

Hypoglycaemia and cardiovascular risk in people with type 2 diabetes

Gary Kilov

Intensive glucose-lowering therapy has been observed to have a modest effect on cardiovascular disease risk in people with type 2 diabetes. Large-scale clinical trials involving high-risk individuals with type 2 diabetes have failed to associate the use of such therapy with significant reductions in participants' risk of cardiovascular events and mortality, when compared to standard glucose-lowering regimens. This article considers the role of severe hypoglycaemia in the observed phenomenon and whether educating and treating individuals to better avoid severe hypoglycaemic episodes might help to improve treatment outcomes and the cardiovascular health of this at-risk group.

Individuals with type 2 diabetes are at increased risk of cardiovascular disease (CVD; Laakso, 2010). CVD is responsible for 60% of deaths among people with type 2 diabetes, through events such as myocardial infarction and stroke (Fox et al, 2007). Studies have investigated the role of intensive glucose-lowering interventions on cardiovascular risk; however, the results have been more modest than expected (Giorgino et al, 2013). Studies such as ADVANCE (Action in Diabetes and Vascular Disease), ACCORD (Action to Control Cardiovascular Risk in Diabetes) and the VADT (Veterans Affairs Diabetes Trial) have failed to associate the use of such therapy with significant reductions in the risk of CVD mortality compared to standard glucose-lowering regimens in high-risk individuals with type 2 diabetes (ADVANCE Collaborative Group, 2008; ACCORD Study Group, 2008; Duckworth et al, 2009, respectively).

The potential impact of hypoglycaemia

It is hypothesised that the occurrence of severe hypoglycaemic episodes might at least partly explain the failure of intensive glucose-lowering regimens to significantly reduce rates of cardiovascular mortality among

individuals with diabetes compared with less intensive therapy (Giorgino et al, 2013; Goto et al, 2013).

Severe hypoglycaemia is defined by the American Diabetes Association's Workgroup on Hypoglycemia (2005) as a hypoglycaemic event that requires assistance of another person to actively administer carbohydrate, glucagon or other resuscitative actions. A seizure or a coma may occur at this time.

A recent meta-analysis has suggested that the development of severe hypoglycaemia in people with type 2 diabetes approximately doubles the risk of CVD compared to no severe hypoglycaemia (Goto et al, 2013). The development of severe hypoglycaemia has been associated with a three-fold increase in the rate of cardiovascular mortality in the ADVANCE study compared to no hypoglycaemia (adjusted hazard ratio [HR], 3.78; $P < 0.001$ [Zoungas et al, 2010]) and a four-fold increase in the VADT (HR, 4.04; $P = 0.01$ [Abaira et al, 2008]). This could be a result of intensive glucose-lowering treatment. Intensive glucose-lowering treatment has been shown to double the risk of severe hypoglycaemia (Boussageon et al, 2011). The development of severe hypoglycaemia has also been associated with an increased risk

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Article points

1. Intensive glucose-lowering therapy has not been associated with a significant reduction in patients' risk of cardiovascular events and mortality when compared to standard glucose-lowering regimens.
2. Severe hypoglycaemia could be a reason for the lack of association between intensive glucose control and reduced cardiovascular risk.
3. Primary healthcare professionals should aim to prescribe appropriately individualised anti-diabetes medication that will maintain the best possible glycaemic control for each patient, while also appropriately minimising each patient's risk of developing severe hypoglycaemia and related complications.

Key words

- Cardiovascular risk
- Severe hypoglycaemia
- Type 2 diabetes

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Page points

1. The development of severe hypoglycaemia has been associated with an increased risk of adverse cardiovascular events and mortality compared to the absence of severe hypoglycaemia individuals with or at high risk of type 2 diabetes.
2. Hypoglycaemia could lead to an increased risk of cardiovascular disease through a variety of pathological mechanisms.
3. Clinicians should seek to minimise the likelihood of hypoglycaemic episodes occurring when managing individuals who have diabetes.

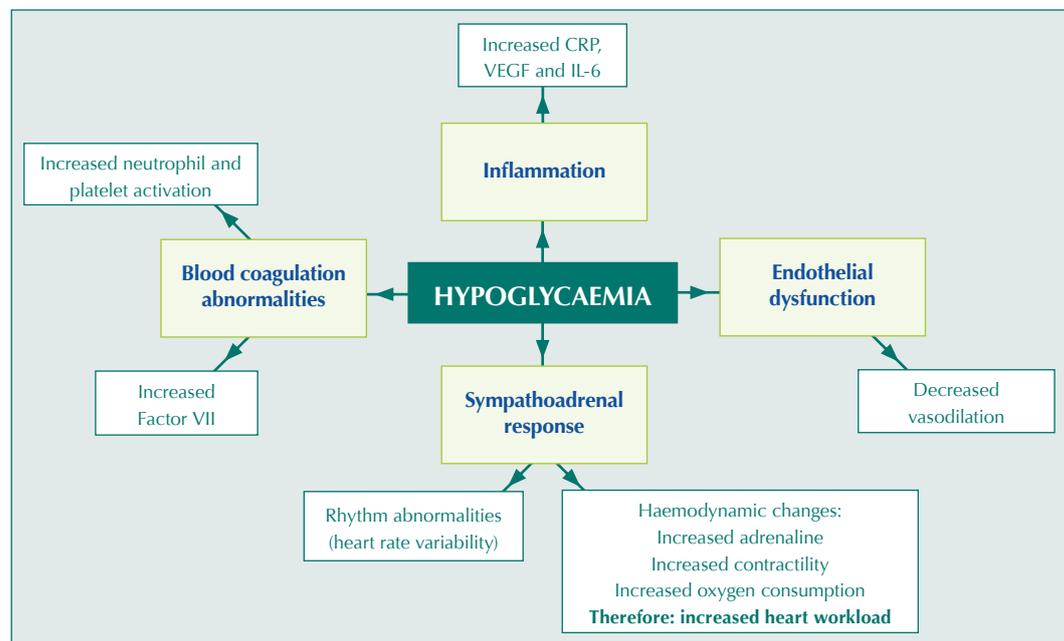


Figure 1. How hypoglycaemia may potentiate cardiovascular disease (Desouza et al, 2010).
CRP=C-reactive protein; IL-6=interleukin-6; VEGF=vascular endothelial growth factor.

of adverse vascular events and mortality (versus the absence of severe hypoglycaemia) among high-risk individuals with early-stage type 2 diabetes, impaired glucose tolerance or impaired fasting glucose, highlighting that this is not something that only affects people with type 2 diabetes (Ceriello, 2010).

Possible pathophysiology

It remains to be proven whether, and to what extent, the development of severe hypoglycaemia might directly contribute to an individual’s risk of major cardiovascular events and related mortality. However, there are certainly many potential mechanisms via which it could do so.

Hypoglycaemia has been associated with a number of potentially adverse haemodynamic changes (e.g. tachycardia, systolic hypertension, elevated cardiac output and myocardial oxygen demand; *Figure 1*) and may also exert a range of pro-thrombotic and pro-inflammatory effects (Snell-Bergeon and Wadwa, 2012; Lalic, 2013; Hanefeld et al, 2013; Rana et al, 2014). Together, such mechanisms could potentially increase the risk of myocardial ischaemia, acute thrombotic events and accelerated atherosclerosis in an

individual who is already at high risk of CVD.

It is also well established that individuals who experience hypoglycaemia are at an increased risk of potentially fatal acute cardiac arrhythmias (Cryer, 2011; Clark et al, 2014). Desouza et al (2010) clearly demonstrated the arrhythmogenic potential of hypoglycaemia by simultaneously using continuous glucose monitors and Holter monitors to detect the effect of hypoglycaemia on electrocardiogram changes.

Advice to clinical practice

Given the apparent potential for severe hypoglycaemic episodes to increase CVD risk, induce a potentially fatal arrhythmic event or both, it seems prudent to seek to minimise the likelihood of such episodes occurring when managing individuals who have diabetes. An important first step in this regard is to always consider a patient’s risk of experiencing a severe hypoglycaemic event, as well as his or her existing susceptibility to potential hypoglycaemia-related complications, when deciding which anti-diabetes regimen to prescribe and setting glycaemic targets (Cryer, 2011; Snell-Bergeon and Wadwa, 2012; Giorgino et al, 2013; Hanefeld et al,

2013; Clark et al, 2014; Rana et al, 2014).

The overall aim should be to prescribe appropriately individualised anti-diabetes therapy: regimens comprising agents that will help to maintain the best possible level of glycaemic control for each patient, while also minimising each patient's risk of developing severe hypoglycaemia and related complications (Snell-Bergeon and Wadwa, 2012).

Final thoughts

The triumvirate of blood pressure reduction, lipid management and optimal glycaemic control have traditionally formed the cornerstones of cardiovascular risk reduction. Perhaps a fourth cardiovascular risk reduction strategy should be added: the mitigation or prevention of hypoglycaemic episodes, given the compelling evidence for their association with increased CVD risk. ■

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“Perhaps a fourth cardiovascular risk reduction strategy should be added: hypoglycaemia avoidance.”