Stress hyperglycemia in acute myocardial infarction

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Key words:
myocardial infarction; blood glucose; hyperglycemia; diabetes mellitus; mortality.

Introduction

Hyperglycemia as a response to stress was firstly described by a French physiologist Claude Bernard in 1855. Since then, a number of studies have shown that stress hyperglycemia (SH) is important in many diseases, e.g. myocardial infarction, apoplexia, sepsis, trauma, and that it correlates with adverse outcome. Increased glucose level during stress is evoked by integrated hormonal, cytokine and nervous counterregulatory signals on glucose metabolic pathways and, therefore, presented in the same time with hyperinsulinemia and insulin resistance. Unlike the diagnostic criteria for diabetes mellitus (DM), there have been methodological problems with defining SH, and the consensus is clearly needed for the definition of SH in AMI. A proposal is that authors should analyze their database in two ways: both by using quartiles and the best cut-off value of glycaemia for mortality in AMI patients.

Even more evidences have accumulated to underline the importance of stress hyperglycemia as a prognosticator in acute myocardial infarction

The Harmonizing Outcomes with Revascularisation and Stents in Acute Myocardial Infarction (HORIZON-AMI) trial, treated with primary percutaneous coronary intervention (PCI), demonstrated the independent prognostic value of admission glucose levels on early and late mortality in both patients with and without known diabetes mellitus (DM). In the retrospective study of 4176 patients without known DM undergoing primary PCI for STEMI, Timmer et al. recently demonstrated the association of elevated glucose level (on admission) and 1-year and long-term mortality and association with larger infarct size. Mladenovic et al. had the similar results in nondiabetic patients with STEMI. Furthermore, in multivariate analysis, in patients without DM, who underwent PCI for the first AMI, SH has proved to be an independent predictor of myocardial salvage index which, assessed by cardiovascular magnetic resonance (CMR), is an independent predictor of clinical outcome. SH was shown to be a good indicator of increased risk for hospital death and predictor of poor outcome in patients with AMI and temporary electrical cardiac pacing, without previously diagnosed DM. High glycaemia on admission predicted increased in-hospital and long-term mortality in patients with STEMI complicated with cardiogenic shock. Importance of SH seem to last for a very long time – even for decades, as demonstrated in the study of Deckers et al. Namely, mortality was 64%, 71%, and 82% at 20 years in patients with normal, mild, and severe hyperglycemia, respectively. Deckers and coworkers analyzed a large number of patients (11,324),
of whom 41% had elevated admission blood glucose (ABG) ≥ 7.8 mmol/L (140 mg/dl). The prevalence of hyperglycemia at admission increased by 22% from 1985 to almost 50% in 2008. Additionally, SH is more important than it used to be earlier, because it was a significantly stronger predictor of adverse 30-day outcome after MI in the last decade than 25 years ago. Moreover, among 1,185 consecutive MI patients studied, raised admission plasma glucose (APG) was associated with increased mortality, irrespective of the initial reperfusion strategy, although the relation was more pronounced in the pre-invasive era (p value for heterogeneity of effects < 0.001) 21.

The presence of stress hyperglycemia association with almost all important clinical events in acute myocardial infarction

SH is related to AMI size, including a high Killip class, low left ventricular ejection fraction (LVEF), cardiogenic shock, requirement for initial cardiopulmonary resuscitation and increased concentrations of cardiac troponin, creatine kinase MB (CK–MB), pro-BNP and lactic acid 24,25. Maximum level of CK and CK-MB were significantly higher in patients with acute hyperglycemia 26. In the group of young patients (18–45 years) with first attack of AMI, initial serum glucose level was the significant independent variable in the prediction of ventricular arrhythmia attack 27. In addition, in the recent study of 1,258 patients with AMI, admission hyperglycemia (> 10 mmol/L, 180 mg/dL) was associated with a significantly higher prevalence of ventricular fibrillation (VF) and ventricular tachycardia (VT) in non-diabetic patients 28. The possible mechanisms leading to VF are higher free fatty acid concentrations, as a consequence of hyperglycemia and insulin resistance, that induce arrhythmias by damaging cardiac-cell membranes and by causing calcium overload 28, 29.

Furthermore, SH was shown to be associated with increased prevalence of atrial fibrillation (AF) in AMI, irrespective of DM status, i.e. in both new onset and in previously diagnosed DM, as well as in patients with elevated fasting glucose 30. The patients with both SH at admission (≥ 8.0 mmol/L, 144 mg/dL) and AF had almost 14.5 times higher in-hospital mortality than the patients who had neither SH nor AF 31. Besides associations with VT/VF and AF, Dzwierz et al. demonstrated a connection of admission glycemia and second to third grade atriventricular (AV) block and pulmonary edema in patients with AMI 32. In DM patients, this association is confirmed for VT/VF and second to third grade AV block, whereas in nondiabetic patients was confirmed for AF and pulmonary edema 31. In the prospective study of 834 patients with STEMI, the association of SH on admission (> 140 mg/dL, 7.77 mmol/L) and a higher incidence of rhythm disturbances: malignant ventricular tachyarrhythmias including VT/VF, new AV block and bundle branch block was recently demonstrated 32.

Nakamura et al. recently evaluated the association of glucose level and clinical variables during primary PCI in patients with STEMI. They demonstrated that corrected thrombolyis in myocardial infarction (TIMI) frame counts were significantly higher in patients with acute hyperglycemia and were independently associated with plasma glucose level. In AMI, hyperglycemia is a predictor of impaired coronary flow before reperfusion 34. The presence of acute hyperglycemia was associated with the impairment of epicardial coronary flow after primary stent implantation. In patients with SH at the time of AMI and temporary electrical cardiac pacing larger myocardial necrosis (i.e. higher troponin level) was noted, as well as: more prevalent Killip class > 1, lower LVEF and systolic blood pressure (BP) on admission 27. Additionally, SH is (in patients without DM) an independent predictor of the extent of myocardial salvage, which is in turn an independent predictor of outcome and the main mechanism by which patients with AMI benefit from reperfusion therapies 18. Moreover, SH is a marker of left ventricular (LV) remodeling, which may help explain post-infarction transition to LV failure 33. Additionally, SH correlates significantly with microalbuminuria, which is a sign of endothelial dysfunction 36.

Indeed, nothing in the organism is just black or white, particularly in such a complex conditions as AMI. We shall not forget that an increased blood concentration is basically an adaptive mechanism for stress (“fight or flight situation”). A recent paper reminds us that not all increases of glycemia in hospitalized patients are dangerous 37. This is also underlined by the recent guidelines for AMI, suggesting less tight glycemia targets and avoiding hypoglycemia, which is very dangerous in this setting.

Recommendations from the American Heart Association Diabetes Committee of the Council on Nutrition, Physical Activity, and Metabolism published to summarize accumulated knowledge, and to trace paths for further research

In 2008 the American Heart Association (AHA) statement on hyperglycemia in AMI, suggested definition of hyperglycemia – APG > 140 mg/dL (7.77 mmol/L) 38. AHA statement recommended, until further data became available, approximation of normoglycemia to be a reasonable treatment goal [suggested range for plasma glucose 90–140 mg/dL (5.0–7.77 mmol/L)], as long as hypoglycemia is avoided 38. Also, further evaluation (preferably before hospital discharge) was recommended for acute coronary syndrome (ACS) patients with hyperglycemia but without prior history of DM, in order to determine the severity of their metabolic derangement. This evaluation may include fasting glucose and glycated hemoglobin (HbA1C) assessment and, in some cases, postdischarge oral glucose tolerance test (OGTT) 38.

The role of stress hyperglycemia as a prognosticator in acute myocardial infection may be further improved by using more appropriate cut-offs

Despite the fact that association of hyperglycemia with poor outcome was repeatedly demonstrated in patients with AMI, there is a lack of consensus on how to achieve the op-

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timal sensitivity and specificity of this prognosticator. A step toward improvement may be to use different cut-off values for SH in AMI patients with and without known (previously diagnosed) DM. It is a logical assumption, given the fact that patients with DM have already impaired glucose regulation. Moreover, patients with DM have a higher average glycemia in comparison with the other AMI patients 39, 40. In the study of 500 AMI patients, the best Receiver operating characteristics (ROC) curve-derived cut-off value for admission serum glucose concentrations in patients without known DM was 8.55 mmol/L (153.9 mg/dL), with the sensitivity 79% and specificity 87% for mortality 41, 42. This value corresponds to the cut-offs which have been used in many studies for AMI patients without DM 23, 30, 32, 43, 44. The best cut-off value in AMI patients with known DM was 18.0 mmol/L (324 mg/dL), which is more than twice higher, and it achieved 64% sensitivity and 75% specificity for in-hospital mortality 41. As shown in meta-analysis, in the studies with diabetic patients the cut-off was usually 10 mmol/L (180 mg/dL) 45.

However, the same cut-off value for SH in all AMI patients was used in most studies in the last decade. In some rare exceptions the cut-off value was different. In the paper from 1989 by Sewdarsen et al. 35 the cut-off value 11 mmol/L (198 mg/dL) was used for patients with DM, as opposed to 8 mmol/L (144 mg/dL) for patients without DM.

**Results of basic investigations on how hyperglycemia worsens outcomes in patients with acute myocardial infarction**

Hyperglycemia contributes to poor outcomes in patients with AMI by several mechanisms. Hyperglycemia has a number of immunomodulatory effects. It can lead to significant oxidative stress 46. By the mechanisms of oxidative stress, hyperglycemia acutely increases cytokine concentrations (interleukin-1β, 6, 8 and 18, tumor necrosis factor-alpha) and exaggerates inflammation 47, 48. This effect is more pronounced in patients with impaired glucose tolerance 49. Glucose excursions can further promote inflammation by increasing leukocyte adhesion molecules, inducing nuclear factor kappa B (NF-kβ) 50 and promoting the procoagulant state 51, 52. Recent studies show that TNF-alpha-induced activation of the NF-kβ pathway plays a critical role in cardiomyocyte apoptosis 53, 54. Hyperglycemia-induced myocardial apoptosis is mediated, in part, by the activation of cytochrome c-activated caspase-3 pathway, which may be triggered by reactive oxygen species (ROS) derived from high levels of glucose 55. Another study also demonstrated that intermittent high glucose concentration enhances apoptosis in human umbilical vein endothelial cells in culture and suggests that variability in glycemic control could be more deleterious to endothelial cells than a constant high concentration of glucose 56.

Moreover, hyperglycemia impairs the polymorphonuclear neutrophil function resulting in decreased intracellular bactericidal activity, opsonic activity and innate immunity 51, 52. Patients with hyperglycemia have enhanced T-cell activation, both CD4+ and CD8+, as well as a large number of natural killer (NK) cells with known role in plaque instability 36.

Further, due to insulin resistance patients with hyperglycemia are especially susceptible to thrombotic events by a concurrent insulin-driven impairment of fibrinolysis and a glucose-driven activation of coagulation 57.

Acute hyperglycemia-induced oxidative stress leads to the inactivation of sarco(endo)plasmic reticulum Ca2+-ATPase (SERCA) and consequently abnormal Ca2+ signaling and contractile dysfunction 38.

Another study demonstrated that hyperglycemia leads to endothelial dysfunction, increased plasma hyaluronan levels and coagulation activation and indicates a potential role for glycocalyx perturbation in mediating vascular dysfunction during hyperglycemia 39.

Furthemore, acute hyperglycemia abolishes ischemic preconditioning in vivo 60.

**Putative pathophysiologic mechanisms of stress hyperglycemia effects on worsening the prognosis and the occurrence of an ischemic event**

SH has the unfavorable independent prognostic role in non-diabetic patients with STEMI, regardless of AMI severity, extension, and treatment 61. It is still difficult to answer the crucial question for practice: Is SH in AMI a risk marker or a therapeutic target 62, 63?

Basically, there are 2 ways, relating SH to worse prognosis in AMI: a) SH is a marker of at least 3 major prognostic factors: advanced age, large actual necrosis in AMI (or hemodynamic instability due to superimposed new myocardial necrosis upon already existing myocardial damage), and increased catecholamine and sympathetic nervous system activity; b) SH is a mediator (active pathophysiologic factor) which contributes to poor outcome. Probably by both direct and indirect effects SH may cause additional harm in AMI 63.

There are evidences that acute hyperglycemia could be harmful by itself, leading to hemodynamic changes (increased heart rate and blood pressure (BP), important determinants of myocardial oxygen need), in addition to elevation of catecholamines 64, 65. Moreover, Ishihara et al. 66 were able to demonstrate, using multivariable analysis, a significant correlation between higher glucose and impaired predischarge LVEF, even after adjustment of acute LVEF. This suggests that acute hyperglycemia is causally associated with further deterioration of LV function following reperfusion in AMI 66, 67.

Irrespective whether they reflect SH as a marker or active player in worsening prognosis in AMI, the following mechanisms (some of them overlap importantly) are currently believed to contribute: increased bodd concentration of free fatty acids (resulting from a relative insulin deficiency), which produce toxic effects on cardiomyocytes, increase myocardial oxygen need, and depress myocardial contractility 68; microvascular obstruction (due to plugging of leukocytes in the coronary capillaries and venules, giving raise to platelet-dependent thrombosis in the capillaries, etc.).

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Microvascular obstruction was considered the reasonable explanation for the findings on contrast-enhanced cardiovascular magnetic resonance (CMR). SH is associated with a higher incidence of TIMI < 3 flow in the infarct-related artery after PCI and even in patients with TIMI 3 flow after PCI patients with SH have higher final TIMI frame counts on angiography; endothelial dysfunction, no-reflow phenomenon, for which glycaemia was the strongest independent predictor; decrease of collateral blood flow to the ischemic area (by adversely affecting nitric oxide availability); electrophysiologic disturbances, resulting in arrhythmias; exaggeration of the inflammatory by the oxidative mechanism; increased immune response, increased apoptosis; increased interstitial fibrosis.

In addition to aforementioned mechanisms relating SH to worse prognosis in AMI, the following might help explaining the higher incidence of new ischemic event: prothrombotic state, generated by hyperglycemia; endothelial dysfunction; decreased of fibrinolytic activity and effect of tissue plasminogen activator. Also, glycaemia is an independent predictor of platelet dependent thrombosis. Moreover, among diabetic patients, those with STEMI and glycaemia > 8.5 mmol/L on admission had a poorer response to clopidogrel. Additionally, improved glycaemic control reduces platelet reactivity in DM patients after PCI. From therapeutic point of view, it may be important that in ACS patients with hyperglycaemia intensive glucose control results in a reduction of platelet reactivity only in the presence of elevated HbA1c levels; decreased nitric oxide bioavailability; possible increased risk for upper gastrointestinal bleeding which may be due to stress ulcer, resulting from decreased gastric mucosal blood flow, increased gastric mucosal permeability with increased acid back-diffusion, and ischemia-reperfusion injury.

In line with the aforementioned, non ST elevation acute coronary syndromes (NSTE-ACS) patients with both diagnosed and undiagnosed DM had significantly higher risk for Global Utilization of Streptokinase and Tissue Plasminogen Activator (TPA) for Occluded (GUSTO) coronary arteries moderate or severe bleeding and need for in-hospital transfusion (as compared to non-diabetics, despite similar age, serum creatinine levels, and rates of invasive procedures and antithrombotic therapy), suggesting that they may be more vulnerable to hemorrhage.

**Stress hyperglycaemia and the major adverse cardiac and cerebrovascular event following primary percutaneous coronary intervention (PPCI)**

In PPCI-treated STEMI patients, SH is a marker of both subsequent mortality and more frequent major adverse cardiac and cerebrovascular events (MACE) in general. SH was also associated with increased 30-day rates of reinfarction, acute renal injury, target vessel revascularization (TVR) and major bleeding in 3,405 patients in the HORIZONS-AMI trial. In the German Acute Coronary Syndromes (ACOS) Registry, in 5,866 STEMI patients, SH (>150 vs <120 mg/dl), was significantly related to increased risk of MACE (composite of death, reinfarction, stroke, or rehospitalization), adjusted OR 1.31, 95%CI 1.00 to 1.71, p < 0.0001.

Tamita et al. studied 275 AMI patients, with the median follow-up interval of 5.3 years. Patients with abnormal fasting glycaemia and/or OGTT had a significantly higher ABG as well as more MACE defined as: cardiovascular death, stroke, non-fatal myocardial infarction or ACS, non-TVr either by coronary artery bypass grafting (CABG) or coronary angioplasty and congestive heart failure that required hospitalisation.

In a study on 2,482 consecutive STEMI patients, those with SH, but without DM, had the highest risk population for in-hospital mortality and MACE (composite end points including death, reinfarction, and TVR).

In the study of Mather et al. patients with high admission glycaemia were significantly more likely to experience clinical MACE, defined as cardiovascular death, recurrent myocardial infarction, coronary revascularization or hospital admission for cardiovascular cause, at any time than normoglycemic patients, Hazard Ratio (HR) 3.82 (95% CI: 1.61, 9.06).

Zhang et al. studied 853 STEMI patients. In-hospital stent thrombosis was also more commonly seen in patients with SH.

In STEMI patients (out of whom 9.5% were treated using PPCI), those who presented glucose ≥ 140 mg/dL (7.7 mmol/L) had higher rates of malignant ventricular tachyarrhythmias, bundle branch block, new atrioventricular block and in-hospital mortality.

Among 4,793 STEMI patients (including 12% treated with PCI), MACE (all-cause mortality, cardiogenic shock, and reinfarction) were significantly more frequent in patients with higher admission glycaemia.

In 6,358 AMI patients without diabetes, SH prior to coronary angiography predicted contrast-induced acute kidney injury (AKI), even after adjusting for confounding variables, most importantly impaired renal function at baseline.

The incidence of cardiac failure, arrhythmia, cardiac death, reinfarction, post-infarction angina pectoris, and MACE was higher in 456 non-diabetics AMI patients who had SH (>11.1 mmol/L vs < 7.8 mmol/L).

Mrdovic et al. incorporated SH in the RISK-PCI score. SH was defined as glycaemia ≥ 6.6 mmol/L at admission. SH was „worthy“ one point (out of 20 in total). Thirty-day MACE comprising death, nonfatal reinfarction and stroke was the primary end point. An 18-fold graded increase in the primary end point was observed between patients in a low risk class and those in a very high risk class.
MACE (reinfarction or heart failure or mortality) were more frequent at follow up of patients with SH (≥ 190 mg/dL, compared with those with admission glucose levels < 190 mg/L) in the study of Pei-Chi et al. 93.

Therapeutic approach to stress hyperglycemia

SH is a powerful predictor in-hospital morbidity and mortality in AMI, both in diabetic and non-diabetic patients 94, 95. A 1 mmol/L increase in glycaemia above the normal range correlates with a 4% raise in mortality for non-DM patients and 5% for known DM patients 96. Despite the importance of the problem in general and in everyday practice, we have no firm, evidence-based knowledge whether intensive treatment to lower hyperglycaemia in AMI will improve prognosis 96. The choice of hypoglycemic drugs, treatment tresholds and targets are the subject of a long-standing debate, and opinions have been sometimes diametral, which may translate into substantial differences in results.

Studies on tight glycemia control by insulin

The first evidence toward intensive glycemic control in intensive care unit came from the proof-of-concept Leuven (Belgium) studies in surgical, medical and the pediatric intensive care unit (ICU), assessed causality. All the 3 trials found that insulin usage to target strict normoglycemia 4.44–6.11 mmol/L (80–110 mg/dL) had led to improved outcomes compared with tolerating hyperglycaemia to 12 mmol/L (215 mg/dL), which is the renal threshold for glycosuria. Targeting blood glucose around 8 mmol/L (145 mg/dL) seems preferable 97–101. Such findings were not confirmed by other well-conducted randomised controlled trials (RCTs) in intensive care ICU patients 95.

Normoglycaemia in Intensive Care Evaluation and Survival Using Glucose Algorithm Regulation (NICE-SUGAR), was the largest such international RCT (n = 6,104 of either medical or surgical ICU patients). It demonstrated that tight glycemic control was associated with higher incidence of severe hypoglycaemia and increased 90-day mortality (24.9% vs 27.5% in the control group, OR: 1.14; 95% CI: 1.02 to 1.08; p = 0.02; the number needed to harm = 38). Excess deaths were mainly cardiovascular. An intermediate blood glucose target 7.77–10 mmol/L (140–180 mg/dL) was safer than targeting normoglycemia 95, 101, 102.

Glucosecontrol (the Comparing the Effects of Two Glucose Control Regimens by Insulin in Intensive Care Unit Patients) RCT included 1,101 patients from medical/surgical ICUs. It was stopped earlier than planned because the incidence of hypoglycaemia (9.8%) was too high and the target glycemic control was not reached 101.

Thus, recent studies in ICUs have not shown improved outcomes in patients allocated to tight blood glucose control, but rather an excess of adverse events related to more frequent hypoglycaemic episodes.

Although there are important similarities between ICU and coronary ICU patients, it is questionable to what extent results could be extrapolated from medical ICU to AMI patients.

The first such, relatively large trial on AMI patients was Diabetes, Insulin Glucose Infusion in Acute Myocardial Infarction (DIGAMI) trial (n = 620 patients). It demonstrated mortality benefit at one year (18.6% vs 26.1%), obtained by tight glucose control through iv insulin 67, 103. The subsequent DIGAMI-2 trial (n = 1,253) showed no mortality benefit of a long-term insulin therapy in patients with both AMI and type 2 DM. Morbidity also did not differ among the groups 94, 102. The opposite results of the two major trials concerning this topic might be the consequence of suboptimal quality of studies 96.

The Hyperglycaemia: Intensive Insulin Infusion in Infarction (HI-5) study on 240 AMI patients did not find a reduction in mortality among patients who received insulin/dextrose infusion therapy, but did find a lower incidence of heart failure (12.7 vs 22.8%, p = 0.04) and reinfarction within 3 months (2.4 vs 6.1%, p = 0.05) 105.

Causal relation between high glycaemia and high morbidity and mortality in AMI is not definitively confirmed, and hyperglycaemia might be an epiphenomenon. Conclusive, large trials seem to be very expensive, precluding their conduct in contemporary economic environment – in the sufficient size to provide reliable answers 95. Thus, recent trials of insulin treatment in AMI patients failed to demonstrate desired reduction in mortality, but showed unwanted, raised incidence of severe hypoglycaemia 69. Recent meta-regression analysis of the studies from 1965–2011 compared a tight glycemia control strategy (by insulin in most patients) with a less intensive regimen. Total number of patients was 2,113 and mortality was not different between the groups 106.

As most studies of this topic were not optimally conducted 107 differences in numerous morbidities between strict glycemic control and conventional treatment were not reported in sufficient details (usually only a couple of them), or not significantly different or not felt important in subsequent meta-analyses. This is presumably due to the absence of definitive consensus about criteria for threshold, targets and means to treat hyperglycaemia in ACS. For example, as far as morbidity is concerned, in a DIGAMI study, groups did not differ regarding reinfarction, ventricular fibrillation, high degree atrioventricular conduction disturbances or congestive heart failure 108. Likewise, the combined total event rate (death, stroke, or reinfarction) did not differ significantly among the 3 groups in DIGAMI 2 104.

Studies using glucose–insulin–potassium infusions

Glucose-insulin-potassium (GIK) infusions were found in AMI to be of no value and even potentially harmful 94, 103, 109, 110. GIK therapy has not induced any improvement in outcome, although various GIK formulations, treatment duration, routes of administration, etc. were tested 108–112.

Glucose-insulin-potassium infusion on mortality in patients with acute ST-segment elevation myocardial infarction (CREATE-ECLA), is the largest scale international study, which randomized 20,201 patients to 24 h GIK or usual care. The CREATE-ECLA showed that high-dose GIK infusion had a neutral effect on mortality, cardiac arrest, and cardio-

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genic shock in STEMI patients. Thus, GIK infusions are not recommended in current clinical guidelines. Timing may be important. For example, the moderate benefit was demonstrated with out-of-hospital GIK administration in comparison with placebo: rates of the composite outcome of cardiac arrest or in-hospital mortality were lower with GIK. Regrettably, there was no improvement in 30-day survival.

**Importance of hypoglycemia, including iatrogenic one**

An association of increased mortality and morbidity with hypoglycemia also has been demonstrated. In a recent meta-regression analysis (which involved 2113 patients), Chatterjee et al. found in the tight glucose control group significantly higher rate of hypoglycemia. Even without achieving target glycemic control, relative risk (RR) was very high (13.40, 95% CI: 6.8–9.8; p < 0.01), absolute risk increase was 12% and a number needed to harm was 9 (95% CI: 6.8–9.8).

Intensive glycemic control also failed to improve CHF, arrhythmias and reinfarction rates. Meta-regression revealed that mortality with intensive glycemic control was worse with increased duration of therapy (p = 0.001, for trend). Therefore, benefit of tight glycemic control in AMI patients with type 2 DM is limited, but risk of serious hypoglycemia is significant. Hypoglycemia relates to prolonged hospital, greater cost of hospitalization, and higher mortality both during hospitalization, and after discharge. Several mechanisms may contribute. For example, hypoglycemia may exacerbate myocardial ischemia and may cause dysrhythmias and sudden death. Hypoglycemia can be particularly dangerous in patients with cardiac autonomic neuropathy. Hypoglycemia is related to prolongation of QT and reentrant arrhythmias, often quoted as crucial for the “dead in bed” syndrome. Too rapid rate of glycemia reduction could be a factor in adverse CVD outcomes. Hypoglycemia can provoke an increase in blood viscosity and coagulation, vasoconstriction by increased secretion of endothelin, platelet activation and aggregation, increased release of inflammatory mediators and cytokines. Hypoglycemia promotes free fatty acid metabolism and reduces glycolysis, with increased cardiac oxygen consumption and with a possible direct toxic effect on cardiomyocytes. Spontaneous hypoglycemia, may be even more dangerous than iatrogenic hypoglycemia. Even in stable CAD patients, under elective procedure, hypoglycemia had an almost three-fold higher risk of MACE (including in-stent restenosis and TVR) at 3 years. Clinical significance of asymptomatic hypoglycemia has not been sufficiently elucidated. A possible difference in spontaneous vs drug-induced hypoglycemia also needs to be additionally evaluated.

A word of caution is needed considering methodology. Many point-of-care (POC) systems do not account for the patient’s hematocrit or degree of oxygenation, both of which may produce errors in glycaemia measurement. Thus, both in anemic and in hypoxic patients, falsely high glycaemia readings may occur.

Recently, a new, promising therapeutic approach for hyperglycemia was proposed, namely, glucagon-like peptide infusion, which exerts insulinotropic and insulinomimetic actions, with a low risk for hypoglycemia.

**Glycemic threshold for therapy**

Sufficient evidence is missing to strongly recommend any specific treatment to manage hyperglycemia in an ACS patient other than trying to keep glycaemia within reasonable levels (usually defined by consensus). A well-designed RCT in ACS is obviously needed to determine glucose treatment thresholds and targets. On the basis of the balance of current evidence, it is prudent to treat hyperglycemia > 180 mg/dL (10 mmol/L), to change the recommendation for the use of insulin to control glycaemia in NSTE-ACS from a more stringent to a more moderate target range, and to avoid hypoglycemia. Similar approach is suggested for ICU patients. Continuous insulin therapy should be started in the ICU, when ABG levels are > 10.0 mmol/L (180 mg/dL) and in those with previous DM when preprandial glucose levels are > 7.77 mmol/L (140 mg/dL) during follow-up. Insulin therapy is the treatment of choice for hyperglycemia in ICUs, initiating continuous intravenous infusion when ABG is > 10.0 mmol/L (180 mg/dL). American Diabetes Association's Standards of Medical Care in Diabetes recommended in 2010 initiating insulin therapy in critically ill patients with blood glucose > 10 mmol/L (> 180 mg/dL) and to target a blood glucose range of 7.8–10.0 mmol/L (140–180 mg/dL).

**Targets for hyperglycemia therapy**

Guidelines for ACS recommend nowadays less strict glycemia control than a few years earlier. Until more data become available the treatment target should be to avoid severe hyperglycemia [glucose concentration > 10–11 mmol/L (> 180–200 mg/dL)] as well as hypoglycemia [< 5 mmol/L (< 90 mg/dL)].

A strategy of "strict, but not too strict" glucose control in STEMI seems to be a practical approach. In the acute phase, it is reasonable to maintain a blood glucose concentration ≤ 11.0 mmol/L (< 198 mg/dL), but absolutely avoid hypoglycemia. It is reasonable to use an insulin-based regimen for hospitalized patients with UA/NSTEMI to achieve and maintain glucose levels < 10 mmol/L (< 180 mg/dL), while avoiding hypoglycemia. The recommended blood glucose target is 7.7–10 mmol/L (140–180 mg/dL) for most patients.

More recent guidelines recommend a more lax control of glycaemia in critically ill patients: between 8–10 mmol/L (144–180 mg/dL).

The aim of glycemic control in the acute phase should be a glucose level < 11.0 mmol/L (< 198 mg/dL), while avoiding fall of glycaemia < 5 mmol/L (< 90 mg/dL).
Treatment of hyperglycemia in an ICU with a strategy of “strict, but not too strict”: glycemic target is 7.77–10 mmol/L (140–180 mg/dL) for most patients, rather than a more stringent target of 6.11–7.77 mmol/L (110–140 mg/dL) 110.

**Insulin infusion as the recommended way to treat hyperglycemia in AMI/ACS**

Current guidelines suggest a dose-adjusted insulin infusion with monitoring of glycemia in some patients 94. In the first instance, we should consider a dose-adjusted insulin infusion with regular monitoring of blood glucose levels 107. Continuous insulin infusion is the currently recommended first-line therapy for patients with AMI and acute hyperglycemia, but it takes time to achieve optimal glucose levels by the time of reperfusion 93. Glycemia should be monitored every hour until the target range is reached, and then every 2 h. Following the acute period (usually the initial 24 h), continuous therapy is stopped and subcutaneous insulin (usually long-acting analogs) started 110.

For patients with type 2 DM and ACS, insulin is not required beyond the first 24 h unless clinically required for the management of their DM. Immediate intensive blood glucose control should be provided to patients with AMI and DM or marked hyperglycaemia (> 11.0 mmol/L). This should last for at least 24 h 126.

The aforementioned is in line with advances for other hospitalized patients. The 2011 American College of Physicians guideline suggests a target blood glucose level of 7.8 to 11.1 mmol/L (140 to 200 mg/dL) if insulin therapy is used in surgical ICU/medical ICU patients. However, firm evidence is missing whether such target-driven glucose control in AMI has meaningful clinical benefits 127.

Dose-adjusted infusions of insulin for 24 h have been recommended for hyperglycemia treatment in all recent AMI/ACS guidelines. Precise suggestions are missing in these and few other related contemporary guidelines 94, 102, 103, 107, 127, 128. The best contemporary guideline addressing treatment of hyperglycemia in an ICU is written by Jacobi et al. 129. A valid insulin therapy includes usage of a reliable insulin infusion protocol, frequent blood glucose monitoring, avoidance of finger-stick glucose testing through the use of arterial /venous glucose samples, and dextrose replacement for hypoglycemia prevention and treatment 129.

Continuous insulin infusion (1 unit/mL) therapy should be initiated after priming new tubing with a 20-mL waste volume. Insulin may be mixed with 0.9% sodium chloride, lactated Ringer’s injection, Ringer’s injection, or 5% dextrose. Insulin may be prepared in glass container. If insulin-induced hypoglycemia (< 3.89 mmol/L, 70 mg/dL) occurs, insulin infusion should be stopped and 10–20 g of hypertonic (50%) dextrose should be administered 129. Glycemia should be measured in 15 min with further dextrose administration as needed to achieve glycemia > 70 mg/dL (3.89 mmol/L), with a goal to avoid iatrogenic hyperglycemia 129.

Insulin use in any patient with hyperglycemia is fraught with problems. Insulin is still often administered incorrectly (e.g., the use of subcutaneous “sliding scales”) 95.

**Recommended approaches to detect diabetes mellitus and impaired glucose tolerance in acute myocardial infarction patients**

DM is another characteristic associated with high risk for adverse outcomes after ACS 102. For adequate treatment, it is important to detect DM and impaired glucose tolerance (IGT), which are prevalent in AMI. An estimated 20% of ACS patients are known to have DM, a further 25% have undiagnosed DM and 40% with IGT. Thus, up to 85% of ACS patients have some degree of dysglycemia at presentation, which persists in a significant proportion of patients at 3 months 96. Therefore, it is reasonable to measure HbA1c and fasting blood glucose in all patients without known DM, who developed hyperglycemia during the acute phase. If equivocal, an oral glucose tolerance test (OGTT) may be needed after discharge. This should preferably be measured 4 days after the acute phase 94. OGTT is suggested because either high ABG, fasting plasma glucose or HbA1c, in AMI patients without DM are not sensitive enough to uncover previously undiagnosed abnormal glucose tolerance or DM 130. Likewise, ACS patients with HbA1c ≥ 6.5% on admission may be considered diabetic while, in those without known DM and HbA1c < 6.5%, OGTT should be performed 1–4 weeks after ACS 123. One should offer all patients with hyperglycemia after ACS, but without known DM, tests for HbA1c levels before discharge and fasting blood glucose levels no earlier than 4 days after the onset of ACS. These tests should not delay discharge. The Center for Clinical Practice at NICE (UK) does not recommend routinely OGTT to patients with hyperglycemia after ACS and without known DM, provided that HbA1c and fasting glycemia are within the normal range 107. The European guidelines on DM, pre-DM, and cardiovascular diseases (CVD) recommend an OGTT in patients with established CVD 130, 131.

**Goals for the next period**

While there is a significant evidence that hyperglycemia is associated with increased mortality and morbidity in AMI, further studies are warranted to guide management in patients with AMI and acute hyperglycemia 67, 132.

Moreover, international consensus statement is needed about: which glucose concentration is the most useful (admission, fasting,...) as a prognosticator in AMI; which cutoffs values of the admission glycemia should be recommended for DM and non-DM pts; should HgbA1C and OGTT be used in routine glucose metabolism evaluation in AMI (and, if yes, when), having cost-effectiveness in mind; algorithm for the treatment of SH.

**Conclusion**

Rapidly accumulating evidence confirms the relation of stress hyperglycemia both with mortality in acute myocardial infarction patients and with major adverse outcome measures. Precise recommendations regarding the target glucose concentration in acute myocardial infarction have already

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been published. New approaches (such as using different cut-off values for patients with and without known diabetes mellitus) may help optimizing utility of stress hyperglycemia in critical illnesses. However, some important questions remain to be answered in near future, as they are relevant to everyday clinical practice.

Acknowledgement
This work was supported by the Serbian Ministry of Education, Science and Technological Development, grant No. III41018.

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Received on November 3, 2012.
Revised on August 28, 2013.
Accepted on November 22, 2013.
OnLine-First March, 2014.