Letters to the Editor
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Clinical trials with ST-segment elevation myocardial infarction

It is with great interest that we read the article ‘Outcomes of patients in clinical trials with ST-segment elevation myocardial infarction among countries with different gross national incomes’ by Orlandini et al.1 We feel obliged to point out that at least what regards Poland as one of the countries with medium gross national income (GNI), some of the data presented are of purely historical value only. The authors state that in the years 1995–2002, only 10.9% of patients participating in clinical trials in medium GNI countries underwent PCI. In Poland, since 2001, the number of STEMI patients treated with primary PCI soared, reaching 22 706 per year in 2005,2 which constitute 34% of all PCI procedures. Given that—according to a recent survey—the incidence of hospitalized STEMI in Poland is between 1000 and 1200 cases per million people each year3 and that the country’s population is ca. 38 million, this means that nowadays between 50% and 60% of all hospitalized patients with STEMI are reperfused with primary PCI. As of April 2006, there were 59 Cathlabs throughout our country that provided round-the-clock PCI service, many of them with an yearly volume of 600–700 primary PCI. Pooled data from Poland’s hospitals performing primary PCI in year 2003 demonstrate 30-day mortality of 7.0% including patients with cardiogenic shock and 4.7% in patients with no shock.5 It is, at present, unlikely that there could be any underusage of invasive treatment of STEMI in Poland to adversely affect the outcome as compared with high GNI countries. Still, the authors may be right when speculating (p. 531) that in medium- or low-GNI countries, investigators may be ‘including a higher risk subset of patients’ and that ‘significantly greater proportion of patients (…) were randomized’ as compared with high-GNI countries. As a matter of fact, this brings any clinical trial closer to real life and should make its results more relevant for clinical practice.

References

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Glucose, insulin, and acute myocardial infarction

Goyal et al.1 reported that higher plasma glucose levels after acute myocardial infarction (AMI) predicts higher mortality in non-diabetic patients, which is not surprising as glucose is pro-inflammatory and insulin has anti-inflammatory actions. Glucose–insulin–potassium (GIK) regimen improves myocardial function during endotoxic shock2,3 and this beneficial action has been attributed to insulin2,4 because of its inhibitory action on tumour necrosis factor-α (TNF-α), macrophage migration inhibitory factor (MIF), superoxide anion production, and increase in the synthesis of eNO4,5 and anti-inflammatory cytokines.2 CREATE-ECLA Trial failed to reproduce the beneficial effects of GIK regimen in AMI,6 as the mean serum glucose levels were 162, 187, and 155 mg% in the GIK infusion group at baseline, 6 h, and 24 h after randomization when compared with 162, 148, and 135 mg% in the control, respectively. The higher serum glucose levels in the GIK group could be responsible for the negative results observed in the CREATE-ECLA trial, as glucose has pro-inflammatory actions, whereas insulin is anti-inflammatory in nature.2,4.5 In fact, lack of increase in mortality in the GIK group, despite the higher serum glucose levels could be due to the anti-inflammatory actions of insulin. Based on the results from the CARDINAL study, I propose that GIK regimen should be given in such a manner that not only plasma glucose levels are maintained ~80–100 mg%, but also production of thrombolytics (inclusion criteria) and not with PCI.

Finally, our analysis shows the differences among different countries in the context of clinical trials and stresses the importance of running them worldwide.

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Clinical trials with ST-segment elevation myocardial infarction: reply

I would like to thank Dr Maciej Karcz and Dr Adam Witkowski for their interest in our article. Their data are based on registries of the Polish Cardiac Society where an increase in Primary Percutaneous Coronary Intervention (PCI) has been observed in patients with STEMI. Nevertheless, we believe that these data do not affect our conclusions because our manuscript was only about mortality in STEMI patients included in clinical trials and our data should not be extrapolated to all STEMI patients in a whole country. Besides, we believe that the differences we observed among different GNI are related more to the biases of the population selected than to a real difference in the whole population. Moreover, it is likely that the proportion of patients treated with PCI in Poland was different from that observed in our analysis as all the trials in our article but one (randomization to control or Glucose-Insulin Potassium) required patients to be treated with
pro-inflammatory cytokines is suppressed and synthesis and release of anti-inflammatory cytokines is enhanced, and failure to do so would give negative results. Since, there could be individual variations in response to the anti-inflammatory actions of insulin in response to GIK regimen this has to be given due weightage. I suggest that the CREATE-ECLA trial results would have been positive, provided the investigators infused adequate amounts of insulin to keep plasma glucose levels ≤110 mg%. This is supported by the observation that intensive insulin treatment improved survival of the critically ill surgical patients and those without diabetes mellitus who had blood glucose concentrations 110–144 mg% (6.1–8.0 mmol/L) had a 3.9-fold higher risk of death than patients without diabetes who had lower glucose concentrations.

Pyruvate, the intermediate product of glucose metabolism, protects myocardium, intestines, hepatic, and renal tissues from reactive oxygen species and cytokines, and ischemia/reperfusion-induced injury. Pyruvate-inhibited TNF-α production, reduced circulating HMGB1 (high-mobility group B1) levels and NF-κB signalling pathways, decreased COX-2 (cyclo-oxygenase-2), and iNOS (inducible nitric oxide synthase), and increased IL-10, pyruvate, and various free radicals, quenched IL-6 mRNA expression in animal models with shock, and suppressed IL-10, pyruvate, and various free radicals need to be measured in addition to plasma glucose concentrations to ensure that GIK regimen adopted is adequate to ensure its beneficial actions. In the absence of such a comprehensive assessment, it is not prudent to discard GIK regimen in the treatment of AMI as being not beneficial.

References

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Glucose, insulin, and acute myocardial infarction: reply

Dr Das comments that the association between the failure of glucose levels to drop during hospitalization and higher mortality following acute myocardial infarction (AMI) in the CARDINAL study is consistent with basic and translational work demonstrating the pro-inflammatory effects of glucose. In addition to its pro-inflammatory effects, glucose may also directly contribute to the pathogenesis of AMI by promoting thrombosis and impairing vasoreactivity.

We and others concur that the maximal benefit of insulin therapy in AMI may be realized only when normalization of glucose levels have been achieved and maintained. This hypothesis is also supported by a meta-analysis of previous trials of insulin therapy in critically ill patients that demonstrated a benefit among trials in which insulin was dosed to achieve a glucose target, but not among trials in which a glucose target was not specified. Although it would be interesting to measure inflammatory markers during insulin infusion in AMI, it is currently impractical to dose insulin based on these markers, as they are markedly elevated in the setting of AMI, few assays are available at the point of care, and the dose of insulin would be necessarily limited by the occurrence of hypoglycaemia. It is our understanding that investigators are already planning a large, simple trial of intensive insulin therapy targeting normoglycaemia in AMI to determine whether this strategy improves clinical outcomes.

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