Glucose-lowering therapy after myocardial infarction: more questions than answers

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This editorial refers to ‘The impact of glucose-lowering treatment on long-term prognosis in patients with type 2 diabetes and myocardial infarction: a report from the DIGAMI 2 trial’ by L.G. Mellbin et al., on page 166 and ‘Glucose lowering treatment in patients with coronary artery disease is prognostically important not only in established but also in newly detected diabetes mellitus: a report from the Euro Heart Survey on Diabetes and the Heart’ by M. Alselmino et al.,† on page 177.

The DIGAMI I study demonstrated in 620 diabetic patients with acute myocardial infarction that insulin–glucose infusion followed by multidose subcutaneous insulin decreases long-term mortality as compared with standard therapy.¹ About 10 years later, the DIGAMI II study reported on 1253 diabetic patients with acute myocardial infarction allocated to three treatment arms including acute insulin–glucose infusion followed by insulin-based long-term glucose control (group 1), insulin–glucose infusion followed by standard glucose control (group 2), and routine metabolic management according to local practice (group 3).² Surprisingly, neither all-cause mortality nor morbidity (stroke and non-fatal reinfarctions) differed between the three groups.³ Mellbin and co-workers have published a post hoc analysis of the DIGAMI II study suggesting that insulin treatment may actually be inferior to conventional management with oral glucose-lowering drugs.⁴ A similar conclusion is provided by Anselmino and co-workers who analysed patients from the Euro Heart Survey on Diabetes and the Heart.⁵

While the messages of the three DIGAMI publications appear to be quite contradictory, they have one important observation in common: good glucose control seems to be an important predictor of long-term mortality in patients with acute myocardial infarction. Indeed, those subgroups with best metabolic control in the DIGAMI I and II studies displayed the most favourable long-term outcome.⁶ While this observation is intuitively quite reasonable, it is characteristic for the research on diabetic patients with myocardial infarction to be only indirectly supported by current evidence from studies that tested various drug regimens.

The lessons from the DIGAMI studies have been subject to multiple comments in the European Heart Journal.⁶,⁷ Now, the post hoc analysis of the same data set revitalizes this debate once again. In particular, diabetic patients discharged after myocardial infarction on insulin treatment experienced a significantly increased risk of non-fatal myocardial infarction and non-fatal stroke as compared with those on metformin therapy. Differences in mortality, however, were not found between the two groups. In the DIGAMI II study the total numbers of fatal and non-fatal events were actually about the same (206 deaths, 216 non-fatal events) such that the power to detect any difference should have been comparable for these end-points. This difference in outcome between fatal and non-fatal events within a post hoc analysis of the DIGAMI II study, along with the differences in outcome after insulin treatment in the DIGAMI I and II studies, complicate the explanation of those results.

Moreover, it should be mentioned that the vast majority of DIGAMI II patients in the present post hoc analysis were not randomized to insulin treatment or other modes of glucose-lowering therapy. The authors tried to overcome this limitation by applying multivariate statistical models and thereby correcting for differences in baseline variables, co-medication, and co-morbidity. This approach, however, clearly falls short of substituting for a prospective randomization process. Furthermore, physicians may have selected insulin treatment in patients with longer duration or impaired therapeutic response to other treatment modalities. Thus, insulin treatment in the current epidemiological analysis of a clinical study may partially reflect a medication bias that identified larger numbers of high risk patients. Indeed, insulin treatment is often instituted when other glucose-lowering medication no longer accomplishes target glucose values.

In agreement with the findings of Mellbin and co-workers³, Anselmino et al, report epidemiological data from a survey including 4676 patients with coronary artery disease from several European countries. About one-third of these patients had known diabetes mellitus; another 450 presented with a newly detected...
diabetes mellitus. The highest event rate was observed in patients with known diabetes on insulin treatment. A second observation from this study was the finding that a new diagnosis of diabetes mellitus without initiation of a respective glucose-lowering therapy appears to be associated with detrimental outcome in the long-term follow-up. As with the post hoc analysis of DIGAMI II, such a study design opens the door for all sorts of treatment bias. In particular, the authors emphasize regional differences in treatment modalities as well as patient characteristics that differ between diabetics treated with or without insulin. Likewise, one may ask the question why some patients received the diagnosis of diabetes, but no consecutive therapy. Nevertheless, this rather large study offers a good overview of current treatment modalities for glucose-lowering in European patients with coronary artery disease and may, thus, help to guide future studies.

Despite the wealth of data provided by Mellbin et al. diabetes mellitus remains a stepchild in the treatment of patients with acute myocardial infarction. Another example for this cheerless conclusion comes from meta-analyses studying the relationship between rosiglitazone and the risk of heart failure and myocardial infarction. The task for the future is clear. We need more, well-designed clinical trials comparing insulin, metformin, insulin sensitizers, dipeptidyl peptidase 4 (DPP-4) inhibitors, and cannabinoid-1 receptor blockers in patients with diabetes in the setting of acute myocardial infarction. The reports of Mellbin and Anselmino provide a clear framework to design such studies.

The European Society of Cardiology (ESC) and the European Association for the Study of Diabetes (EASD) have identified the necessity and accepted the challenge of improving care for diabetes mellitus and coronary artery disease by developing a joint, evidence-based guideline that was published very recently in this journal. Quoting these guidelines, risk reduction of patients with coronary artery disease and diabetes mellitus is accomplished very well by non-pharmacological interventions, including structured patient education and lifestyle interventions. Furthermore, a comprehensive pharmacological approach aimed at a tight control of dyslipidemia, arterial hypertension, and blood glucose levels is pivotal. Regarding low-density protein (LDL) cholesterol, statin therapy should be initiated with a treatment target of 70–77 mg/dL in diabetic patients with coronary artery disease. This class I recommendation (level of evidence B) is based on data from a large number of secondary prevention trials using statins. Moreover, the benefits of tight blood pressure control with a target below 130/80 mmHg have resulted in a class I recommendation (level of evidence B). Recent data from the ADVANCE collaboration group strongly support this recommendation.

Regarding glycaemic control, however, the picture is not so clear. Despite compelling evidence that diabetic microangiopathy and neuropathy can be reduced by tight glycaemic control, the relationship between hyperglycaemia and macroangiopathy is—although suggestive—much less well established. More importantly, the treatment approach to achieve glycaemic control is not well specified and, in contrast to the treatment of dyslipidemia and hypertension, cannot be based on solid evidence. For example, metformin therapy in overweight diabetic subjects is primarily based on the UKPDS 34 study and resulted in a class IIa recommendation. The work presented by Mellbin et al. and Anselmino et al. as well as a substudy from the BARI investigators, now provides further evidence for considering early treatment with metformin in patients with diabetes. Furthermore, early initiation of insulin therapy in diabetics failing to achieve glucose targets has only received a class IIb, level of evidence C recommendation, while the impact of late (as late as possible) initiation of insulin therapy remains rather unknown. Taken together, glucose-lowering therapy after myocardial infarction offers more questions than answers. It’s time to change gear, and the studies by both Mellbin et al. and Anselmino et al. are a most welcome starting point.

Conflict of interest: none declared.

References


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**CLINICAL VIGNETTE**

**Giant left ventricular pseudoaneurysm: a rare complication following left ventricular rupture caused by myocardial infarction**

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Six months after a myocardial infarction, a 62-year-old man was admitted with exertional dyspnoea (NYHA Class III).

Transthoracic echocardiography revealed a large pseudoaneurysm of the left ventricular (LV) free wall and a severe mitral regurgitation due to leaflet tethering caused by the altered ventricular geometry (Panel A).

Magnetic resonance imaging (MRI) demonstrated a thin aneurysmal wall (2–3 mm) and a maximum internal end-systolic pseudoaneurysmal dimension of $87 \times 56 \times 84$ mm (Panel B). Moreover, a thrombus formation and an almost completely scarred wall of the pseudoaneurysm were documented by late enhancement (Panel C).

Coronary angiography revealed subtotal stenoses of the left circumflex and right coronary arteries; ventricular angiography was not performed because of the potential risk of pseudoaneurysmal rupture.

During subsequent heart surgery (Panel D), the pseudoaneurysm was incised, its fibrous wall was resected, and the ruptured LV myocardium was sutured with a patch plasty. Moreover, the mitral valve needed to be replaced with a mechanical prosthesis, and a myocardial revascularization of the right coronary artery was performed. The patient made an uneventful recovery.

Although acute free intrapericardial rupture usually causes cardiac tamponade and death, LV pseudoaneurysm formation may be a very uncommon finding in chronic myocardial infarction.

Panel A. Four-chamber view demonstrating the giant pseudoaneurysm (asterisk); LV: left ventricle, LA: left atrium.

Panel B. Magnetic resonance imaging (1.5 T balanced Turbo-Field-Echo, b-TFE): four-chamber view showing end-systolic pseudoaneurysmal diameters of $87 \times 56 \times 84$ mm (asterisk), and the jet of the severe mitral regurgitation.

Panel C. Magnetic resonance imaging (1.5 T; balanced TFE): short-axis view demonstrating the myocardial scar of the entire wall of the pseudoaneurysm by late enhancement, and the mural thrombus (see arrow).

Panel D. Intraoperative finding: pseudoaneurysmal sack shortly before incision during operative resection. (Courtesy of K. Minami, Department of Cardiovascular Surgery, Nihon University School of Medicine, Japan).

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