

EDITORIAL

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 2015.¹ 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.² In special indications such as cardiogenic shock, additional tools like microaxial pumps or extracorporeal life support might provide additional benefit.³ 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.⁴⁻⁶ On the contrary, insulin worsens outcome after myocardial infarction.⁷ 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 as risk modifiers mortality in acute myocardial infarction (Figure 1).

Anaemia affects at least 20% of STEMI patients⁸ 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.⁹ 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,¹⁰ but retrospective analyses demonstrate an increased risk for re-infarction after blood transfusion.¹¹ Iron deficiency results in mitochondrial injury, and intravenous iron administration is potentially associated with improved infarct healing and remodelling although reliable data are lacking.¹² 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.¹³ Low-dose erythropoietin is less dangerous, but without any effect on cardiac function after STEMI.¹⁴

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.¹⁵ 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.¹⁶

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.¹⁷ 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.¹⁸ In particular, the second group without glucose intolerance, serum cortisol is one of the major determinants for stress hyperglycaemia.¹⁹ Cortisol levels are an independent predictor for mortality and they correlate with the severity of myocardial infarction.²⁰ 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.²¹ In line with this, there is a much stronger relationship between hyperglycaemia and myocardial injury in nondiabetic than in diabetic patients.²²

Hyperglycaemia directly affects both the platelet functions and fibrin structure.²³ 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.²⁴ This may explain why thrombus aspiration shows some beneficial effects in patients with hyperglycaemia.²⁵ Furthermore, there is a strong link between heart failure and insulin resistance with reciprocal interference.²⁶ Correcting hyperglycaemia is not that simple: there is a U-shaped curve between glucose levels and death in STEMI²⁷ and in critically ill patients.²⁸ 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.^{29,30}

In this context, the paper by Shitole et al published in this journal deals with a very important question: does a cautious insulin

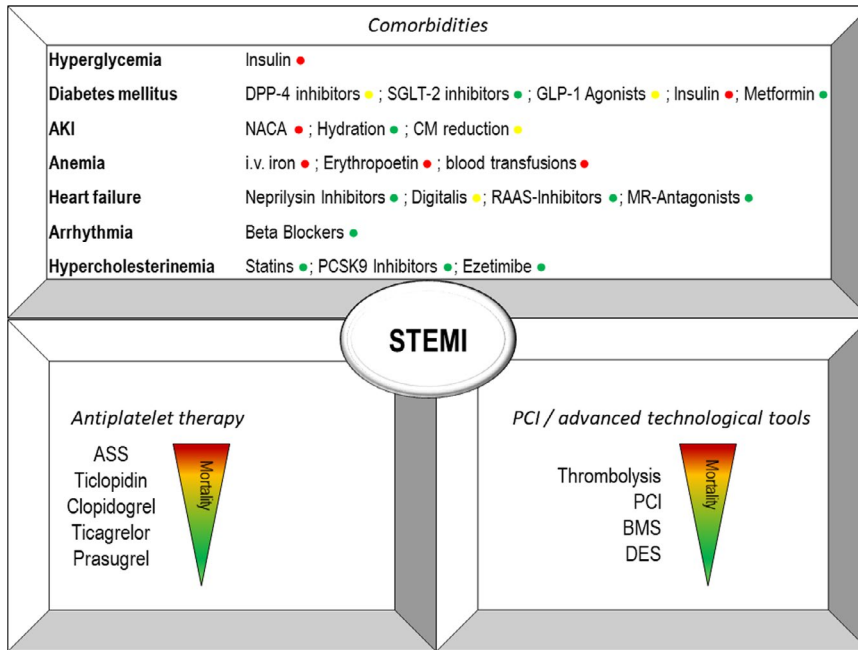


FIGURE 1 Overview of current therapy approaches to STEMI-treatment with the degree of evidence (green = good, yellow = moderate, red = bad)

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 had 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.

ACKNOWLEDGEMENTS

Research was funded by the German Research Foundation (DFG SFB1116 TP B06 to CJ and MK).

DISCLOSURES

None.

Raphael Romano Bruno 
Malte Kelm
Christian Jung

Division of Cardiology, Pulmonology, and Vascular Medicine, Medical Faculty, University Hospital Düsseldorf, Düsseldorf, Germany

Correspondence

Christian Jung, University Hospital Düsseldorf, Düsseldorf, Germany.
Email: christian.jung@med.uni-duesseldorf.de

ORCID

Raphael Romano Bruno  <https://orcid.org/0000-0003-3776-3530>

REFERENCES

- Puymirat E, Simon T, Cayla G, et al. Acute myocardial infarction: changes in patient characteristics, management, and 6-month outcomes over a period of 20 years in the FAST-MI Program (French Registry of Acute ST-Elevation or Non-ST-Elevation Myocardial Infarction) 1995 to 2015. *Circulation*. 2017;136(20):1908-1919.
- Szummer K, Jernberg T, Wallentin L. From early pharmacology to recent pharmacology interventions in acute coronary syndromes: JACC state-of-the-art review. *J Am Coll Cardiol*. 2019;74(12):1618-1636.
- Huang C-C, Hsu J-C, Wu Y-W, et al. Implementation of extracorporeal membrane oxygenation before primary percutaneous coronary intervention may improve the survival of patients with ST-segment elevation myocardial infarction and refractory cardiogenic shock. *Int J Cardiol*. 2018;269:45-50.
- Wang M-T, Lin S-C, Tang P-L, et al. The impact of DPP-4 inhibitors on long-term survival among diabetic patients after first acute myocardial infarction. *Cardiovasc Diabetol*. 2017;16(1):89.
- LeBras MH, Barry AR, Koshman SL. Cardiovascular safety outcomes of new antidiabetic therapies. *Am J Health Syst Pharm*. 2017;74(13):970-976.
- Sajja AP, Dey AK, Guha A, Elnabawi Y, Joshi AA, Kalra A. SGLT-2 inhibitors and GLP-1 agonists: first-line therapy for diabetes with established cardiovascular disease. *J Cardiovasc Pharmacol Ther*. 2019;24(5):422-427.
- Bataille V, Ferrières J, Danchin N, et al. Increased mortality risk in diabetic patients discharged from hospital with insulin therapy after an acute myocardial infarction: data from the FAST-MI 2005 registry. *Eur Heart J Acute Cardiovasc Care*. 2019;8(3):218-230.
- Moghaddam N, Wong GC, Cairns JA, et al. Association of anemia with outcomes among ST-segment-elevation myocardial infarction patients receiving primary percutaneous coronary intervention. *Circ Cardiovasc Inte*. 2018;11(12):e007175.
- Wester A, Attar R, Mohammad MA, et al. Impact of baseline anemia in patients with acute coronary syndromes undergoing percutaneous coronary intervention: a prespecified analysis from the VALIDATE-SWEDEHEART trial. *J Am Heart Assoc*. 2019;8(16):e012741.
- O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines. *Circulation*. 2013;127(4):e362-e425.
- Gili S, D'Ascenzo F, Lococo MF, et al. Impact of blood transfusion on in-hospital myocardial infarctions according to patterns of acute coronary syndrome: insights from the BleeMACS registry. *Int J Cardiol*. 2016;221:364-370.
- Florian A, Ludwig A, Rösch S, et al. Positive effect of intravenous iron-oxide administration on left ventricular remodelling in patients with acute ST-elevation myocardial infarction – a cardiovascular magnetic resonance (CMR) study. *Int J Cardiol*. 2014;173(2):184-189.
- Najjar SS, Rao SV, Melloni C, et al. Intravenous erythropoietin in patients with ST-segment elevation myocardial infarction: REVEAL: a randomized controlled trial. *JAMA*. 2011;305(18):1863-1872.
- Minamino T, Higo S, Araki R, et al. Low-dose erythropoietin in patients with ST-segment elevation myocardial infarction (EPO-AMI-II) – a randomized controlled clinical trial. *Circ J*. 2018;82(4):1083-1091.
- Szummer K, Lundman P, Jacobson SH, et al. Relation between renal function, presentation, use of therapies and in-hospital complications in acute coronary syndrome: data from the SWEDEHEART register. *J Intern Med*. 2010;268(1):40-49.
- Bruno RR, Nia AM, Wolff G, et al. clinical experiences with a novel contrast volume reduction system during invasive coronary angiography. *IJC Heart Vasc*. 2019;23:100377.
- O'Sullivan JJ, Conroy RM, Robinson K, Hickey N, Mulcahy R. In-hospital prognosis of patients with fasting hyperglycemia after first myocardial infarction. *Diabetes Care*. 1991;14(8):758-760.
- Cheung NW, Wong KYC, Kovoor P, McLean M. Stress hyperglycemia: a prospective study examining the relationship between glucose, cortisol and diabetes in myocardial infarction. *J Diabetes Complicat*. 2019;33(4):329-334.
- Wong KYC, Wong V, Ho JT, Torpy DJ, McLean M, Cheung NW. High cortisol levels in hyperglycaemic myocardial infarct patients signify stress hyperglycaemia and predict subsequent normalization of glucose tolerance. *Clin Endocrinol*. 2010;72(2):189-195.
- Bain RJ, Fox JP, Jagger J, Davies MK, Littler WA, Murray RG. Serum cortisol-levels predict infarct size and patient mortality. *Int J Cardiol*. 1992;37(2):145-150.
- Aronson D, Hammerman H, Kapeliovich MR, et al. Fasting glucose in acute myocardial infarction: incremental value for long-term mortality and relationship with left ventricular systolic function. *Diabetes Care*. 2007;30(4):960-966.
- Eitel I, Hintze S, Waha SD, et al. Prognostic impact of hyperglycemia in nondiabetic and diabetic patients with ST-elevation myocardial infarction insights from contrast-enhanced magnetic resonance imaging. *Circ Cardiovasc Imag*. 2012;5(6):708-718.
- Sigirci S, Yildiz SS, Keskin K, et al. The predictive value of stress hyperglycemia on thrombus burden in nondiabetic patients with ST-segment elevation myocardial infarction. *Blood Coagul Fibrinolysis*. 2019;30(6):270-276.
- D'Onofrio N, Sardu C, Paolisso P, et al. MicroRNA-33 and SIRT1 influence the coronary thrombus burden in hyperglycemic STEMI patients. *J Cell Physiol*. 2019;1-15. <https://doi.org/10.1002/jcp.29064>
- Sardu C, Barbieri M, Balestrieri ML, et al. Thrombus aspiration in hyperglycemic ST-elevation myocardial infarction (STEMI) patients: clinical outcomes at 1-year follow-up (vol 17, pg 512, 2018). *Cardiovasc Diabetol*. 2018;17:152.
- Marsico F, Gargiulo P, Marra AM, Parente A, Paolillo S. Glucose metabolism abnormalities in heart failure patients insights and prognostic relevance. *Heart Fail Clin*. 2019;15(3):333-340.
- Kosiborod M, McGuire DK. Glucose-lowering targets for patients with cardiovascular disease: focus on inpatient management of patients with acute coronary syndromes. *Circulation*. 2010;122(25):2736-2744.
- Investigators N-SS, Finfer S, Chittock DR, et al. Intensive versus conventional glucose control in critically ill patients. *N Engl J Med*. 2009;360(13):1283-1297.
- Ibanez B, James S, Agewall S, et al. 2017 ESC guidelines for the management of acute myocardial infarction in patients presenting with ST-segment elevation: the task force for the management of acute myocardial infarction in patients presenting with ST-segment elevation of the European Society of Cardiology (ESC). *Eur Heart J*. 2018;39(2):119-177.
- O'Gara PT, Kushner FG, Ascheim DD, et al. 2013 ACCF/AHA guideline for the management of ST-elevation myocardial infarction: executive summary: a report of the American College of Cardiology Foundation/American Heart Association Task Force on Practice Guidelines: developed in collaboration with the American College of Emergency Physicians and Society for Cardiovascular Angiography and Interventions. *Catheter Cardiovasc Interv*. 2013;82(1):E1-E27.