Hypoglycaemia in diabetic patients: highly undesirable by cardiologists

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This editorial refers to ‘Does hypoglycaemia increase the risk of cardiovascular events? A report from the ORIGIN trial†’, by the ORIGIN Trial Investigators, on page 3137

Cardiovascular diseases constitute a major clinical problem for patients with type 2 diabetes mellitus (T2DM), being the most common cause of death in this population.1,2 It fully justifies the concept of a close collaboration between diabetologists and cardiologists for the optimal integrated management of diabetic patients with cardiovascular diseases in everyday clinical practice,2 which has been reflected by the launching guidelines on diabetes, pre-diabetes, and cardiovascular diseases jointly written and promoted by the European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD).3,4

‘Lower is not necessarily better’: a lesson which cardiologists have recently learnt

Type 2 diabetes mellitus is a metabolic disease characterized by insulin resistance and glucose intolerance, resulting in fasting and post-prandial hyperglycaemia. Hyperglycaemia has been traditionally viewed as the major risk factor responsible for clinical complications in diabetic patients (including cardiovascular events), and therefore has naturally become a primary therapeutic target in T2DM.6 The UKPDS study was the first to provide evidence that in newly diagnosed T2DM patients intensive glucose control may reduce the risk of microvascular complications, also with modest effects on cardiovascular outcomes.6,7 Thus, the concept ‘the lower, the better (glucose level)’ was proposed by all diabetology guidelines as a paradigm for T2DM treatment, and only recently has been challenged by the results of three clinical trials: ACCORD, ADVANCE, and VADT.7–9 In the ADVANCE and VADT studies, an intensive glucose control strategy did not significantly reduce the risk of cardiovascular endpoints,8,9 whereas the ACCORD study reported higher cardiovascular and all-cause mortality among those receiving an intensive glucose-lowering therapy.7 In an attempt to explain the lack of expected superiority of strict glycaemic control which could favour ‘the lower the better’ strategy, numerous potential reasons have been proposed and discussed.10 Only recently, hypoglycaemia and associated triggered pathomechanisms, complicating the intensive glucose control strategy, have been proposed as a potential explanation of neutral/negative effects on cardiovascular events in diabetic patients assigned to the intensive therapy arm.10–12

Is hypoglycaemia deleterious for the cardiovascular system?

An adequate supply of energetic substrates (e.g. glucose) to the peripheral tissues is critical for homeostasis maintenance. Hypoglycaemia is a fundamental stimulus in physiology, which triggers complex evolutionary highly conservative adaptive mechanisms, aiming to restore the circulating glucose level to be adequate for metabolic needs (mainly protecting the central nervous system).13 The key element of this response is a rapid activation of the sympathetic nervous system accompanied by the counter-regulatory hormone secretion.13 As hypoglycaemia itself elicits mechanisms which are protective in their primary nature, how do we explain the deleterious effects of hypoglycaemic events on the cardiovascular system?

The annual incidence rate of severe hypoglycaemia is 0–3% in adult patients with T2DM, and the variability results from the application of different definitions of severe hypoglycaemia and the different clinical profile of investigated populations (the severity and duration of T2DM, previous cardiovascular events, applied antidiabetic therapies, demographic characteristics).14 Post-hoc analyses from the ADVANCE and ACCORD trials as well as several smaller studies summarized in a systematic review14 have demonstrated that the occurrence of episodes of severe hypoglycaemia in diabetic patients has a detrimental impact on cardiovascular outcomes.15–17

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In the ADVANCE trial, which recruited T2DM patients with a history of major macrovascular or microvascular disease or at least one other cardiovascular risk factor, 2.1% of diabetic patients experienced severe hypoglycaemia (defined as a blood glucose level <50 mg/dL with a transient dysfunction of the central nervous system requiring help from another person) during the median follow-up of 5 years (2.7% and 1.5% in the intensive and standard glycaemic control arms, respectively).15 Severe hypoglycaemia was shown to be strongly related to an increased risk of the first macrovascular event (death from a cardiovascular cause, non-fatal myocardial infarction, or non-fatal stroke) as well as to higher all-cause, cardiovascular and non-cardiovascular mortality rates.15 In the ACCORD trial, which included diabetic patients with cardiovascular disease or at high cardiovascular risk, the symptomatic severe hypoglycaemic events (a blood glucose level <50 mg/dL) requiring any assistance occurred in 15.9% vs. 5.0% of subjects assigned to the intensive vs. standard glycaemic control arms (annual incidence of these events: 3.14% vs. 1.03% in the respective arms17), whereas the symptomatic severe hypoglycaemic events (a blood glucose level <50 mg/dL) requiring any medical assistance occurred in 10.3% vs. 3.4% of patients randomized to the intensive vs. standard therapy arms.16 Symptomatic, severe hypoglycaemia was associated with higher annual mortality in diabetic patients in both study arms.16

The significance of hypoglycaemia for cardiovascular outcomes in diabetic patients seems to be equivocal.10,14,18 However, it still remains unclear whether hypoglycaemia itself negatively affects outcomes in these patients, triggering a set of detrimental pathomechanisms (discussed below), or, alternatively, whether hypoglycaemia is just an epiphenomenon, reflecting the disease severity and the comorbidity burden, simply identifying those at high risk of poor cardiovascular outcomes.10,14,18 Indeed, diabetic patients who are more likely to develop severe hypoglycaemic events are older, have lower body mass index, impaired renal function, a history of microvascular complications, dementia, previous hypoglycaemic events, a longer duration of T2DM, worse education, and are receiving more intensive glycaemic control.14–17 Interestingly, however, the recent meta-analysis by Goto et al. suggests that the contribution of distinct clinical characteristics along with the presence of co-morbidities in the associations between hypoglycaemia and poor cardiovascular outcomes is of a minor (if any) importance, again placing hypoglycaemia itself in the centre of factors detrimental for the cardiovascular system.18

The study of Mellbin et al.19 provides further complementary and strong evidence that the episodes of severe hypoglycaemia are detrimental and even fatal in the long-term perspective for patients with cardiovascular risk factors and concomitant T2DM or pre-diabetes. The population of >12 000 patients investigated in the ORIGIN trial is of a particular clinical interest for cardiologists.20 They had rather mild T2DM (or pre-diabetes) and did not require a complex antidiabetic therapy, but in contrast the majority of them suffered from cardiovascular disease and/or experienced a cardiovascular event (arterial hypertension in 79%, myocardial infarction in 35%) with a therapy of statin, angiotensin-converting enzyme (ACE) inhibitor/angiotensin receptor blocker (ARB), and antiplatelets in 54, 69, and 69% of patients, respectively. Such a cardiovascular risk profile, at least partially, explains the relatively high rate of cardiovascular complications (15% all-cause deaths, 9% cardiovascular deaths, 33% cardiovascular hospitalizations, 5% arrhythmic deaths—during a median follow-up of 6.2 years) in the population with well-controlled diabetes [a median, interquartile range of glycated haemoglobin (HbA1c) of 6.4%, 5.8–7.4% in both study arms].20

In the population of the ORIGIN trial, severe hypoglycaemia (defined as a symptomatic hypoglycaemia requiring assistance with prompt recovery after glucose/glucagon administration and/or with a documented glucose level <36 mg/dL) occurred in 5.7% and 1.8% patients assigned for the insulin glargine and standard therapy groups, respectively. Most importantly, after adjustment for the propensity score and regardless of HbA1c level, the occurrence of severe hypoglycaemia allowed the identification of those at high risk of either all-cause, cardiovascular, or arrhythmic death. Therefore, the authors have demonstrated that the problem of severe hypoglycaemia in patients with cardiovascular risk factors and dysglycaemia is not marginal, and has clinically relevant prognostic consequences. The authors need to be congratulated for their well-planned and well-executed collection of hypoglycaemic events. It should be emphasized that the precise identification of hypoglycaemia episodes is very difficult in everyday clinical practice and also in the setting of a clinical trial. This relates to the fact that substantial numbers of hypoglycaemia episodes are asymptomatic, and, for those which are symptomatic, there is a huge inconsistency and an intraindividual variability in symptom reporting.21

Can pathomechanisms triggered by hypoglycaemia explain everything?

There is substantial experimental and clinical evidence indicating that hypoglycaemia, particularly when persistent and/or recurrent, triggers directly and indirectly a set of pathomechanisms detrimental for the cardiovascular system (Figure 1). Most importantly, the unfavourable effects of hypoglycaemia are particularly deleterious in those with prior cardiovascular disease (coronary artery disease or heart failure).10–13

The fundamental mechanism induced directly by hypoglycaemia is sympatho-adrenal activation, i.e. a rapid and strong reflex stimulation of the sympathetic system along with the activation of the adrenal medulla with subsequent catecholamine release (mainly epinephrine).10–13,22,23 Additionally, hypoglycaemia evokes the hormonal response, which includes: the suppression of endogenous insulin secretion, the release of glucagon, and the release of growth hormone and cortisol (an activation of the hypothysis–pituitary–adrenal axis).24

There is also evidence that hypoglycaemia can trigger the activation of the renin–angiotensin–aldosterone system (RAAS), and, indeed, there are mutual links between the RAAS and hypoglycaemia in diabetic subjects. In healthy subjects, hypoglycaemic hyperinsulinaemia increases plasma renin activity along with serum aldosterone in a dose-dependent fashion.24 Moreover, it is suggested that angiotensin II released during the insulin-induced hypoglycaemia facilitates the sympathetic-adrenal reflex response by interacting with its specific receptors at several anatomical neuron localizations.27

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The activation of the sympatho-adrenal system and the RAAS reveals numerous unfavourable effects evoked in different tissues and organs (through direct and indirect mechanisms reviewed in 10–13), such as: haemodynamic changes (vasoconstriction, tachycardia, increased afterload, reduced renal flow 28), vascular and myocardial remodelling (including deranged electrical properties of cardiomyocytes), endothelial dysfunction, inflammation, platelet activation, and induction of coagulation. Hypoglycaemia and the associated aforementioned mechanisms may also facilitate the development of ventricular arrhythmias, mainly due to QT interval prolongation and Ca^{2+} overload in cardiomyocytes. 29 Additionally, hypoglycaemia itself and the circulating catecholamines may lead to hypokalaemia, which further increases the risk of ventricular arrhythmias. 29

The problem of arrhythmias associated with hypoglycaemia in T2DM has been rather neglected, whereas severe hypoglycaemia appeared to increase the risk of arrhythmic death in the ORIGIN trial. 19 46% of cardiovascular deaths in the ACCORD trial were assigned as unexpected, 7 and finally in the VADT study there was a trend towards higher rates of sudden death in the intensive glycaemic control arm as compared with the standard therapy arm. 5

Taking into account that hypoglycaemia triggers numerous reactions potentially involved in the pathophysiology of cardiovascular diseases, one could speculate that recurrent hypoglycaemic events constitute a neglected trigger leading to the progression of the disease, which may ultimately end up as a syndrome of heart failure.

**Conclusions**

In clinical practice, regardless of the mechanism underlying clinical and prognostic detrimental consequences of severe hypoglycaemia, it should be always mostly unwanted by cardiologists treating a patient with T2DM and concomitant cardiovascular disease. Cardiologists should always keep in mind that the episodes of severe hypoglycaemia complicate the treatment of T2DM (perhaps more often than expected), can elicit numerous responses with detrimental effects on the cardiovascular system potentially leading to the further progression of the disease, and finally severe hypoglycaemia is a strong prognosticator of additional risk of cardiovascular complications.

The complementary results of the ORIGIN trial 19 are in accordance with the recent guidelines on diabetes, pre-diabetes, and
cardiovascular diseases, which now broadly recognize the importance of hypoglycaemia stressing that: ‘...attention should be paid to avoidance of hypoglycaemia whilst achieving glycaemic goals in an individualized manner. ...’

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References


