This editorial refers to ‘Meta-analysis of admission hyperglycaemia in acute myocardial infarction patients treated with primary angioplasty: a cause or a marker of mortality’, by Kuljit Singh et al., on page 220.

Acute myocardial infarction (AMI) is a leading cause of morbidity and mortality in worldwide population. Patients admitted to Emergency Care Unit and/or Intensive Coronary Care Unit remain at high risk of recurrent events, hospitalization, and cardiovascular death. In last decades, diabetic mellitus (DM) affected patients have been diagnosed as one of four patients with AMI. New randomized controlled trials have investigated pharmacologic and non-pharmacologic management strategies to reduce all-cause mortality for patients with diabetes and AMI. In fact, the International American and European guidelines have reported evidence-based recommendations for treating AMI and DM. Parallel to an innovative and broader use of anti-ischaemic and anti-remodelling drugs to treat AMI, the primary angioplasty (primary percutaneous coronary intervention [pPCI]) therapeutic development has drastically reduced the mortality in affected patients. The not discusssable percutaneous coronary intervention (PCI) impact in AMI patients prognosis is not so great as expected in DM patients. Moreover, we have to consider DM patients, as a population of patients with different clinical characteristics, that render more difficult the best clinical pharmacological and non-pharmacological treatment (pPCI) to reduce worse prognosis during AMI. For these reasons, we have to improve current clinical diagnosis and treatment, and planning future strategies for DM affected by AMI.

The current study

In the current study, Singh and co-workers evidenced that ‘despite rapid revascularization and treatment of hyperglycaemia, patients with acute hyperglycaemia (AH) continue to have worse prognosis, and that AH is most likely a predictor rather than cause of high mortality. In AH, the presence of relatively higher clinical and angiographic predictors of mortality is the reason for worse outcomes in this sub-group of patients’. We have to recognize that this is a great clinical impact study. However, to get a more complete picture on the usefulness of glycaemic control during the acute event, I believe that the data presented by the authors should also be analysed based on the glycaemic targets achieved by the various trials. We must point out that we have no glycaemic targets suggested by the guidelines. In 2001, authors have assessed the effect of the normalization of blood glucose with insulin infusion on mortality in critical patients hospitalized in intensive care units. In this study, treated patients were divided into two groups: group intensive insulin infusion vs. the conventional group. Both groups have reached the target, defined as survival in intensive units in the hospital, but there was a net increase in survival in the population treated with insulin intensively. The effectiveness of intensive treatment with insulin has been investigated in NICE study. In this multi-centre study, authors have enrolled 3000 patients in the intensive glycaemic target (80–110 mg/dL) and 3000 in the conventional group (glycaemic target > 180 mg/dL). This multi-centre study showed that the control group had a mortality rate lower than the group treated intensively, and that there is not additional benefit attributable to lower glucose levels in the blood below the range of ~140–180 mg/dL. On other hand, I agree with the authors that hyperglycaemia has been shown to be detrimental at the cellular level, as KATP function and oxidative stress. For these observations, it may be interesting to investigate and to report also other effects such as the increase of inflammation, the reduction of angiogenic factors, and finally the increase in the pro-thrombotic activity (Figure 1). In fact, the inflammatory burden in the peri-infarct region is associated with worse short- and mid-term outcomes because the inflammatory response in this region probably may amplify myocardial necrosis. In this context, we have shown that hyperglycaemic stress during MI is associated with increased levels of some inflammatory markers, including C-reactive protein and interleukin-18, and enhanced expression of natural killer cells (CD16/CD56) associated with reduced expression of some T cells (CD152) known to limit the immune process in patients presenting with AMI. These results fit with animal...
studies showing increased levels of pro-inflammatory cytokines (tumour necrosis factor-α, interleukin-6, and interleukin-18) and peroxynitrite (an index of oxidative stress) in the heart tissue of hyperglycaemic mice. As observed in another study, the glucose levels correlated strictly with myocardial apoptosis and greater infarct size. Finally, analysis of ventricular biopsy specimens obtained from type 2 diabetic patients presented with acute coronary syndromes and undergoing coronary bypass surgery have shown reduced expression of some important angiogenic factors, such hypoxia-inducible factor-1α and vascular endothelial growth factor, compared with non-diabetic patients with ischaemia. All these results shown us that hyperglycaemia may amplify the inflammatory and oxidative responses pathways during myocardial ischaemia. Moreover, hyperglycaemia may lead to a reduced angiogenesis during myocardial ischaemia and AMI, affecting the regenerative potential of myocardium during acute infarction. Considering all together, these study observations report us that hyperglycaemia, altering inflammatory, and oxidative stress in myocardial acute infarcted tissue may lead to an abnormal myocardial damage extension size. For all these known and reported molecular aspects, AH

Figure 1 A schematic representation of different myocardial ischaemic phases. From upper to lower part denotes all relevant aspects investigated in this article, in the sequence divided as: abnormal glucose metabolism, coronary microvascular function, acute myocardial infarction, myocardial salvage, and myocardial infarction extension. These aspects are consequently related one by one. The abnormal glucose metabolism is a triggering mechanism that affecting coronary microvascular function by inflammation, apoptosis, oxidative processes, and angiogenesis may lead to acute myocardial infarction and to myocardial muscle damage entity (myocardial salvage vs. myocardial infarction extension). All the aspects, as discussed before, are related to complex molecular pathways as: SIRT1 signalling via platelet-activating factor receptor activation, inflammatory immune process, nitric oxide synthase, angiogenic factors, endothelial progenitor cell level and differentiation, endothelial progenitor cell numbers, heart inflammation, and remodelling. The abnormal glucose metabolism, controlling the coronary microvascular function, may regulate all these processes. These processes, differently up- or down-regulation expressed, may contribute more and/or less to myocardial muscle savage and/or damage extension, during acute myocardial infarction. Controlling these molecular pathways may represent the probability to save or to extent the myocardial infarction area size during myocardial infarction.
may lead to the investigated common phenotypic effect, represented by worse prognosis during AMI.\textsuperscript{4}

**Clinical implications and future perspectives**

The results of the study by Singh et al.\textsuperscript{4} show that despite rapid PCI intervention and treatment of hyperglycaemia, AH at hospital admission is a worse prognosis predictor risk factor. This relevant aspect may be due to the presence of higher clinical and angiographic predictors of mortality that may explain the reason for worse outcomes in this sub-group of patients. If preventive therapies may control all these complexes risk factors, a necessary future step may be represented by introducing new therapies to balance the inflammatory acute and oxidative-reductive stress in AH patients during AMI. In the next, the pPCI added to a better glycemic control (more intensive pharmacological treatment and/or lower glycaemic target), may be associated to anti-inflammatory and antioxidative therapies. The modulation of oxidative stress and the inflammatory responses to AMI in AH patients could represent the best approach to promote angiogenesis reducing apoptosis and myocardial infarct size. Until now we have not relevant large randomized clinical trials to investigate all these complex molecular, metabolic, and clinical aspects.

Controlling these molecular pathways may represent the probability to save the myocardial infarction area size extension during myocardial infarction. The implementation of new evidence-based therapy may represent a necessary step to reduce in future the impact of hyperglycaemia during AMI in pPCI-treated patients. Our future hope is to treat as best we can the hyperglycaemia during AMI, to save more myocardial muscle during AMI and to improve clinical outcomes.

**References**


