was the DEVOTE trial.69 Patients with type 2 diabetes at increased risk of cardiovascular disease experienced rates of severe hypoglycaemia which were 40 % lower together with a non-significant 9% lower incidence of cardiovascular events when treated with insulin degludec as compared to glargine U100.

*Future research*

While the acute and potential harmful responses to non-severe controlled hypoglycaemia described above have been studied in detail, knowledge of the effects of severe or long-lasting (e.g. nocturnal) hypoglycaemia is lacking. It is possible that the documented responses to non-severe hypoglycaemia may be exaggerated and some effects may only occur during severe hypoglycaemia. Furthermore, knowledge about the duration of potential adverse responses is absent. This is important as a very transient pro-coagulant inflammatory response is less likely to enhance the risk of cardiovascular morbidity than a more prolonged one. It is also unclear whether exposure to repeated moderate hypoglycaemia has a cumulative effect.

A better understanding of modulating factors is needed to explain the relation between hypoglycaemia and cardiovascular disease risk. In the ADVANCE study, only plasma levels of IL-6, but not those of CRP or fibrinogen, were independently associated with cardiovascular events or death in patients with type 2 diabetes.76 The Edinburgh Type 2 Diabetes Study (ET2DS) found no evidence that increased levels of inflammatory factors influenced the relation between severe hypoglycaemia and cardiovascular complications in people with type 2 diabetes.13 It is also unclear how long pro-inflammatory conditions and reduced endothelial function persist after resolution of hypoglycaemia.

Hyperglycaemia-induced modifications of the epigenome have been suggested to explain the phenomenon of glycaemic memory, i.e. the observation that vascular damage caused by prior chronic hyperglycaemia persists despite good current glycaemic control 77 It is possible that epigenetic factors also contribute to the effects of hypoglycaemia on the cardiovascular system. State-of-the-art imaging techniques, including PET, functional MRI and MRS, are needed to visualise with greater precision how hypoglycaemia affects cardiac and cerebral perfusion and the uptake and metabolism of nutrients in these organs.78

It is also important to establish whether the effects of recurrent episodes of hypoglycaemia are cumulative or diminutive. In healthy humans, exposure to two consecutive hypoglycaemic episodes resulted in greater impairment of endothelial function than one episode, although this was not the case for the elevation of pro-inflammatory cytokines.79 In contrast, it has recently been reported that the acute inflammatory responses to hypoglycaemia were blunted in patients with type 1 diabetes and impaired awareness of hypoglycaemia, possibly due to the reduced counterregulatory hormone response.42 In rats, recurrent hypoglycaemia protects against hypoglycaemia-induced death or neuronal damage,80,81 rather than amplifying the risk for these events. Conversely, an exaggerated counterregulatory hormone response, particularly of epinephrine and cortisol, could explain why those with poorer glycaemic control might be at greater risk when they experience a hypoglycaemic event.82

Experimental research on severe hypoglycaemia has mainly been performed using rat models. Since such experiments cannot be undertaken in humans for ethical reasons, replication should be sought in larger animal models with cardiovascular function that better resembles human physiology.83

Finally, little is currently known about differences in the vulnerability to the potentially deleterious cardiovascular effects of iatrogenic hypoglycaemia, or the underlying mechanisms, between various patient subgroups. For example, it is unlikely that hypoglycaemia exerts the same effect, or the same cardiovascular response in young people with type 1 diabetes who are otherwise healthy compared to older subjects with type 2 diabetes and advanced atherosclerosis. Susceptibility to cardiac arrhythmias during hypoglycaemia appears to be confined to a few individuals84 but what determines this and how they can be identified remains unknown. This is obviously important with respect to balancing benefits of glycaemic control optimisation against the risks of hypoglycaemia. Furthermore, establishing that these effects are present in individuals without co-morbidities would help to establish that hypoglycaemia is a risk factor rather than simply a risk marker.

*Conclusion*

It has been known that hypoglycaemia can be fatal since the introduction of insulin therapy nearly a century ago. Numerous reports exist of an association between hypoglycaemia and cardiovascular events or death, with statistical evidence that the association is not entirely attributable to confounding by comorbidities, and recent reports of hypoglycaemia-induced mortality indicate rates of up to 8% or more in type 1 diabetes. This review has highlighted the many mechanisms whereby hypoglycaemia may increase the risk of cardiovascular disease and mortality and oppose the potential benefits of strict glycaemic control. Lower haemoglobin A1c levels are associated with an increased frequency of severe hypoglycaemia and with increased mortality and cardiovascular events in people with diabetes.85 Importantly low HbA1c levels do not appear to be associated with increased CV risks in populations treated with medication that do not cause hypoglycaemia as a side-effect. Thus, iatrogenic hypoglycaemia appears to be a risk factor for death in people with diabetes. There remains however the prospective evidence that strict metabolic control applied early in the course of both type 1 and type 2 diabetes reduces mortality, despite an increase in hypoglycaemia risk. Collectively, these findings underscore the importance of careful balancing of potential benefits and potential harms and individualising glycaemic goals in people with diabetes treated with insulin or an insulin secretagogue.

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Novo Nordisk representatives were not present at the meeting of the expert panel, had no role in the design or content of the review, were unaware of its content, and had no right to approve or disapprove the final report.

Duality of Interest

PA has served on scientific advisory boards and/or as a lecturer for AstraZeneca, Boehringer Ingelheim/Lilly, Bristol-Myers Squibb, GlaxoSmithKline, Janssen, Merck Sharp & Dohme, Novartis and Sanofi. BC has had research grant support from Halozyme and Lilly to the former MidAmerica Diabetes Associates. PEC has served on scientific advisory boards for Novo Nordisk. BEdG has served on scientific advisory boards for Novo Nordisk and received research grant support from AstraZeneca and Sanofi. SRH has served on scientific advisory boards and provided consultancy for which his institution has received remuneration from Lilly, Novo Nordisk, Takeda, Boeringher Ingelheim and Zealand has served as a speaker for which he received remuneration from AstraZeneca, Lilly, Novo Nordisk and Takeda and has received research support from Medtronic UK Ltd. BMF has served on scientific advisory boards and/or as a speaker for Novo Nordisk, Lilly, Boehringer Ingelheim, Roche, Abbott and Merck Sharp & Dohme. LG-F has served as a consultant or speaker and/or has received research grant support from Abbott Diabetes Care, AstraZeneca, Dexcom, Johnson & Johnson and Merck Sharp & Dohme. TJ has served as a speaker for Novo Nordisk, Lilly, Medtronic and Sanofi. KK has served as a consultant or speaker for AstraZeneca, Boehringer Ingelheim, Janssen, Lilly, Merck Sharp & Dohme, Novartis, Novo Nordisk and Sanofi and has received research grant support from AstraZeneca, Boehringer Ingelheim, Lilly, Novartis, Novo Nordisk, Roche and Sanofi. LAL has served as a consultant has provided CME on behalf of, and/or has research funding from Abbott, AstraZeneca, Boehringer Ingelheim, Eli Lilly, GlaxoSmithKline, Janssen, Merck Sharp & Dohme, Novo Nordisk, Sanofi, and Servier. RJM has served on scientific advisory boards for Novo Nordisk and Sanofi. UP-B has served on scientific advisory boards or as speaker for AstraZeneca, Bristol-Myers Squibb, Novo Nordisk, and Sanofi-Aventis and received research grant from Novo Nordisk, ERS has undertaken consultancy for Sanofi, Novo Nordisk, Lilly, Locemia and Medtronic and received grant support from Lilly. SZ has participated in scientific advisory boards and educational meetings for which her institution has received remuneration from AstraZeneca, MSD Australia, Novo Nordisk Australia and Servier Laboratories. No other potential conflicts of interest relevant to this article were reported.

Table 1. Studies linking hypoglycaemia to cardiovascular events and mortality

|  |  |  |  |  |  |  |
| --- | --- | --- | --- | --- | --- | --- |
|  | **PublicationYear** | **Severity** | **Diabetes type** | **Sample size** | **Follow up** | **Effect size (adjusted)** |
|  |  |  |  |  |  |  |
| **Clinical Trial Cohorts** |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
| DEVOTE 312 | 2018 | SH | Type 2 | 7637 | median 2·0 yrs | CVD HR 1·38 (0·96-1·96) |
|  |  |  |  |  |  | All cause death HR 2·51 (1·79-3·50) |
|  |  |  |  |  |  |  |
| EXAMINE11 | 2017 | SH | Type 2 | 5380 | median 1·5 yrs | CVD HR 2·42 (1·27-4·60) |
|  |  |  |  |  |  | CVD post SH HR 1·60 (0·80, 3·20) |
|  |  |  |  |  |  |  |
| ORIGIN86 | 2013 | SH | Type 2 | 12,537 | median 6·2 yrs | CVD HR 1·58 (1·24-2·02) |
|  |  |  |  |  |  | CV death HR 1·71 (1·27-2·30) |
|  |  |  |  |  |  | All cause death HR 1·74 (1·39-2·19) |
|  |  |  |  |  |  | Arrhythmic death HR 1·77 (1·17-2·67) |
|  |  | Non-severe hypoglycaemia |  |  |  | No association |
|  |  |  |  |  |  |  |
| VADT6 | 2011 | SH | Type 2 | 1791 | median 5·6 yrs | CVD HR 1·88 (1·03-3·43) |
|  |  |  |  |  |  |  |
| ADVANCE8 | 2010 | SH | Type 2 | 11,140 | median 5·0 yrs | CVD HR 3·53 (2·41-5·17) |
|  |  |  |  |  |  | CV death HR 3·79 (2·36-6·08) |
|  |  |  |  |  |  | All cause death HR 3·27 (2·29-4·65) |
|  |  |  |  |  |  |  |
| ACCORD 82 | 2010 | SH | Type 2 | 10,194 | mean 3·5 yrs | All cause death int HR 1·41 (1·03-1·93) |
|  |  |  |  |  |  | All cause death st HR 2·30 (1·46-3·65) |
|  |  |  |  |  |  |  |
| **Epidemiological Cohorts** |  |  |  |  |  |  |
|  |  |  |  |  |  |  |
| ARIC87 | 2018 | SH | Type 2 | 1209 | median 15·3 yrs | CHD HR 2·02 (1·27-3·20) |
|  |  |  |  |  |  | CV death HR 1·64 (1·15-2·34) |
|  |  |  |  |  |  | All cause death HR 1·73 (1·38-2·17) |
|  |  |  |  |  |  |  |
| Taiwan database88 | 2016 | SH | Type 1 | 4361 | 5 yrs | CVD HR 2·74 (1·96-3·85) |
|  |  |  |  |  |  |  |
| Japanese database89 | 2016 | SH | Type 2 | 58,223 | mean 2·3 yrs | CVD HR 3·39 (1·25-9·18) |
|  |  |  |  |  |  |  |
| US Academic Primary Care Network90 | 2016 | Not defined | Type 1 and Type 2 | 9173 | 6 yrs | CHD HR 2·15 (1·24-3·74) without previous CAD |
|  |  |  |  |  |  | CHD HR 3·01 (1·15-7·91) in high vascular risk patients |
|  |  |  |  |  |  | CHD HR 4·62 (1·65-12·9) in those aged >= 65 years |
|  |  |  |  |  |  |  |
| Vincent Type 2 Diabetes Registry (Korea)91 | 2016 | SH | Type 2 | 906 | median 10·4 yrs | All cause death HR 2·64 (1·39-5·02) |
|  |  |  |  |  |  | CV death HR 6·34 (2·02-19·87) |
|  |  |  |  |  |  |  |
| Dutch and Danish Cohorts92 | 2016 | SH | Type 1 | Dutch 482 | 6·5 yrs | All cause death No association |
|  |  |  |  | Danish 269 | 12 yrs | CV death No association |
|  |  |  |  |  |  |  |
| Joint Asia Diabetes Registry93 | 2016 | Mild hypoglycaemia | Type 2 | 18,589 | mean 3·9 yrs | CVD HR 1·16 (0·94-1·43) |
|  |  |  |  |  |  | All cause death HR 1·03 (0·78-1·36) |
|  |  |  |  |  |  |  |
| CREDIT study94 | 2016 | SH | Type 2 insulin treated | 2999 | 4·0 yrs | CV death HR 1·10 (0·34-3·57) |
|  |  |  |  |  |  | All cause death HR 1·22 (0·59-2·53) |
|  |  |  |  |  |  |  |
| UK GP database9 | 2015 | SH | Type 1 and 2 insulin treated  | 3260 Type 1 | median 5·0 yrs | Type 1 CVD secondary HR 1·10 (0·40-3·01) |
|  |  |  |  |  |  | Type 1 CVD HR 1·92 (1·31-2·79) |
|  |  |  |  | 10,422 Type 2 | median 4·8 yrs | Type 2 CVD secondary HR 1·70 (1·09-2·64) |
|  |  |  |  |  |  | Type 2 CVD HR 1·50 (1·19-1·88) |
|  |  |  |  |  |  |  |
| Scottish13 | 2014 | SH | Type 2 | 1066 | mean 4·0 yrs | CVD HR 1·60 (1·13-2·26) |
|  |  |  |  |  |  |  |
| Swedish Diabetes Register95 | 2014 |  | Type 1 | 1839 | 5 yrs | All cause death HR 1·25 (1·02-1·53) |
|  |  |  |  |  |  |  |
| German Primary Care database96 | 2013 | SH | Type 2 | 25,712 | mean 2·0 yrs | CVD HR 2·11 (1·06-4·20) |
|  |  |  |  |  |  |  |
| Taiwan database97 | 2013 | SH | Type 2  | 2500 | 10 yrs | CVD HR 2·26 (1·93-2·65) |
|  |  |  |  |  |  | CHD HR 1·63 (1·28-2·08) |
|  |  |  |  |  |  | Stroke HR 1·64 (1·29-2·07) |
|  |  | Mild hypoglycaemia |  |  |  | CVD HR 2·21 (1·98-2·47) |
|  |  |  |  |  |  |  |
| US Veterans Network98 | 2012 | SH |  | 1522 | median 3·9 yrs | CVD HR 2·00 (1·63-2·44) |
|  |  |  |  |  |  |  |
| Medicare database99 | 2011 | SH | Type 2 | 860,845 | mean 1 yr | CVD HR 1·79 (1·69-1·89) |

*Figure Legends*

Figure 1. Association of Severe Hypoglycemia with the Risk of an Adverse Clinical Outcome or Death. The hazard ratio represents
 the risk of an adverse clinical outcome or death among patients reporting severe hypo­glycaemia as compared with those not reporting
 severe hypoglycemia. The centers of the squares are placed at the point estimates and the horizontal lines represent
 the corresponding 95% confidence intervals. The area of each square is proportional to the inverse of the variance of each estimate.
Reproduced from Zoungas et al8 with permission from NEJM.org

Figure 2. Pathophysiological cardiovascular consequences of hypoglycaemia

Figure 3. Glucose levels captured by the continuous glucose monitoring system for the evening prior to, and the morning of ,the patient’s death are illustrated. The patient measured and entered calibrations are represented by the 4 circles. Timing of the patient’s meals, exercise and correction insulin boluses are represented by the bars along the bottom of the graph.
Reproduced from Tanenberg et al.47 with permission from Endocrine Practice.

Figure 4. Typical QT measurement with a screen cursor placement from a subject during euglycaemia (left panel),
showing a clearly defined T wave, and hypoglycaemia (right panel), showing prolonged repolarisation and a prominent U wave.
Reproduced from Marques et al48 with permission from John Wiley & Sons

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