Editorial

Insulin vs. strict blood glucose control to achieve a survival benefit after AMI?

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This editorial refers to 'Intense metabolic control by means of insulin in patients with diabetes mellitus and acute myocardial infarction (DIGAMI 2): effects on morbidity and mortality'† by K. Malmberg et al., on page 650

Patients with diabetes mellitus have a 1.5–2 times higher risk of death after myocardial infarction than do non-diabetic patients. In diabetic myocardium, the consumption of fatty acid as metabolic fuel is thought to be increased, whereas glycolysis is impaired both in ischaemic and non-ischaemic areas. As the consumption of fatty acids instead of glucose requires more oxygen, such a shift may be deleterious particularly when oxygen supply is limited. More than four decades ago, the concept of infusing glucose together with insulin and potassium (GIK) to protect the ischaemic myocardium was introduced. Early clinical studies on the effect of such a 'metabolic cocktail' yielded promising results suggesting that GIK might be a way to reduce morbidity and early mortality in patients with an acute myocardial infarction (AMI). As the possible mechanism behind a cardioprotective effect of GIK, Opie proposed the promotion of glycolysis in cardiomyocytes and the diversion of fatty acids to adipocytes thereby reducing oxygen consumption in the heart. With the advent of aggressive and acute revascularization strategies (thrombolysis and percutaneous transluminal coronary angioplasty), the potential of metabolic supportive therapy with GIK was not further pursued.

In 1995, the Diabetes and Insulin-Glucose infusion in AMI (DIGAMI) study was the first to randomize diabetic patients with an AMI to either 'intensive insulin therapy' or standard treatment. Intensive insulin therapy comprised intravenous infusion of GIK as soon as possible after the AMI and continued for 48 h. Thereafter, patients in the intensive insulin therapy group were submitted to a 'strict' blood glucose control regimen with subcutaneous insulin continued for ~3 months after discharge. This intervention resulted in a mean blood glucose level after 24 h of 9.6 mmol/L when compared with a significantly higher 11.7 mmol/L in the control group. At hospital discharge (8.2 vs. 9.0 mmol/L) and 3 months follow-up (8.5 and 9.0 mmol/L), small differences in blood glucose control between the two study groups were maintained. In the intensive treatment arm, mortality risk at 1 year was reduced by a relative 29%. In addition, there was a significant decrease in re-infarction and new heart failure. It remained unclear, however, how much of the benefit was due to an acute effect of GIK and how much was mediated by strict blood glucose control with insulin in the days and months after the AMI. Therefore, Malmberg et al. embarked on a subsequent study, DIGAMI 2. In this study, patients with diabetes mellitus and AMI were randomized into three groups. The first group received GIK infusion for 24 h followed by an insulin-based long-term glucose control aiming for the current target for fasting blood glucose levels in diabetes mellitus of 5–7 mmol/L. The second group received GIK infusion for 24 h followed by 'standard' glucose control. The third group received 'routine management' according to the local practice. This was indeed the correct study design to answer the question that was raised and the authors ought to be congratulated for their intention to scrutinize their initial findings. Unfortunately, however, several unanticipated problems arose which substantially limited possible conclusions from this study. The first obstacle was that the set target for fasting blood glucose of 5–7 mmol/L for group 1 was never reached. More dramatically, the level of blood glucose control ended up being identical in all three study groups, and this despite the fact that...
more patients in group 1 received insulin, albeit at low and infrequent dosages. The second issue was that patient recruitment did not proceed as planned which, in view of the limited funding, was problematic. For these reasons, the study was stopped early, when only fewer than half of the planned number of patients had been included. There were no differences in morbidity or mortality among the three study groups.

What do these results tell us and how are they reconciled with recent insights in the benefits of insulin therapy and blood glucose control in acutely ill patients?

First, the data clearly show that 24 h of GIK infusion did not affect outcome after AMI and thus that the benefit of the intervention in DIGAMI 1 is explained by the better acute and/or chronic blood glucose control and not by GIK. Secondly, although DIGAMI 2 was designed to assess the impact of tight blood glucose control, the protocol failed to result in a lower blood glucose concentration in group 1 despite more patients receiving insulin. All three groups remained similarly hyperglycaemic throughout the study with an average blood glucose level of around 8.5 mmol/L. Nevertheless, multivariate logistic regression analysis pointed out that the severity of hyperglycaemia was independently associated with the risk of adverse outcome. Hence, the data also clearly indicate that the administration of insulin in the days and months following AMI without achieving better glucose control does not improve outcome. In contrast, two previous randomized controlled trials assessing the impact of intensive insulin therapy on outcome of acute illnesses, that did achieve the separation of blood glucose control in the two study arms, did reveal a significantly better outcome with intensive insulin therapy. These studies are the DIGAMI 1, as described earlier, and the ‘intensive insulin therapy in intensive care’ study. The latter study included patients after surgery or trauma, 60% of those were after high-risk cardiac surgery. Intensive insulin therapy in this study resulted in average blood glucose levels of 5.7 mmol/L during intensive care, vs. 8.5 mmol/L in the conventional group, and reduced hospital mortality by 34%. Although the time window and the set target level of blood glucose control for the intervention group differed substantially between DIGAMI 1 and the ‘insulin in intensive care’ study, they both succeeded in separating the two study groups for the level of blood glucose. A post hoc analysis of the intensive care study clearly indicated that it was precisely the tight blood glucose control, and not the amount of insulin administered, which explained the mortality benefit of intensive insulin therapy in this patient population. In fact, there was no threshold below which no further improvement occurred, suggesting that the closer to normal blood glucose is controlled, the better the outcome. Recent work further revealed that also several morbidity benefits of intensive insulin therapy, such as protection of the central and peripheral nervous system of brain-injured patients, the protection of mitochondrial integrity and function, the prevention of sepsis, anaemia, and organ failure in intensive care patients, appear to be mediated by the prevention of glucose toxicity rather than by insulin receptor-mediated signals. Also for beneficial effects of insulin on the myocardium, the prevention of glucose toxicity may thus be crucial, rather than the switch in fuel utilization, as was originally proposed by Opie. Alternatively, however, insulin-receptor mediated metabolic changes could still be involved but may either require a dose of insulin which is higher, high enough to overcome the insulin resistance, or may be antagonized by concomitant, persisting hyperglycaemia. The latter possibility is underbuilt by the observation that anti-inflammatory effects of insulin, for example, are totally abrogated by concomitant hyperglycaemia. An example of another effect of insulin that follows, but may act independent of the tight glycaemic control, is the effect on lipid metabolism. In stressed, severely ill patients, dyslipidaemia is present (high levels of triglycerides and low levels of HDL- and LDL-cholesterol) which is restored, at least partially, when insulin therapy is titrated to normoglycaemia. Lipoproteins co-ordinate the transportation of lipid components (cholesterol, triglycerides, phospholipids, lipid-soluble vitamins) and scavenge toxins whereby they may prevent death in animal models. The lowering of circulating triglycerides is in line with Opie’s proposed shift of lipid-substrate away from injured/hypoperfused cells, such as cardiomyocytes in AMI, to the adipose storage tissue. However, such effects on lipid metabolism only occur when the dose of insulin is high enough to overcome insulin resistance. Absence of an effect on blood glucose unveils absence of a lipid effect. But when blood glucose is lowered, the concomitant improvement of the deranged lipidaemia appears to explain a significant part of the survival benefit and may even surpass the effect of glycaemic control.

In summary, available data indicate that the prevention of glucose toxicity is the effective part of the ‘intensive insulin therapy’, or, alternatively, that the insulin dose in DIGAMI 2 was not high enough to achieve the other glucose-independent effects. If the former is the case, then other, easier and perhaps safer ways of glycaemic control should urgently be tested in this setting, as correctly alluded to by Malmberg et al. If, however, the other metabolic/systemic effects of insulin accompanying the glycaemic control do play a major role, then these alternative glucose-lowering strategies may fail to show benefit in AMI or other forms of acute ischaemia/reperfusion injuries. Future studies should be carefully designed to assess the relative impact of both actions. Until results of such studies are available, the current data point to synergy between the prevention of glucose toxicity on the one hand and the distinct insulin-receptor mediated effects on the other. Future development of tools that will allow frequent and precise (non-invasive) measurement of blood glucose levels and, eventually, of an automated system for insulin-titrated tight blood glucose control will be of utmost importance for future research and for correct and safe implementation of the intervention. We anxiously await the development and validation of such devices.
References


