Spotlight on comorbidities in STEMI patients

Mortality for myocardial infarction is at its lowest historical level for 20 years, but the decline of STEMI-associated mortality stopped in 2015. In general, STEMI patients benefit from an improved organization of care, new drugs (eg, P2Y12 inhibitors such as prasugrel and ticagrelor), greater experience in percutaneous coronary intervention (PCI) and shorter times to reperfusion. Technical advantages consist, for example, of improved drug-eluting stents. Of course, the enhanced use of primary and secondary prevention (statins, beta blockers and RAAS inhibition) contributes to the decrease in mortality. In special indications such as cardiogenic shock, additional tools like microaxial pumps or extracorporeal life might provide additional benefit. In diabetes, several new drugs such as sodium glucose cotransport 2 inhibitors, glucagon-like peptide 1 agonists and DPP-4 inhibitors are safe and had shown beneficial effects in cardiovascular diseases. On the contrary, insulin worsens outcome after myocardial infarction. Overall, despite many efforts, for comorbidities in general medicine we still do not have specific treatment options to address specifically the worse impact of comorbidities in the acute setting of STEMI, such as modifiers of a metabolic switch in myocardial ischaemia. Comorbidities such as anaemia, renal failure and hyperglycaemia seem the next frontier to investigate their impact on mortality in acute myocardial infarction (Figure 1).

Anaemia affects at least 20% of STEMI patients and contributes in a highly significant manner to STEMI mortality. For example, a baseline haemoglobin value <10 g/dL results in a nearly 10 times higher mortality rate. Anaemia is independently associated with adverse outcome. However, unless there is ongoing ischaemia, guidelines recommend transfusion only when the haemoglobin level is <8 mg/dL, but retrospective analyses demonstrate an increased risk for re-infarction after blood transfusion. Iron deficiency results in mitochondrial injury, and intravenous iron administration is potentially associated with improved infarct healing and remodelling although reliable data are lacking. Erythropoietin α was thought to offer anti-apoptotic and tissue-protective effects, but its application was associated with higher rates of adverse cardiovascular events without any beneficial effect in STEMI. Low-dose erythropoietin is less dangerous, but without any effect on cardiac function after STEMI.

Renal failure, both in the form of chronic kidney disease and as acute kidney injury, is associated with an impaired outcome in STEMI. Renal dysfunction is a common comorbidity and affects 30%-40% of patients with myocardial infarction resulting in a worse prognosis. However, apart from ensuring sufficient hydration and limiting the total amount of contrast media, there are no evidenced-based measures against contrast-induced nephropathy. Recently, the combination of a fluid pathway resistance modulator and an automatic power injection system was released, promising a reduction of the needed contrast media without a loss in image quality.

Stress hyperglycaemia is defined as elevated levels of fasting blood glucose levels occurring in critically ill, but without the preceding diagnosis of diabetes. It affects up to 30%-80% of patients in various hospital cohorts and is strongly associated with a poor in-hospital prognosis after myocardial infarction. This observation is independent of other risk factors, such as the infarct size. Stress hyperglycaemia in myocardial infarction is not fully understood. In general, two different types of stress hyperglycaemia must be distinguished: first, patients with underlying glucose intolerance and second, patients with severe stress without glucose intolerance. In particular, the second group without glucose intolerance, serum cortisol is one of the major determinants for stress hyperglycaemia. Cortisol levels are an independent predictor for mortality and they correlate with the severity of myocardial infarction. Fasting glucose is of great importance in nondiabetic patients predicting independently long-term mortality, but it is of very limited use for risk prediction in diabetic patients. In line with this, there is a much stronger relationship between hyperglycaemia and myocardial injury in nondiabetic than in diabetic patients.

Hyperglycaemia directly affects both the platelet functions and fibrin structure. In fact, these hyperglycaemic thrombi display higher levels of MicroRNA-33, increased reactive oxygen species, and pro-inflammatory/pro-coagulable markers, which results in a significantly augmented pro-coagulable state of the thrombi. This may explain why thrombus aspiration shows some beneficial effects in patients with hyperglycaemia. Furthermore, there is a strong link between heart failure and insulin resistance with reciprocal interference. Correcting hyperglycaemia is not that simple: there is a U-shaped curve between glucose levels and death in STEMI and in critically ill patients. Current guidelines recommend considering a glucose-lowering in patients with glucose levels above 180-200 mg/dL but advise strictly to avoid hypoglycaemia. However, patients in an acute phase with longer existing diabetes, older age, more comorbidities or advanced cardiovascular disease might benefit from a less strict glucose control.

In this context, the paper by Shitole et al published in this journal deals with a very important question: does a cautious insulin
treatment provide any benefit in STEMI? Shitole et al used a continuous insulin infusion therapy (CIIT) with a standardized infusion pump. A fingerstick glucose measurement was performed every hour, and the administration rate was adjusted accordingly. Unfortunately, the definition of hyperglycaemia changed during the study period: initially (2008-2009), hyperglycaemia was defined as ≥150 mg/dL with very strict target glucose levels of 80-120 mg/dL. In the beginning of 2010, the definition was raised to ≥180 mg/dL with an adjusted glucose target of 100-180 mg/dL. It is important to emphasize that preexisting diabetes was no exclusion criterion. In consequence, the study cohort included both patients with stress hyperglycaemia with and without diabetes or glucose intolerance. Therefore, the protocol mixed two groups with some major differences.

For analysis, patients were divided into three different groups according to their initial glucose level (<140 mg/dL; 140-179 mg/dL or ≥180 mg/dL). Only at this point, stress hyperglycaemia was detached from preexisting diabetes (in-hospital HbA1c <6.5%, no history of diabetes, initial glucose ≥180 mg/dL). Of note, 32.6% of all patients and 67.5% in patients with a glucose level of ≥180 mg/dL suffered from preexisting diabetes. Regarding short- and long-term outcomes, results were inconsistent, showing a trend towards negative findings for the group with the highest glucose levels. This particular group was subdivided into a group with CIIT (“interventional” group) and without CIIT (“control” group). Both groups had some significant differences. Most importantly, preexisting diabetes was found 82.14% in the “interventional” group, but only 60.74% in the “control” group. Technically, CIIT was successful, with a more efficient decline of glucose levels. As might have been expected, this “more effective” glucose-lowering resulted in a significant rise in hypoglycaemic episodes at all time points. However, the occurrence of hypoglycaemia was not related to a negative outcome. CIIT resulted in >threefold and >twofold increased risks in-hospital and 1-year mortality, respectively. Interestingly, there was no difference in patients who were treated according to the definitions from 2008/2009 and from 2010. Finally, the subgroup of stress hyperglycaemia (12.6% of all patients) demonstrated no significant difference towards patients with preexisting diabetes. Unfortunately, no additional data are presented regarding this specific subgroup.

This paper offers many new insights into STEMI and its comorbidities: patients were recruited in a socioeconomically disadvantaged urban area; this cohort is not a highly selected study population, but it reflects life conditions of a significant number of people. CIIT did not result in the breakthrough in the treatment of the comorbidity of hyperglycaemia in STEMI.

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