The difficult task of glycaemic control in diabetics with acute coronary syndromes: finding the way to normoglycaemia avoiding both hyper- and hypoglycaemia

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This editorial refers to ‘Association between hyper- and hypoglycaemia and 2 year all-cause mortality risk in diabetic patients with acute coronary events’† by A.M. Svensson et al., on page 1255

Considering glycaemic control in diabetes, we often think that all metabolic syndromes are born equal and, as for cholesterol, ‘the less the better’. Perhaps not in diabetes. Diabetes mellitus is a metabolic syndrome characterized by absolute or relative insulin deficiency. Despite the simplicity of the concept of insulin deficiency and hyperglycaemia, the mechanisms underlying the variable complications of diabetes are often unclear.

Diabetics are a high cardiovascular risk population at increased risk of new or recurrent episodes of atherothrombosis, and these patients with acute coronary syndromes have the worse outcome when compared with non-diabetics, independently from the therapeutic approach.1 Furthermore, even new onset stress hyperglycaemia in patients with acute myocardial infarction (AMI) predicts adverse outcome.2,3 Nevertheless how much and how anti-diabetic treatment affects survival in patient with AMI is still unclear. Svensson et al.4 report the prognostic value of admission and in-hospital glycaemic values in patients admitted with AMI. The authors have studied more than 700 consecutive diabetic patients treated at a single institution and followed for >2 years. Mortality in this cohort was >30% at 2 years, and glycaemic control was predictive of outcome.4

Interestingly, when compared with the patients with optimal in-hospital glycaemic control, those with suboptimal glycaemic control [lowest value >6.6 mmol/L (≥120 mg/dL)] and those with hypoglycaemia during the hospitalization [lowest value ≤3.0 mmol/L (≤55 mg/dL)] all had worse outcome at long-term follow-up. The authors conclude that ‘in the setting of ACS among patients with diabetes, hyperglycaemia on arrival and hypoglycaemia during hospitalization are both independently associated with the worse adjusted all-cause 2-year mortality risk’.4 Although neither of these concepts is completely new, the association between in-hospital glycaemic control and long-term outcome is disturbing because a clear pathophysiologic explanation is lacking.

Hyperglycaemia and adverse outcome: overwhelming evidence

The negative prognostic value of hyperglycaemia at admission in AMI patients and acutely ill patients in general has been extensively reported and discussed.2 While fasting hyperglycaemia in diabetes is the result of absolute or relative insulin deficiency, an acute increase in glycaemia related to increased activity of counterregulatory hormones is usually referred to as ‘stress hyperglycaemia’. Stress is the physiologic/pathologic response to sudden changes in the homeostasis. In AMI, stress responses are aimed to optimize short-term cardiovascular performance and include both enhanced adrenergic and glucocorticoid response. The degree of hyperglycaemia may therefore reflect, to some extent, the underlying stress. This view of hyperglycaemia as a simple marker may, however, be inappropriate.

Hyperglycaemia and myocardial metabolism

One possible interpretation of the association between hyperglycaemia and adverse outcome is the consideration that, despite hyperglycaemia, the myocardium is actually in glucose starvation due to increased insulin-resistance, with a shift towards free fatty acid metabolism and impaired cardiac performance.5,6 On this basis, the DIGAMI trial suggested that optimal glycaemic control with insulin in patients with AMI was beneficial by allowing intracellular glucose uptake by the ischaemic myocardium.7 Failure to confirm these results by the very recent DIGAMI 2 trial, however, questions the validity of these concepts.8 Nevertheless, the benefits of treatment of hyperglycaemia is unquestionable and optimal glycaemic control is
Hyperglycaemia and inflammation

Diabetes, inflammation, and atherothrombosis are variably integrated processes. Inflammation may have a role in promoting insulin-resistance, and diabetes certainly promotes inflammation. Both metabolic alterations associated with diabetes and inflammation seem to play a major role in promoting atherothrombosis. As the evidence in support of the association between inflammation and prognosis in ACS is overwhelming, the association between hyperglycaemia and adverse prognosis may be mediated by an increased inflammatory response in patients with hyperglycaemia, which ultimately may itself be responsible for worsening insulin-resistance. Hyperglycaemia is associated with increased levels of inflammatory markers in patients with AMI, and in acutely ill patients in general. In experimental studies, hyperglycaemia itself potentiates cytotoxic activities by leucocytes. Hyperglycaemia may, therefore, represent another aspect of the inflammatory response associated with acute coronary syndromes.

Hyperglycaemia and apoptosis

A direct toxic effect of hyperglycaemia on myocytes has been postulated. Cai et al. have studied the effects of hyperglycaemia in the mouse myocardium. They found that hyperglycaemia induced increased apoptosis in vivo and adverse left ventricular remodelling, and have also shown direct toxicity of hyperglycaemia on myocytes in an in vitro model. These results in experimental diabetes have been confirmed in other experimental settings. As apoptosis is a major form of cardiomyocyte death in acute and subacute MI, negative effects of hyperglycaemia may be related to enhancement of such a process.

Hypoglycaemia and adverse prognosis: bad news

As the evidence in support of adverse effects of hyperglycaemia increased, the treatment of in-hospital hyperglycaemia became more aggressive. In the DIGAMI trial, as many as 20% of patients experienced at least one episode of hypoglycaemia during the hospital stay. The landmark article by Fisher et al. showed that hypoglycaemia in the hospital...
setting is a relatively common event and that patients with hypoglycaemia have the worse outcome. Notably, the deaths (occurring either early or late) were not directly related to the hypoglycaemic event, and the authors conclude in their paper that hypoglycaemia was most likely a manifestation of the underlying disease, such as renal insufficiency, liver disease, sepsis, and other conditions of impaired glucose counterregulation.13

Svensson et al.4 show that patients admitted with AMI with at least one episode of hypoglycaemia during hospitalization had worse outcome than those without hypoglycaemia, and an even higher mortality rate than those with suboptimal glycaemic control. Accordingly, the authors conclude that hypoglycaemia is a marker of increased risk in patients with AMI.

In their well-written paper, the authors discuss how they were not able to identify the mechanistic link between hypoglycaemia and long-term mortality. As discussed earlier, hypoglycaemia during admission may be a marker of underlying diseases associated with increased mortality. Perhaps, however, it is not so simple. In their study, Svensson et al.4 attempted to correct the findings of increased mortality associated with hypoglycaemia by means of multivariable analysis. Although multivariable analysis carries some imprecision, the lack of confounding factors raises the question on whether hypoglycaemia may represent more than a simple marker of disease. However, looking into Svensson’s data in detail some comments need to be made. One limitation of their analysis may be found in using categorical classification of renal function into normal and abnormal. A cut-off for creatinine of 1.37 mg/dL may have led to the underestimation of renal insufficiency rates, especially in those patients who developed hypoglycaemia and who had a lower BMI. A body-mass, age-, and sex-corrected glomerular filtration rate would have been appropriate, especially considering the fact that despite the relative insensitivity of the criteria used, patients with hypoglycaemia showed a trend towards higher rates of renal failure (36.4 vs. 33.3 and 31.4%), and in consideration of the fact that creatinine levels predict adverse outcome in patients with ACS. In addition, hypoglycaemia might be a proxy for inadequate caloric intake and malnutrition, which can occur in the sickest patients, such as those in cardiogenic shock or pulmonary edema, especially when they are unable to feed themselves.

Nevertheless, even accounting for potential confounding factors, the hypothesis that hypoglycaemia may itself promote adverse outcome needs to be considered.

Hypoglycaemia, adrenergic and metabolic derangements, and myocardial ischaemia

Hypoglycaemia is associated with symptoms and signs of adrenergic stimulation. The large benefits obtained by the use of betablockers in patients with ACS highlights how adrenergic stimulation in ACS may be detrimental and suggests that hypoglycaemia may be associated with adverse outcomes by means of enhanced adrenergic response.

The adrenergic response may be responsible also for the increased incidence of myocardial ischaemia in patients with hypoglycaemia. Desouza et al.14 have indeed shown a correlation between hypoglycaemic events and myocardial ischaemia in patients with coronary artery disease.

Hypoglycaemia may be responsible also for impaired myocardial metabolism and increased apoptosis in the setting of AMI, and potential benefits of the glucose-insulin potassium (GIK) therapy may be due to restauration of metabolic functions and prevention of apoptosis.5

Hypoglycaemia and long-term outcome

The association of hypoglycaemia with adverse long-term outcome is unclear. As previously addressed, one possibility is that hypoglycaemia simply reflects underlying disease and therefore long-term outcome is unfavorable because of the underlying conditions. However, it should be acknowledged that diabetic patients with hypoglycaemia tend to have recurrent hypoglycaemic events, and that hypoglycaemia-associated autonomic failure may occur in these patients. Autonomic failure is particularly risky as patients become unaware of the hypoglycaemic episodes and acute complications of hypoglycaemia occur more commonly.

Glycaemic control: where do we go from here?

According to the study by Svensson et al.4 ‘judicious glycaemic management’ should be used for patients with AMI as both suboptimal treatment and overtreatment may be associated with adverse outcomes (Figure 1).

Although we do not know with certainty whether either hyperglycaemia or hypoglycaemia directly promote adverse outcome, they should be recognized as important and independent prognostic markers in patients with AMI.

It is not surprising that the corresponding author of the paper by Svensson et al.4 qualified herself as a registered nurse (RN). Optimal glycaemic control is indeed often delegated to the skills of RNs, who are in charge of efficacy of treatment and prompt recognition of treatment failure or complications. Indeed only in the setting of optimal ICU nursing, intensive but watchful glycaemic control is likely to be beneficial.

However, whether the benefits of intensive glycaemic control outweigh the potential risks of hypoglycaemia is unknown, and requires further studying. Therefore, whenever glycaemic control is considered, optimal control should be attempted and hypoglycaemia should be kept in mind as an alert sign for increased risk of adverse outcome.

Regarding the type of regimen that should be used for optimal glycaemic control ‘the jury is still out’.15 Recent studies failed to confirm the benefits of intensive insulin treatment over standard glycaemic control, but did prove that a better glycaemic control is associated with overall better outcome.

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